CLINICAL STUDY PROTOCOL

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study Evaluating the Safety and Efficacy of Intravenous Iloprost in Subjects With Systemic Sclerosis Experiencing Symptomatic Digital Ischemic Episodes (AURORA Study)

Investigational Product: Iloprost Injection, for intravenous use
Protocol Number: ES-301

Sponsor:
Eicos Sciences, Inc.
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Amendment 3: 18 May 2020

SIGNATURE PAGE

STUDY TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study Evaluating the Safety and Efficacy of Intravenous Iloprost in Subjects With Systemic Sclerosis Experiencing Symptomatic Digital Ischemic Episodes (AURORA Study)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

PPD _____

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Eicos Sciences, Inc., a CiVi Biopharma, Inc. Affiliated Company

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INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Eicos Sciences, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Eicos Sciences, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Eicos Sciences, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Declaration of Helsinki, Institutional Review Board Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study Evaluating the Safety and Efficacy of Intravenous Iloprost in Subjects With Systemic Sclerosis Experiencing Symptomatic Digital Ischemic Episodes (AURORA Study)

PROTOCOL NUMBER: ES-301

INVESTIGATIONAL PRODUCT: Iloprost Injection, for intravenous use

PHASE: 3

INDICATION(S): Treatment of patients with systemic sclerosis (SSc) experiencing symptomatic digital ischemic episodes

OBJECTIVES:

The primary objective is to evaluate the efficacy of iloprost compared to placebo on the change from baseline in symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic Raynaud's phenomenon (RP) attacks, in subjects with SSc.

The secondary objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the overall severity of RP attack symptoms
- To evaluate the efficacy of iloprost compared to placebo on the weekly total duration of symptomatic RP attacks
- To evaluate the safety and tolerability of iloprost

The exploratory objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the worst pain associated with symptomatic RP attacks
- To evaluate the efficacy of iloprost compared to placebo on the worst numbness associated with symptomatic RP attacks
- To evaluate the efficacy of iloprost compared to placebo on the worst tingling associated with symptomatic RP attacks
- To evaluate the efficacy of iloprost compared to placebo on the worst discomfort associated with symptomatic RP attacks
- To evaluate the efficacy of iloprost compared to placebo on the Raynaud's Condition Score
- To evaluate the efficacy of iloprost compared to placebo on symptomatic RP attack duration
- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall change in symptomatic Raynaud's attacks (Patient Global Impression of Change [PGIC])

- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall severity in symptomatic Raynaud's attacks (Patient Global Impression in Severity [PGIS])
- To evaluate the patient assessment of overall benefit compared to side effects
- To evaluate the effect of iloprost compared to placebo on biomarkers of SSc

POPULATION:

The population for this study is male and female subjects ≥18 years of age with a diagnosis of SSc as defined by the 2013 American College of Rheumatology criteria/European League Against Rheumatism (EULAR) criteria. Eligible subjects with SSc will also be experiencing symptomatic digital ischemic episodes.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Male or female subjects must be ≥18 years of age.
2. Subjects must have a diagnosis of SSc as defined by the 2013 American College of Rheumatology criteria/EULAR criteria.
3. Subjects must have a diagnosis or history of RP, self-reported or reported by a physician, with at least a 2-phase color change in finger(s) of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion.
4. Subjects must have a minimum of 10 symptomatic RP attacks, documented in the electronic patient-reported outcomes (ePRO) diary, occurring over at least 3 separate days of the 5-day eligibility period.
    - Note: A symptomatic Raynaud's attack for this study is defined as at least 1 color change of the subject's finger(s) (blue, white, or red) associated with at least 1 symptom (pain, numbness, tingling, and/or discomfort of the finger[s]). The attack is considered over when the color changes back to pre-attack color (normal) and the symptoms return to the subject's pre-attack level.
5. Subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period.
6. Female subjects of childbearing potential (defined as female subjects who have experienced menarche and who are not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) and male subjects must agree to use contraception for the duration of the study.
7. Subjects must be willing and able to comply with the study requirements and give informed consent for participation in the study; where permitted by local regulations, a legally authorized representative will be allowed to sign the consent form as a proxy for subjects who are unable to physically sign but are able to give a verbal informed consent.

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Female subjects who are pregnant or breastfeeding prior to randomization.
2. Subjects with systolic blood pressure <85 mmHg (sitting position) at screening.
3. Subjects with an estimated glomerular filtration rate <15 mL/min/1.73 m^2 at screening as determined by the Modification of Diet in Renal Disease equation.
4. Subjects with an alanine aminotransferase and/or aspartate aminotransferase value >3 × the upper limit of normal at screening.
5. Subjects who have a digital ulcer infection within 30 days of screening.
6. Subjects with a history of cervical or digital sympathectomy, or botulism toxin injections in their hands [for RP or digital ulcers] within 90 days of screening. Subjects should not have a planned botulism toxin or sympathectomy during their participation in the study.
7. Subjects with gangrene or digital amputation within 6 months of screening.
8. Subjects with current intractable diarrhea or vomiting.
9. Subjects with a risk of clinically significant bleeding events, including those with coagulation or platelet disorders at screening.
10. Subjects with a history of major trauma or hemorrhage within 30 days of screening.
11. Subjects with clinically significant chronic intermittent bleeding, such as active gastric antral vascular ectasia or active peptic ulcer disease, within 60 days of screening.
12. Subjects who have had any cerebrovascular events (eg, transient ischemic attack or stroke) within 6 months of screening.
13. Subjects with a history of myocardial infarction or unstable angina within 6 months of screening. Subjects should not have a planned coronary procedure during their participation in the study.
14. Subjects with acute or chronic congestive heart failure (New York Heart Association Class III [moderate] or Class IV [severe]) at screening.
15. Subjects with a history of more than mild restrictive or congestive cardiomyopathy uncontrolled by medication or implanted device.
16. Subjects with a history of life-threatening cardiac arrhythmias.
17. Subjects with a history of hemodynamically significant aortic or mitral valve disease.
18. Subjects with a history of known pulmonary hypertension, pulmonary arterial hypertension, or pulmonary veno-occlusive disease.
19. Subjects with a history of significant restrictive lung disease, defined as forced vital capacity <45% predicted and diffusing capacity of the lungs for carbon monoxide <40% predicted (uncorrected for hemoglobin).
20. Subjects with scleroderma renal crisis within 6 months of screening.

21. Subjects with a concomitant life-threatening disease with a life expectancy <12 months.
22. Subjects who have a clinically significant disorder that, in the opinion of the Investigator, could contraindicate the administration of study drug, affect compliance, interfere with study evaluations, or confound the interpretation of study results.
23. Subjects who have taken or are currently taking any parenteral, inhaled, or oral prostacyclin or prostacyclin receptor agonists (eg, epoprostenol, treprostinil, iloprost, and selexipag) within 8 weeks of screening.
24. Subjects who have initiated or had a dose change of any of the following within 2 weeks of screening: oral, topical, or intravenous (IV) vasodilators (eg, calcium channel blockers, phosphodiesterase-5 (PDE5) inhibitors [eg, sildenafil, tadalafil, or vardenafil], nitrates, and fluoxetine).
25. Subjects with any history of acetaminophen intolerability (eg, allergic reaction to acetaminophen).
26. Subjects with any malignancy that requires treatment during the study period, that has required treatment within 1 year of screening (including excision of skin cancer) or that is currently not in remission.
27. Subjects who have used any investigational medication or device for any indication within 30 days or 5 half-lives (whichever is longer) of screening.
28. Subjects who have participated in ES-201 or ES-301 studies and were randomized and treated with study drug.

STUDY DESIGN AND DURATION:

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of iloprost on the frequency of and relief from symptomatic digital ischemic episodes in subjects with SSc. Subjects are allowed to continue receiving stable standard of care therapies for the management of symptomatic RP (eg, calcium channel blockers, angiotensin-converting enzyme inhibitors, statins, fluoxetine, and low dose acetylsalicylic acid) or may participate without the use of background standard of care therapies.

The study will target randomizing approximately 180 subjects, with the intention to achieve this target by 31 March 2021:

- At any time prior to 31 March 2021, if there are 180 subjects randomized, the recruitment for subjects will stop. The subjects already in the screening period would continue to randomization only if such randomization would occur prior to 31 March 2021; such subjects, post randomization, would continue through the post-treatment efficacy period.
- If there are fewer than 180 subjects randomized by 31 March 2021, then randomization will stop on that date.
- Subject enrollment may be halted by the Sponsor at any time for any reason.

The study consists of an up to 30-day screening period during which subjects will complete a daily ePRO diary to record information regarding all symptomatic RP attacks (eg, severity of symptoms and duration) and analgesic medication use (prescription and over-the-counter). The

up to 30-day screening period consists of a 5-day eligibility period and an up to 25-day baseline ePRO diary completion period:

- During the 5-day eligibility period, eligible subjects will have a minimum of 10 symptomatic RP attacks, documented in the ePRO diary, occurring over at least 3 separate days of the 5-day eligibility period.
- The baseline ePRO diary completion period is a minimum of 10 days and a maximum of 25 days prior to the day of randomization. While 10 days is the preferred baseline ePRO completion period, it may be necessary to extend the baseline ePRO diary completion period beyond 10 days in order to accommodate the preferred Monday to Friday dosing schedule. All eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period. The ePRO symptomatic RP attack data from this time period will be used for the calculation of the baseline frequency of symptomatic RP attacks.

Eligible subjects will be randomized in a 1:1 ratio to iloprost injection for IV use or placebo. Randomization will be stratified based on the use of phosphodiesterase inhibitors at screening. Study drug administration will begin on Day 1 (Visit 2), and subjects will receive study drug for 5 consecutive days (eg, Monday through Friday) as a continuous IV infusion over 6 hours each day via a peripheral line utilizing the NovaCath™ Integrated IV Catheter System or a peripherally inserted central catheter (PICC) using an infusion pump.

Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration each day of administration. On Day 1 (Visit 2), study drug will be initiated at a starting dose of 0.5 ng/kg/min, and dose increases will occur every 30 minutes (±5 minutes) in increments of 0.5 ng/kg/min up to 2.0 ng/kg/min or the individual tolerated dose. If dose-limiting adverse events (eg, headache, flushing, jaw pain, myalgia, nausea, or vomiting) occur that cannot be tolerated by the subject, then the dose will be reduced in a stepwise manner by 0.5 ng/kg/min every 30 minutes (±5 minutes), until a tolerated dose is determined. If symptomatic hypotension or a dose-limiting adverse event occurs during administration of study drug at the starting dose (ie, 0.5 ng/kg/min), the study drug infusion will be discontinued and reinitiation of the study drug infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be obtained 15 minutes (±15 minutes) prior to study drug administration and monitored 15 minutes (±5 minutes) after all up-titrations. If the subject experiences symptomatic hypotension or any other adverse event that cannot be tolerated, as determined by the Investigator, during administration of study drug, the dose will be reduced or the study drug infusion will be stopped until the symptoms resolve, at which point the study drug can be reinitiated at a previously tolerated dose. The maximum tolerated dose will be maintained for the remaining 6-hour daily period. At the end of the 6-hour study drug infusion period, the dose will be stopped. Vital signs will be obtained 15 minutes (±5 minutes) after completion of the study drug infusion.

On Days 2 to 5 (Visits 3 to 6), the study drug infusion will be started using the highest study drug infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the study drug infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in the dose (in 0.5 ng/kg/min increments) and subsequent up-titration is allowed to the Day 1 highest tolerated dose. A lower starting dose may be initiated on Days 3 to 5 (Visits 4 to 6) if the subject does not tolerate the previous days' highest tolerated dose as a starting dose. Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug

administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.

Subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease) will require a reduced starting dose (0.25 ng/kg/min) and modified dose titration (0.25 ng/kg/min up to 1.0 ng/kg/min; titrate in a stepwise manner by 0.25 ng/kg/min increments as described above for tolerability).

Subjects will be contacted via telephone on Day 8 (+2 days) (Visit 7) to remind subjects to continue to complete the daily ePRO diary; subjects will complete the ePRO diary through Day 21. On Day 22 (+2 days) (Visit 8), subjects will be contacted via telephone to assess adverse events and reminded to return to the clinic for the Day 35 visit (+7 days) (Visit 9) for post-treatment evaluations. A follow-up visit will occur 30 days after the last administration of study drug on Day 35 (+7 days) (Visit 9).

Subjects who discontinue study drug early will remain in the study (unless the subject withdraws consent) and complete the daily ePRO diary through Day 21 as well as post-treatment study assessments.

The total duration of the study for a subject will be up to approximately 9 weeks.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The study drugs (iloprost injection for IV use and matching placebo) will be supplied in vials packaged in blinded and numbered study drug kits (5 vials per kit). The study drugs (iloprost and placebo) will appear as identical solutions within identical vials, except 100 mcg of iloprost will be added to the active study drug vials. The study drug product must be diluted with sodium chloride 0.9% in a drug reservoir (IV bag) prior to use.

Subjects will receive the study drug IV infusions for 5 consecutive days (eg, Monday to Friday). Study drug will be administered after dilution as a continuous IV infusion over 6 hours each day via a peripheral line utilizing the NovaCath Integrated IV Catheter System (or a PICC) using an infusion pump.

EFFICACY VARIABLES:

The primary efficacy endpoint is the change of symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic RP attacks, from baseline to the end of the efficacy follow-up.

For the endpoint calculated using data from the ePRO diary, the baseline value will be the (weekly) average of the inputs during the 10- to 25-day baseline ePRO diary completion period, and the postbaseline value will be the (weekly) average of the inputs during Days 8 through 21.

The secondary efficacy endpoints include changes from baseline to the end of the efficacy follow-up in the following:

- Severity of RP attacks as determined by the overall severity of RP attack symptoms (using a Numeric Rating Scale [NRS]). The symptom (pain, numbness, discomfort, or tingling) with the worst average baseline value for each subject will be used for evaluating the subject's

overall severity. If more than 1 symptom has the same value, the symptom used for analysis will be based on the following order of rank: pain>numbness>tingling>discomfort.

- Weekly total duration of symptomatic RP attacks.
- Proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline.

The exploratory efficacy endpoints include changes from baseline to the end of the efficacy follow-up in the following:

- Proportion of days without symptomatic RP attacks
- NRS for worst pain associated with symptomatic RP attacks
- NRS for worst numbness associated with symptomatic RP attacks
- NRS for worst tingling associated with symptomatic RP attacks
- NRS for worst discomfort associated with symptomatic RP attacks
- Proportion of pain responders, defined as subjects that have a 50% reduction in worst pain associated
- Proportion of numbness responders, defined as subjects that have a 50% reduction in worst numbness associated
- Proportion of tingling responders, defined as subjects that have a 50% reduction in worst tingling associated
- Proportion of discomfort responders, defined as subjects that have a 50% reduction in worst discomfort associated
- Proportion of total weekly duration responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic attacks
- Raynaud's Condition Score
- Duration of symptomatic RP attacks (average duration of an attack)
- Patient assessment of overall change in symptomatic Raynaud's attacks (PGIC)
- Patient assessment of overall severity in symptomatic Raynaud's attacks (PGIS)
- Patient assessment of overall benefit compared to side effects

Additionally, depending on the results of the primary and secondary efficacy analyses, the effect of iloprost on plasma biomarkers may be evaluated.

SAFETY VARIABLES:

Safety parameters will include all adverse events, physical examination findings, vital sign measurements (heart rate and blood pressure), 12-lead electrocardiogram findings, and standard clinical laboratory measurements (chemistry and hematology).

STATISTICAL ANALYSES:

The Intent-to-Treat (ITT) Population is defined as all randomized subjects who initiate study drug infusion on Day 1. The ITT Population is the primary efficacy analysis population.

The Per-Protocol (PP) Population is defined as all subjects in the ITT Population who complete at least Day 21 without any major protocol deviations. The primary analysis will be repeated on the PP Population.

The Safety Population is defined as all randomized subjects who initiate study drug infusion. The Safety Population will be used for all safety analyses.

All available efficacy data (weekly frequency of symptomatic RP attacks, severity of symptomatic RP attacks, Raynaud's Condition Score, weekly total duration of symptomatic RP attacks, the duration of symptomatic RP attacks [average duration of an attack], overall change in symptomatic RP, overall patient severity in symptomatic RP attack) will be listed for the ITT Population. Efficacy measurements will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group (iloprost injection for IV use and placebo). Baseline, change from baseline, and percent change from baseline to endpoint will be presented for each efficacy measurement for the ITT Population.

A fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 2-sided 0.05 level first, followed by testing the secondary efficacy endpoints at the 2-sided 0.05 level in the following hierarchical manner: (1) overall severity of RP attack symptoms, (2) weekly total duration of symptomatic RP attacks, and (3) proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline. Inferential conclusions about these efficacy endpoints will require statistical significance of the previous endpoints and the primary efficacy endpoint.

Primary efficacy analyses

The primary efficacy endpoint is the change in symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic RP attacks from baseline to the end of the efficacy follow-up. The baseline weekly frequency of symptomatic RP attacks is defined as the average weekly number of symptomatic RP attacks that occur during the 10- to 25-day baseline ePRO diary completion period. The double-blind weekly frequency of symptomatic RP attacks is defined as the average weekly number of symptomatic RP attacks that occur during Days 8 through 21. The weekly frequency is calculated by taking the sum of the number of attacks over the time period, divided by the number of days with data reported (including 0 attacks) in the time period, and multiplied by 7.

The primary efficacy analysis on the primary efficacy endpoint will be performed based on an analysis of covariance (ANCOVA) model, including randomized treatment group and randomized stratification (ie, use of phosphodiesterase inhibitors at screening) as factors and baseline weekly frequency of symptomatic RP attacks as a covariate. The treatment comparisons will be estimated together with the 95% confidence interval and p-value. The primary analysis will be performed on the ITT Population.

For subjects in the ITT Population with a missing primary efficacy endpoint, the following imputation rule will be used: if there are values available for fewer than 7 days between Day 8

and Day 21, the missing daily values between Day 8 and Day 21 (inclusive) required to total 7 days values will be imputed by (1) the average value of the subjects in the same treatment group on the same study day if it is intermittent missing daily values, or (2) the average value of the subjects in the placebo group on the same study day if the subject has discontinued (early termination) from the study.

The primary efficacy analysis will also be repeated for the PP Population.

Primary efficacy measurements will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group (iloprost injection for IV use and placebo). Baseline, change from baseline, and percent change from baseline to endpoint will be presented for each efficacy measurement for the ITT Population.

Secondary efficacy analyses

The secondary efficacy analyses will be performed on the ITT Population. Secondary efficacy endpoints in the hierarchical step-down testing procedure include changes from baseline to the end of the efficacy follow-up in the following: (1) overall severity of RP attack symptoms, (2) weekly total duration of symptomatic RP attacks, and (3) the proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline.

For subjects in the ITT Population with a missing secondary efficacy endpoint, the same imputation method as used for the primary efficacy analysis will be used. Overall severity will be derived after the imputation for each symptom. Responders will be derived after the imputation of the missing weekly total duration of symptomatic RP attacks and overall severity.

The ANCOVA model will be used to analyze the change from baseline to the end of the efficacy follow-up in overall severity of RP attack symptoms and weekly total duration of symptomatic RP attacks. A logistic regression model will be used to estimate the proportion of responders within each treatment group. These analyses will include randomized treatment group and randomized stratification as factors and baseline value as a covariate.

Sample size determination

The study will target randomizing approximately 180 subjects.

The study will be stratified based on the current use of oral PDE5 inhibitors. Eighty-six subjects per arm, at the end of the efficacy evaluation time point, will provide ≥85% power to detect a 5.5 improvement between iloprost and the placebo group for the mean change from baseline to the end of the efficacy follow-up in the weekly frequency of symptomatic RP attacks, assuming a common standard deviation of 12 and use of a traditional 2-sided 0.05 level test. Assuming a rate of missingness of 5% before Day 8, 90 subjects in each treatment group are planned.

Exploratory efficacy analyses

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided by treatment group for the exploratory endpoints on the ITT Population.

The ANCOVA model will be used to analyze the continuous efficacy endpoints and will include randomized treatment group and randomized stratification as factors and baseline value as a covariate. The treatment comparisons will be estimated together with the 95% confidence

interval. P-values will be provided. The ANCOVA model for PGIC will include only randomized treatment group and randomized stratification as factors since there is no PGIC value at baseline.

The same logistic model for the secondary efficacy analysis will be used for the exploratory categorical endpoints on the ITT Population. The odds ratio between iloprost and placebo will be provided together with the p-value.

Subjects with missing values will be excluded. No imputation is needed.

Safety analyses

All safety analyses will be performed on the Safety Population. Subjects will be analyzed by the treatment received.

Safety measures will be summarized descriptively. Qualitative variables will be summarized using counts and percentages by treatment group at each study visit. A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the administration of study drug. Treatment-emergent adverse events will be summarized by the Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term. Tables will be provided for overall incidence and incidence by SOC and preferred term for TEAEs, drug-related TEAEs, TEAEs by maximum severity, serious adverse events, and TEAEs leading to treatment discontinuation.

Laboratory and vital sign parameters will be presented using descriptive statistics for observed values at each visit and changes from baseline, as appropriate. Abnormal physical examination findings will be presented in a by-subject data listing. Descriptive statistics will be provided for ECG data. Details of any abnormalities will be included in subject listings.

DATA MONITORING COMMITTEE:

The Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of clinical study subjects and for enhancing the integrity of the study. To address this mission, the DMC will have ongoing access to efficacy and safety data, and information regarding the quality of study conduct.

STEERING COMMITTEE:

The Steering Committee will be responsible for providing overall guidance to Eicos Sciences, Inc. on study protocol development, execution of the study, analysis, and reporting of the study.

SITES: Up to 35 sites in the United States

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
bFGF	Basic fibroblast growth factor
cAMP	Cyclic adenosine monophosphate
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CXCL4	C-X-C motif ligand 4
DMC	Data Monitoring Committee
DU	Digital ulcer
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
ePRO	Electronic patient-reported outcomes
ET	Early termination
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IL	Interleukin
IP receptor	Prostacyclin receptor
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
MMP-2	Matrix metalloproteinase-2
NRS	Numeric Rating Scale
PAH	Pulmonary arterial hypertension
PAOD	Peripheral arterial occlusive disease
PDE5	Phosphodiesterase-5
PDGF	Platelet-derived growth factor
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

Abbreviation	Definition
PICC	Peripherally inserted central catheter
PINP	Amino-terminal propeptide of type 1 collagen
PK	Pharmacokinetic(s)
PP	Per-Protocol
RP	Raynaud's phenomenon
SAE	Serious adverse event
sE-selectin	Soluble E-selectin
sICAM-1	Soluble intercellular adhesion molecule-1
SOC	System organ class
SSc	Systemic sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event
TPA	Tissue plasminogen activator
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
VWF	von Willebrand factor

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Overview of Systemic Sclerosis

Systemic sclerosis (SSc) is a heterogeneous disease whose pathogenesis is characterized by 3 hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix.[1] The pathogenesis of SSc involves autoimmune mechanisms, which contribute to vascular damage, mainly to small arteries and arterioles, and excessive accumulation of collagen and other extracellular matrix components in the skin and internal organs.

Systemic sclerosis is an orphan disease. Incidence rates and prevalence estimates are fairly similar for Europe, the United States, Australia, and Argentina, suggesting a prevalence of 150 to 300 cases per million, with a lower prevalence noted in Scandinavia, Japan, the United Kingdom, Taiwan, and India.[2] The data consistently report prevalence estimates that equate to less than 100,000 persons in the United States.

The clinical manifestations and the prognosis of SSc vary, with the majority of patients having skin thickening and variable involvement of cardiovascular, gastrointestinal, musculoskeletal, and pulmonary systems.[3] Subsets of SSc can be discerned, (eg, limited cutaneous SSc, diffuse cutaneous SSc, and without skin involvement [sine SSc]).[1]

1.1.1 Digital Ischemia in Systemic Sclerosis

Vascular dysfunction is one of the earliest manifestations of SSc and is thought to be a major factor in its pathogenesis.[4,5,6] Occlusive vasculopathy is the hallmark lesion of all forms of SSc and is seen in different organs involved, such as skin, lungs, kidneys, etc.[7,8]

Digital ischemic episodes are the most common manifestation of vascular abnormalities in SSc and is a universal feature of SSc disease, affecting more than 95% of patients.[9,10,11] Digital ischemic episodes represent vasoconstriction of the digital arteries, precapillary arterioles and cutaneous arteriovenous shunts.[12] The term Raynaud's phenomenon (RP) is used to describe these digital ischemic episodic events.[12]

Raynaud's phenomenon is characterized by abnormal functioning of the cutaneous vessels involved in the thermal regulation of blood flow. The ischemic phase of the attack presents by demarcated pale or cyanotic skin limited to the digits. It typically initiates in 1 or several digits after exposure to cold temperatures or a stressful situation and then spreads symmetrically to all fingers of both hands. The distinctive features often associated with RP include pain, numbness, tingling, and discoloration of digits due to vasospasms (typically occurring after exposure to cold temperatures or stress). Hand impairment is nearly universal in SSc patients. Raynaud's phenomenon is also associated with significant disability and psychological impact.[13] In addition to pain, annoyance, and functional disability of symptomatic RP attacks, many patients with SSc report that they change their daily routine to accommodate their RP and may have significant anxiety associated with their disease, often expressing fears of ischemic digital ulcers (DUs) and auto-amputation. Digital ischemic episodes can also represent the first sign of critical ischemia of a digit.[12] Depending on the severity of the underlying vascular insult and size of the vessel involved, superficial ulceration or deep-tissue necrosis with gangrene and amputation can result.[12]

Ischemic DUs are a frequent external manifestation of vasculopathy in SSc.[14] Many factors are implicated in the pathogenesis of DUs in the setting of SSc. These include: 1) impaired afferent

vasomotion (highlighted by the intimal hyperplasia of arterioles), 2) disrupted microvasculature including capillary and lymphatic, 3) leukocyte and platelet activation and adherence to injured endothelium, and 4) hemorheological alterations typical of SSc.[8] The disease is also characterized by insufficient angiogenesis and defective vasculogenesis contributing further to tissue ischemia.[15]

Ischemic DUs are generally due to aberrant vasculopathy and usually occur on the pulp of the fingers. Digital ulcers are defined as a denuded area of de-epithelized tissue.[16] Ulcers can also occur over bony prominences such as proximal or metacarpophalangeal joints with well-demarcated borders and may be caused by trauma and ischemia. The majority of the published data has focused on ischemic DUs. Digital ulcers occur in up to 58% of patients with limited or diffuse SSc and often occur early in the disease course.[17,18,19] A 30% annual incidence of SSc DUs has been reported in the literature, suggesting approximately 20,000 adult patients experience DUs secondary to SSc yearly in the United States (based on current United States Census data).[20] Of those patients who experience a DU, more than half have persistent or recurrent DUs for at least 6 months.[17,18,19,20]

Several studies have shown that the lesions heal slowly, lead to substantial pain and functional disability, and are associated with complications such as scarring, loss of distal tissue, infection, gangrene, and amputation. These symptoms lead to reduced quality of life, an increased frequency of hospitalization, and decreased survival.[9,18,21,22]

1.1.2 Current Management of Digital Ischemia in Patients With Systemic Sclerosis

Currently, there are no Food and Drug Administration (FDA)-approved therapies to treat SSc associated with digital ischemia. Management of digital ischemic episodes or DUs in SSc includes nonpharmacologic, pharmacologic, and surgical interventions. Multiple pharmacologic agents are used in clinical practice to counteract RP and prevent/reduce the burden of DUs (eg, calcium channel blockers, angiotensin receptor blockers, angiotensin-converting enzyme [ACE] inhibitors, alpha-adrenergic blockers, and serotonin inhibitors), although many lack supportive data and none are approved for such use in the United States. Management of SSc vascular diseases includes vasodilators (including medications approved for pulmonary arterial hypertension [PAH] such as prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 [PDE5] inhibitors, and soluble guanylate cyclase stimulators). Phosphodiesterase-5 inhibitors, prostacyclin analogs (iloprost), and bosentan have been endorsed by the 2016 updated European League Against Rheumatism (EULAR) recommendations for the treatment of SSc.[23] None of these drugs are approved for SSc RP in the United States.

In general, immunosuppressive therapies are not effective for vasculopathy associated with SSc, as highlighted in PAH and scleroderma renal crisis.[24]

In addition to the above strategies aimed at specific intervention, established SSc DUs often require treatments for secondary effects, such as use of opioids and other analgesics for pain and aggressive use of systemic and local antibiotics for infection.[25] Efforts to promote healing are often unsatisfactory, and surgical intervention resulting in permanent tissue loss may be necessary. Thus, there remains a clear, unmet medical need for a pharmacological therapy that will treat and affect the natural course of DUs in SSc.

1.2 Overview of Iloprost

Iloprost, a stable analog of prostacyclin, has been used for over a decade as an inhaled formulation to treat PAH (both within and outside of the United States) and as an intravenous (IV) formulation for occlusive arterial diseases (outside of the United States) due to its pharmacological effects on vascular cells and platelets.[26,27] Iloprost is a potent prostacyclin receptor (IP receptor) agonist. Pharmacology studies have shown that iloprost increases the cAMP levels in human platelets of various species through stimulation of adenylate cyclase, leading to inhibition of platelet aggregation. In addition, iloprost has been shown to cause vasodilation through stimulation of the IP receptor on smooth muscle cells. The commercially approved forms of iloprost (Ilomedin® and Ventavis®) consist of 2 diastereoisomers that contrast in conformation of a methyl group at the carbon 16 position. The current commercial formulation uses a fixed racemic mixture of 16(S) and 16(R) diastereoisomers (47:53). The 16(S) is substantially more potent than the 16(R) in vasodilating and inhibiting collagen-induced platelet aggregation.

1.2.1 Regulatory Status of Iloprost

The inhaled formulation of iloprost received marketing authorization in the European Union in September 2003, and Schering AG began commercializing the product (Ventavis) in early 2004.

Ventavis is indicated for the treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms, and lack of deterioration. Studies establishing effectiveness predominately included patients with New York Heart Association Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

The IV formulation of iloprost was first approved in the early 1990s in Europe and has since received marketing approvals in 30 European and non-European countries under the tradename Ilomedin. The approved indications for Ilomedin in the European Union include: 1) treatment of patients with severe peripheral arterial occlusive disease (PAOD), particularly those at risk of amputation and in whom surgery or angioplasty is not possible; 2) treatment of advanced thromboangitis obliterans (Buerger's disease) with critical limb ischemia in cases where revascularization is not indicated; 3) treatment of patients with severe disabling RP unresponsive to other therapies; and 4) treatment of moderate or severe primary and secondary PAH, such as New York Heart Association Functional Classes III and IV.

1.2.2 Rationale for Iloprost for the Treatment of Symptomatic Raynaud's Phenomenon Secondary to Systemic Sclerosis

Iloprost is a synthetic analog of prostacyclin. Iloprost may improve outcomes and restore function lost due to SSc by enhancing cutaneous blood flow, reducing microvascular inflammation, reducing/reversing fibrosis, and decreasing platelet aggregation.[28,29,30,31,32,33]

1.2.3 Summary of Iloprost Mechanism of Action

Iloprost is thought to dilate systemic arterial vascular beds through stimulation of the IP receptor on smooth muscle cells. Iloprost has been shown to inhibit vasoconstriction induced by arachidonic acid and phenylephrine.[34,35] Pharmacology studies have shown that iloprost also increases the cAMP levels in human platelets of various species through stimulation of adenylate cyclase, leading to inhibition of platelet aggregation and adhesion.[31,32] Iloprost is thought to have

anti-inflammatory and immunomodulating effects. It reduces neutrophil adhesion and chemotaxis, and has been shown to downregulate the intracellular expression of interleukin (IL)-6 and tumor necrosis factor-alpha in human monocytes.[36,37] Iloprost has been suggested to possess antifibrotic effects, as it has been shown to prevent bleomycin-induced fibrosis and reverse established right ventricular fibrosis in animal models.[29,33]

1.2.4 Clinical Pharmacology

Pharmacokinetic (PK) studies have been conducted with iloprost in healthy volunteers and in a variety of patient populations using different formulations and routes of administration. The PK and systemic exposures associated with these formulations and routes of administration are very well characterized in the literature. A vast majority of the clinical pharmacology and clinical studies published in the literature are with the IV formulation of iloprost.

In PK studies in animals, there was no evidence of interconversion of the 2 diastereoisomers of iloprost. In human PK studies, the 2 diastereoisomers were not individually assayed.

Iloprost has a short half-life of 20 to 30 minutes and has linear PK following IV administration at doses of 1 to 3 ng/kg/min. Approximately 60% of iloprost is bound to plasma protein (75% to albumin). The total plasma clearance of iloprost in healthy individuals is 20 mL/min/kg.[38]

In vitro studies reveal that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost. Iloprost is metabolized principally via β-oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprost was pharmacologically inactive. Clearance in normal subjects was approximately 20 mL/min/kg. A mass-balance study using IV and orally administered [3H]-iloprost in healthy subjects (n=8) showed recovery of 81% of the total radioactivity over 14 hours postdose, with 68% and 12% recoveries in urine and feces, respectively. In patients with liver cirrhosis, the mean clearance in Child-Pugh B subjects (n=5) was approximately 10 mL/min/kg. For patients requiring intermittent dialysis (n=7), the mean area under the plasma concentration-time curve from time 0 to 4 hours was 230 pg*h/mL compared to 54 pg*h/mL for patients with renal failure (n=8) not requiring intermittent dialysis and 48 pg*h/mL for normal healthy volunteers. Dialysis did not affect iloprost plasma concentrations.[26]

Iloprost PK has been investigated in patients suffering from renal insufficiency who are not on dialysis with serum creatinine >2 mg/dL and patients on dialysis.[39] This study demonstrated that the PK profile for iloprost in patients with renal failure, and not on dialysis was similar to that observed in PAOD patients and healthy volunteers. Patients on dialysis have a reduced clearance of iloprost by a factor of 4. The iloprost dosing regimen requires titration, so more careful titration should be considered for patients on dialysis.[39,40]

Iloprost PK has also been investigated in patients suffering from liver cirrhosis. The study demonstrated that iloprost clearance was reduced by a factor of 2 in patients suffering from hepatic dysfunction compared with healthy subjects. The iloprost dosing regimen requires titration, so more careful titration should be considered for patients with liver impairment. However, apart from a reduction of the starting dose (of approximately 50%) for titration, special recommendations are not necessary for patients with impaired liver function.[41]

1.2.5 Summary of Iloprost Clinical Experience in Systemic Sclerosis

Several proof-of-concept studies have been conducted evaluating the effects of IV iloprost in patients with SSc. These studies evaluated the effects of iloprost in SSc patients with RP and DUs.

Two placebo-controlled studies that support the Eicos Sciences, Inc. development program were published by Fredrick M Wigley, MD and sponsored by Berlex Laboratories and the Scleroderma Society.[42,43]

The first study evaluated the effect of treatment with IV iloprost in patients with RP and ischemic ulcers secondary to SSc. In this double-blind, placebo-controlled, randomized, parallel-group study, 35 patients with SSc-associated RP were randomized to receive iloprost (0.5 to 2.0 ng/kg/min) or placebo by continuous infusion for 6 hours on 5 consecutive days. Patients were examined every 2 weeks for a follow-up period of 10 weeks. The study evaluated patient diaries recording RP symptoms and attacks. Digital cutaneous lesions including digital ischemic ulcerations, fissures, and paronychia were counted, described, and photographed at entry and on each follow-up assessment. [42]

Of the 35 patients enrolled, 34 completed the 5 days of infusion. One patient discontinued treatment on Day 2 due to chest and thigh pain of uncertain etiology. Thirty-three patients completed 10 weeks of follow-up; 1 patient in the placebo group withdrew at the 8-week follow-up due to a new DU. A total of 11 patients, 7 treated with iloprost and 4 receiving placebo, had cutaneous finger lesions (DUs, fissures, or paronychia) at baseline. At the Week 10 study visit, 6 of the 7 patients treated with iloprost had complete healing of all lesions compared to none of the 4 patients taking placebo ($p=0.015$). Digital tip ulcers were present in 4 patients in each treatment group. All of the iloprost patients had complete healing at Weeks 6, 8, and 10 compared to none of the 4 patients receiving placebo ($p=0.029$). One of the placebo patients reported partial healing of DUs. Of the patients with no lesions at baseline, 3 of 11 patients receiving iloprost and 3 of 13 patients receiving placebo developed new lesions. The total number of DUs that developed was less in iloprost (11 DUs) compared to placebo (29 DUs). At least 1 adverse event was reported in all 18 patients receiving iloprost and by 10 of the 17 patients receiving placebo. The most common adverse events reported in the iloprost group were headache, nausea, vomiting, and jaw or thigh pain.[42]

The second study evaluated the effect of IV iloprost in treating patients with RP secondary to SSc. In a follow-up, multicenter (12 sites), double-blind, placebo-controlled, randomized, parallel-group study, 131 SSc patients with RP were randomized to receive iloprost (0.5 to 2.0 ng/kg/min) or placebo by continuous infusion for 6 hours on 5 consecutive days. The study follow-up period was 9 weeks, and patients were re-examined at 3, 6, and 9 weeks after completion of the infusion. The study evaluated patient diaries recording RP symptoms and attacks. Physicians' assessment of overall treatment effect was recorded. Digital cutaneous lesions were recorded on Days 1 and 5 of the infusion and at Weeks 3, 6, and 9 of the follow-up period. The protocol defined a healing response as a reduction in number of finger lesions from baseline of at least 50%. Data for cutaneous lesions were analyzed for the subset of patients who successfully completed 5 days of infusion and had at least 6 weeks of follow-up.[43]

A total of 131 patients (64 iloprost and 67 placebo) enrolled and 126 successfully completed the 5-day infusion. Of these, 114 patients (56 iloprost and 58 placebo) completed at least 6 weeks of follow-up. A total of 17 patients (8 iloprost and 9 placebo) withdrew from the study. The patients receiving iloprost had a decreased RP severity score at Weeks 3, 6, and 9. The treatment difference

was greater at Weeks 1 to 3 (p=0.006) and Weeks 4 to 6 (p=0.05) than at Weeks 7 to 9 (p=0.09). A comparison of the changes over the entire study period (Weeks 1 to 9) showed a greater mean decrease in the iloprost group (-34.8%) than the placebo group (-19.7%) (p=0.01). In the subset of patients with digital cutaneous lesions at baseline, the mean decrease in RP severity score remained the same as those in the entire group given iloprost (-34.5%), but the effect was less in those who received placebo in this subset (-9.9%) (p=0.01).[43]

Patients receiving iloprost had a greater decrease in frequency of RP attacks than those receiving placebo at every follow-up assessment. The mean decrease in attack frequency per week during the entire study was 39.1% in patients receiving iloprost compared to 22.2% in patients receiving placebo (p=0.005). In the subset of patients with digital cutaneous lesions, there was a mean decrease in attack frequency during the entire follow-up period of 36% in patients receiving iloprost and 14.1% in patients receiving placebo (p=0.064).[43]

A total of 73 patients (35 iloprost and 38 placebo) had digital cutaneous lesions at baseline. A greater number of patients receiving iloprost had at least a 50% reduction from baseline in the total number of lesions at all times during the 9-week follow-up period. The group receiving iloprost had a greater proportion of patients who completely healed (no remaining original lesions and no new lesions) at all times during the study compared to placebo (p>0.20 at Week 9). The most common adverse events reported by patients receiving iloprost were headache, flushing, nausea, jaw pain, diarrhea, and vomiting. The side effects were reversible and controlled by a reduction of the infusion rate of iloprost.[43]

In addition to the 2 studies summarized above, there is a large amount of published data in Europe on the successful use of intermittent or continuous iloprost for management of DUs secondary to SSc.[44,45,46,47,48,49]

1.3 Rationale

Intravenous iloprost has market authorization in Europe and Australia and is the standard of care treatment for RP and DUs in subjects with SSc in Europe. However, this treatment is not currently available within the United States. In clinical practice, there is a high unmet need for effective pharmacologic therapies for subjects with SSc experiencing symptomatic digital ischemic episodes. This Phase 3 study will evaluate the safety and efficacy of iloprost on the frequency of and relief from symptomatic digital ischemic episode in subjects with SSc. There are several significant feasibility challenges to studying subjects with SSc experiencing symptomatic digital ischemic episodes. First, the population is very small,[2,50] estimated at approximately 70,000 adult subjects with SSc in the United States (based on United States Census from 04 July 2016). For subjects with SSc, RP is a problem throughout the year, but the symptoms have been reported to be reduced by about 50% in the summer months.[51] To ensure recruitment and limit the impact of seasonal variation in temperature on the incidence of attacks, this study will be conducted primarily during the fall and winter months.

Due to the global coronavirus disease 2019 (COVID-19) pandemic, recruitment in the ES-301 study was paused on 12 March 2020. In alignment with FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020), the study will be restarted in the fall of 2020, providing the option for screening, infusions, and/or follow-up visits to be conducted remotely, if needed. With the anticipated reemergence of

COVID-19 in the fall and winter of 2020, the Investigator, in discussion with the subject, will determine if an on-site or decentralized (remote) visit is appropriate for the subject.

At institutions where on-site visits and study drug infusions are possible, and the Investigator determines it is safe to conduct the study, enrollment and treatment of subjects should proceed per protocol. For institutions where on-site visits and/or study drug infusions are not possible, or the Investigator determines it is not safe for the subject to receive study drug infusions at the site, the subject will be provided an optional consent form for the decentralized study visits. If the subject agrees, he or she will need to opt-in for decentralized study visits including but not limited to study drug infusion visits. Additional training, tools, and documentation will be provided to the institution to allow for appropriate Investigator oversight of the decentralized study visits (conducted by trained but non-study nursing personnel at the subject's home and/or at alternative infusion sites) and subject safety during the conduct of the study. The decentralized study drug infusions will follow the same institutional infusion plans with trained and qualified nursing and pharmacy staff, one-on-one nursing care, Investigator oversight, and safeguards via telemedicine. Refer to the Infusion Manual for Decentralized Infusions and Appendix E for additional details.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of iloprost compared to placebo on the change from baseline in symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic RP attacks, in subjects with SSc.

2.2 Secondary Objectives

The secondary objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the overall severity of RP attack symptoms
- To evaluate the efficacy of iloprost compared to placebo on the weekly total duration of symptomatic RP attacks
- To evaluate the safety and tolerability of iloprost

2.3 Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the worst pain associated with symptomatic RP attacks.
- To evaluate the efficacy of iloprost compared to placebo on the worst numbness associated with symptomatic RP attacks.
- To evaluate the efficacy of iloprost compared to placebo on the worst tingling associated with symptomatic RP attacks.
- To evaluate the efficacy of iloprost compared to placebo on the worst discomfort associated with symptomatic RP attacks.
- To evaluate the efficacy of iloprost compared to placebo on the Raynaud's Condition Score.
- To evaluate the efficacy of iloprost compared to placebo on symptomatic RP attack duration.
- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall change in symptomatic Raynaud's attacks (Patient Global Impression of Change [PGIC]).
- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall severity in symptomatic Raynaud's attacks (Patient Global Impression of Severity [PGIS]).
- To evaluate the patient assessment of overall benefit compared to side effects.
- To evaluate the effect of iloprost compared to placebo on biomarkers of SSc. These biomarkers include C-X-C motif ligand 4 (CXCL4), soluble E-selectin (sE-selectin), vascular endothelial growth factor (VEGF), tissue plasminogen activator (TPA), basic fibroblast growth factor (bFGF), soluble intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule 1 (VCAM-1), amino-terminal propeptide of type 1 collagen (PINP), matrix metalloproteinase-2 (MMP-2), endostatin, von Willebrand factor (VWF), endothelin-1, angiopoietin-1, angiopoietin-2, thromboplastin, IL-10, IL-6, platelet-derived growth factor

(PDGF), vascular endothelial cadherin, cAMP, and chemistry panel parameters (creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of iloprost on the frequency of and relief from symptomatic digital ischemic episodes in subjects with SSc. Subjects are allowed to continue receiving stable standard of care therapies for the management of symptomatic RP (eg, calcium channel blockers, ACE inhibitors, statins, fluoxetine, and low dose acetylsalicylic acid) or may participate without the use of background standard of care therapies.

The study will target randomizing approximately 180 subjects, with the intention to achieve this target by 31 March 2021:

- At any time prior to 31 March 2021, if there are 180 subjects randomized, the recruitment for subjects will stop. The subjects already in the screening period would continue to randomization only if such randomization would occur prior to 31 March 2021; such subjects, post randomization, would continue through the post-treatment efficacy period.
- If there are fewer than 180 subjects randomized by 31 March 2021, then randomization will stop on that date.
- Subject enrollment may be halted by the Sponsor at any time for any reason.

The study consists of an up to 30-day screening period during which subjects will complete a daily electronic patient-reported outcomes (ePRO) diary to record information regarding all symptomatic RP attacks (eg, severity of symptoms and duration) and analgesic medication use (prescription and over-the-counter). The up to 30-day screening period consists of a 5-day eligibility period and an up to 25-day baseline ePRO diary completion period:

- During the 5-day eligibility period, eligible subjects will have a minimum of 10 symptomatic RP attacks, documented in the ePRO diary, occurring over at least 3 separate days of the 5-day eligibility period.
- The baseline ePRO diary completion period is a minimum of 10 days and a maximum of 25 days prior to the day of randomization. While 10 days is the preferred baseline ePRO completion period, it may be necessary to extend the baseline ePRO diary completion period beyond 10 days in order to accommodate the preferred Monday to Friday dosing schedule. All eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period. The ePRO symptomatic RP attack data from this time period will be used for the calculation of the baseline frequency of symptomatic RP attacks.

Eligible subjects will be randomized in a 1:1 ratio to iloprost injection for IV use or placebo. Randomization will be stratified based on the use of phosphodiesterase inhibitors at screening. Study drug administration will begin on Day 1 (Visit 2), and subjects will receive study drug for 5 consecutive days (eg, Monday through Friday) as a continuous IV infusion over 6 hours each day via a peripheral line utilizing the NovaCath™ Integrated IV Catheter System or a peripherally inserted central catheter (PICC) using an infusion pump.

Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration each day of administration. On Day 1 (Visit 2), study drug will be initiated at a starting dose of 0.5 ng/kg/min, and dose increases will occur every

30 minutes (±5 minutes) in increments of 0.5 ng/kg/min up to 2.0 ng/kg/min or the individual tolerated dose. If dose-limiting adverse events (eg, headache, flushing, jaw pain, myalgia, nausea, or vomiting) occur that cannot be tolerated by the subject, then the dose will be reduced in a stepwise manner by 0.5 ng/kg/min every 30 minutes (±5 minutes), until a tolerated dose is determined. If symptomatic hypotension or a dose-limiting adverse event occurs during administration of study drug at the starting dose (ie, 0.5 ng/kg/min), the study drug infusion will be discontinued and reinitiation of the study drug infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be obtained 15 minutes (±15 minutes) prior to study drug administration and monitored 15 minutes (±5 minutes) after all up-titrations. If the subject experiences symptomatic hypotension or any other adverse event that cannot be tolerated, as determined by the Investigator, during administration of study drug, the dose will be reduced or the study drug infusion will be stopped until the symptoms resolve, at which point the study drug can be reinitiated at a previously tolerated dose. The maximum tolerated dose will be maintained for the remaining 6-hour daily period. At the end of the 6-hour study drug infusion period, the dose will be stopped. Vital signs will be obtained 15 minutes (±5 minutes) after completion of the study drug infusion.

On Days 2 to 5 (Visits 3 to 6), the study drug infusion will be started using the highest study drug infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the study drug infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in the dose (in 0.5 ng/kg/min increments) and subsequent up-titration is allowed to the Day 1 highest tolerated dose. A lower starting dose may be initiated on Days 3 to 5 (Visits 4 to 6) if the subject does not tolerate the previous days' highest tolerated dose as a starting dose. Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.

Subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease) will require a reduced starting dose (0.25 ng/kg/min) and modified dose titration (0.25 ng/kg/min up to 1.0 ng/kg/min; titrate in a stepwise manner by 0.25 ng/kg/min increments as described above for tolerability).

Subjects will be contacted via telephone on Day 8 (+2 days) (Visit 7) to remind subjects to continue to complete the daily ePRO diary; subjects will complete the ePRO diary through Day 21. On Day 22 (+2 days) (Visit 8), subjects will be contacted via telephone to assess adverse events and reminded to return to the clinic for the Day 35 visit (+7 days) (Visit 9) for post-treatment evaluations. A follow-up visit will occur 30 days after the last administration of study drug on Day 35 (+7 Days) (Visit 9).

Subjects who discontinue study drug early will remain in the study (unless the subject withdraws consent) and complete the daily ePRO diary through Day 21 as well as post-treatment study assessments.

The total duration of the study for a subject will be up to approximately 9 weeks.

A Data Monitoring Committee (DMC) and a Steering Committee will be utilized in the study. See Sections 9.2.3 and 9.2.4 for details.

3.2 Study Indication

The indication of this study is treatment of patients with SSc experiencing symptomatic digital ischemic episodes.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. Male or female subjects must be ≥18 years of age.
2. Subjects must have a diagnosis of SSc as defined by the 2013 American College of Rheumatology criteria/EULAR criteria.
3. Subjects must have a diagnosis or history of RP, self-reported or reported by a physician, with at least a 2-phase color change in finger(s) of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion.
4. Subjects must have a minimum of 10 symptomatic RP attacks, documented in the ePRO diary, occurring over at least 3 separate days of the 5-day eligibility period.
    - Note: A symptomatic Raynaud's attack for this study is defined as at least 1 color change of the subject's finger(s) (blue, white, or red) associated with at least 1 symptom (pain, numbness, tingling, and/or discomfort of the finger[s]). The attack is considered over when the color changes back to pre-attack color (normal) and the symptoms return to the subject's pre-attack level.
5. Subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period.
6. Female subjects of childbearing potential (defined as female subjects who have experienced menarche and who are not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) and male subjects must agree to use contraception for the duration of the study.
7. Subjects must be willing and able to comply with the study requirements and give informed consent for participation in the study; where permitted by local regulations, a legally authorized representative will be allowed to sign the consent form as a proxy for subjects who are unable to physically sign but are able to give a verbal informed consent.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Female subjects who are pregnant or breastfeeding prior to randomization.
2. Subjects with systolic blood pressure <85 mmHg (sitting position) at screening.
3. Subjects with an estimated glomerular filtration rate <15 mL/min/1.73 m^2 at screening as determined by the Modification of Diet in Renal Disease equation.
4. Subjects with an alanine aminotransferase and/or aspartate aminotransferase value >3 × the upper limit of normal at screening.
5. Subjects who have a DU infection within 30 days of screening.
6. Subjects with a history of cervical or digital sympathectomy, or botulism toxin injections in their hands [for RP or digital ulcers] within 90 days of screening. Subjects should not have a planned botulism toxin or sympathectomy during their participation in the study.

7. Subjects with gangrene or digital amputation within 6 months of screening.
8. Subjects with current intractable diarrhea or vomiting.
9. Subjects with a risk of clinically significant bleeding events, including those with coagulation or platelet disorders at screening.
10. Subjects with a history of major trauma or hemorrhage within 30 days of screening.
11. Subjects with clinically significant chronic intermittent bleeding, such as active gastric antral vascular ectasia or active peptic ulcer disease, within 60 days of screening.
12. Subjects who have had any cerebrovascular events (eg, transient ischemic attack or stroke) within 6 months of screening.
13. Subjects with a history of myocardial infarction or unstable angina within 6 months of screening. Subjects should not have a planned coronary procedure during their participation in the study.
14. Subjects with acute or chronic congestive heart failure (New York Heart Association Class III [moderate] or Class IV [severe]) at screening.
15. Subjects with a history of more than mild restrictive or congestive cardiomyopathy uncontrolled by medication or implanted device.
16. Subjects with a history of life-threatening cardiac arrhythmias.
17. Subjects with a history of hemodynamically significant aortic or mitral valve disease.
18. Subjects with a history of known pulmonary hypertension, PAH, or pulmonary veno-occlusive disease.
19. Subjects with a history of significant restrictive lung disease, defined as forced vital capacity <45% predicted and diffusing capacity of the lungs for carbon monoxide <40% predicted (uncorrected for hemoglobin).
20. Subjects with scleroderma renal crisis within 6 months of screening.
21. Subjects with a concomitant life-threatening disease with a life expectancy <12 months.
22. Subjects who have a clinically significant disorder that, in the opinion of the Investigator, could contraindicate the administration of study drug, affect compliance, interfere with study evaluations, or confound the interpretation of study results.
23. Subjects who have taken or are currently taking any parenteral, inhaled, or oral prostacyclin or IP receptor agonists (eg, epoprostenol, treprostinil, iloprost, and selexipag) within 8 weeks of screening.
24. Subjects who have initiated or had a dose change of any of the following within 2 weeks of screening: oral, topical, or IV vasodilators (eg, calcium channel blockers, PDE5 inhibitors [eg, sildenafil, tadalafil, or vardenafil], nitrates, and fluoxetine).
25. Subjects with any history of acetaminophen intolerability (eg, allergic reaction to acetaminophen).

26. Subjects with any malignancy that requires treatment during the study period, that has required treatment within 1 year of screening (including excision of skin cancer) or that is currently not in remission.
27. Subjects who have used any investigational medication or device for any indication within 30 days or 5 half-lives (whichever is longer) of screening.
28. Subjects who have participated in ES-201 or ES-301 studies and were randomized and treated with study drug.

4.3 Withdrawal Criteria

Subjects should be listed as having withdrawn consent only when the subject no longer wishes to participate in the study and no longer authorizes the Investigators to make efforts to continue to obtain their outcome data.

Every effort should be made to encourage subjects to remain in the study and complete the ePRO diary for the entire duration of the study. Subjects will be educated on the continued scientific importance of their data, even if they discontinue study drug. Ideally, if subjects withdraw their consent, it should be done in writing.

Withdrawn subjects will not be replaced.

In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

4.3.1 Discontinuation of Study Drug

A subject in this clinical study may discontinue study drug for any of the following reasons:

- Subject requests to discontinue study drug.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
- Pregnancy.
- Requirement of prohibited concomitant medication.
- Subject fails to comply with protocol requirements or study-related procedures.

A missed or discontinued dose/infusion day (eg, due to lack of venous access or inability to access the infusion site) does not constitute study drug discontinuation. In this situation, a subject may continue subsequent infusions per protocol. If a subject discontinues (early termination [ET]) from the study at any time prior to Day 35 (+7 days) (Visit 9), every attempt should be made to have the subject complete an ET visit (see Section 6.7). Unless the subject withdraws consent, subjects who discontinue study drug early will remain in the study for further acquisition of endpoint measurements through Day 21 as well as post-treatment study assessments. The reason for subject discontinuation of study drug must be documented in the electronic case report form (eCRF).

4.3.2 Withdrawal of Subjects From the Study

Participation of a subject in this clinical study may be discontinued for any of the following reasons:

- Subject withdraws consent or requests discontinuation from the study for any reason.
- Death of the subject.
- Termination of the study by the Sponsor or the regulatory authority.

The reason for subject withdrawal from the study must be documented in the eCRF.

5 STUDY TREATMENTS

5.1 Treatment Groups

Eligible subjects will be randomized by Interactive Response Technology (IRT) in a 1:1 ratio to the following treatment groups:

- Iloprost injection for IV use
- Placebo injection for IV use

5.2 Rationale for Dosing

Intravenous iloprost for the treatment of RP is well established in European guidelines and practice. The dosing in this study is based on the iloprost dosing titration algorithm that has been used in proof-of-concept studies in subjects with SSc [42,43,52] and current labeling outside the United States (Ilomedin).[27]

5.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Eligible subjects will be randomized to 1 of the 2 treatment groups listed in Section 5.1.

Randomization will be stratified based on the use of phosphodiesterase inhibitors at screening.

Individual treatment assignments will be blinded to the Sponsor, Investigator, study personnel, and subjects throughout the course of the study. All individuals directly involved in the conduct of the study, including data management personnel, will remain blinded to treatment assignments.

5.4 Breaking the Blind

It is not expected that emergency unblinding will be needed due to the short half-life of iloprost and the lack of a known antidote. Adverse events due to iloprost typically resolve quickly once treatment with iloprost has been stopped.

To all extent possible, study personnel will attempt to safeguard the integrity of the blinding in order to minimize bias in the conduct of the study.

Breaking of the blind should not occur except in the case of a medical emergency and whenever possible after discussion with the Medical Monitor. In such a case, the Investigator may access this information by contacting the Sponsor or its designee. If the blind is broken for an individual subject, the blinding should be preserved for the remainder of the subjects throughout the duration of the study. In such a case, study personnel may be notified of that individual subject's treatment assignment without jeopardizing blinding for the overall study.

If the blind is broken for a subject, the subject will be encouraged to continue his/her randomized treatment unless it would be medically contraindicated to do so; this decision will be based on Investigator consultation with the Medical Monitor. All subjects should be encouraged to continue study visits to the end of the study whether or not they remain on his/her randomized treatment.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The study drugs (iloprost injection for IV use and matching placebo) will be supplied in vials packaged in blinded and numbered study drug kits (5 vials per kit). The study drugs (iloprost and placebo) will appear as identical solutions within identical vials, except 100 mcg of iloprost will be added to the active study drug vials. The study drug product must be diluted with sodium chloride 0.9% in a drug reservoir (IV bag) prior to use.

Study drug will be packaged according to current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

Study drug will be labeled according to the requirements of local law and legislation, as well as current GMP and GCP guidelines.

Study drug must be stored according to labeled storage conditions in a secure limited access area.

5.5.2 Study Drug Preparation and Dispensing

Dilution of study drug product for use as a continuous IV infusion over 6 hours is as follows: A total of 1 mL of study drug should be withdrawn into a sterile syringe using aseptic technique. The study drug in the sterile syringe should be transferred to a drug reservoir (IV bag) containing 99 mL of sodium chloride 0.9% to make a 1000 ng/mL (1 mcg/mL) concentration.

The drug reservoir should always be dispensed in a pump drug reservoir with instructions for use as described in the Pharmacy Manual.

5.5.3 Study Drug Administration

The fully diluted study drug will be administered at the site by personnel who are trained on how to prepare the IV site and how to administer the continuous IV infusion over 6 hours via a peripheral line or a PICC using an infusion pump. Prior to the first study drug infusion, the NovaCath Integrated IV Catheter System will be inserted into a small peripheral vein in the hand or arm using aseptic technique by a trained healthcare professional. If the subject's peripheral veins do not support the placement of a peripheral line, a trained healthcare professional will insert a PICC. When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment. The NovaCath Integrated IV Catheter System (peripheral catheter system) should be replaced when clinically indicated (eg, loss of line patency, signs of phlebitis, etc) or required by institutional policy. If peripheral venous access cannot be obtained in a subject during an infusion visit, the study drug infusion will be missed on that day. If no peripheral venous access is possible, a PICC should be considered. Refer to the Infusion and/or Pharmacy Manual for additional information regarding infusion preparation and administration.

Subjects will receive the study drug IV infusions for 5 consecutive days (eg, Monday to Friday). Study drug will be administered after dilution as a continuous IV infusion over 6 hours each day via a peripheral line utilizing the NovaCath Integrated IV Catheter System (or a PICC) using an infusion pump.

Unless a subject has taken an acetaminophen-containing prescription or nonprescription (over-the-counter) drug product within 4 hours prior to study drug administration, subjects will be

premedicated with a single dose of 2 acetaminophen extended-release tablets (650 mg each), 30 minutes (±15 minutes) prior to study drug administration.

Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration each day of administration.

5.5.3.1 Dosing weight

The weight of the subject at screening may be used with the dose rate card (Appendix C or Appendix D) to determine the starting flow rate for each subject. If the weight of the subject at screening is used, it should be confirmed on Day 1 (Visit 2).

5.5.3.2 First study drug infusion

On Day 1 (Visit 2), study drug will be initiated at a starting dose of 0.5 ng/kg/min, and dose increases will occur every 30 minutes (±5 minutes) in increments of 0.5 ng/kg/min up to 2.0 ng/kg/min or the individual tolerated dose. If dose-limiting adverse events (eg, headache, flushing, jaw pain, myalgia, nausea, or vomiting) occur that cannot be tolerated by the subject, then the dose will be reduced in a stepwise manner by 0.5 ng/kg/min every 30 minutes (±5 minutes), until a tolerated dose is determined. If symptomatic hypotension or a dose-limiting adverse event occurs during administration of study drug at the starting dose (ie, 0.5 ng/kg/min), the study drug infusion will be discontinued and reinitiation of the study drug infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be obtained 15 minutes (±15 minutes) prior to study drug administration and monitored 15 minutes (±5 minutes) after all up-titrations. If the subject experiences symptomatic hypotension or any other adverse event that cannot be tolerated, as determined by the Investigator, during administration of study drug, the dose will be reduced or the study drug infusion will be stopped until the symptoms resolve, at which point the study drug can be reinitiated at a previously tolerated dose. The maximum tolerated dose will be maintained for the remaining 6-hour daily period. At the end of the 6-hour study drug infusion period, the dose will be stopped. Vital signs will be obtained 15 minutes (±5 minutes) after completion of the study drug infusion.

5.5.3.3 Study drug infusion Days 2 to 5 (Visits 3 to 6)

On Days 2 to 5 (Visits 3 to 6), the study drug infusion will be started using the highest study drug infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the study drug infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in dose (in 0.5 ng/kg/min increments) and subsequent up-titration is allowed to the Day 1 highest tolerated dose. A lower starting dose may be initiated on Days 3 to 5 (Visits 4 to 6) if the subject does not tolerate the previous days' highest tolerated dose as a starting dose. Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.

Subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease) will require a reduced starting dose (0.25 ng/kg/min) and modified dose titration (0.25 ng/kg/min up to 1.0 ng/kg/min; titrate in a stepwise manner by 0.25 ng/kg/min increments as described above for tolerability). Refer to Appendix D for the study drug dose titration and study drug IV infusion pump rate for subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease).

Table 1 outlines the dose titration schedule.

Table 1. Iloprost Dose Titration

Titration and Maintenance	Time Point	Dose	Instructions
Starting dose	0 min; Day 1 (Visit 2)	0.5 ng/kg/min	Discontinue and attempt to reinitiate the study drug infusion if the subject does not tolerate 0.5 ng/kg/min starting dose.
Up-titration (±5 min)	30 min; Day 1 (Visit 2)	1.0 ng/kg/min	Reduce the dose to 0.5 ng/kg/min (starting dose) if the subject does not tolerate the 1.0 ng/kg/min dose.
	60 min; Day 1 (Visit 2)	1.5 ng/kg/min	Reduce the dose to 1.0 ng/kg/min if the subject does not tolerate the 1.5 ng/kg/min dose.
	90 min; Day 1 (Visit 2)	2.0 ng/kg/min	Reduce the dose to 1.5 ng/kg/min if the subject does not tolerate the 2.0 ng/kg/min dose.
	120 min; Day 1 (Visit 2) (Hours 2 to 6)	2.0 ng/kg/min, or highest tolerated dose	Reduce dose in a stepwise manner if the subject experiences dose-limiting adverse events.
Maintenance	Days 2 to 5 (Visits 3 to 6)	2.0 ng/kg/min, or highest dose tolerated on previous day	The highest tolerated dose will be administered for the remaining days without up- or down-titration, unless the subject does not tolerate the study drug infusion or adverse events occur that necessitate a reduction in dose (in 0.5 ng/kg/min increments) and subsequent up-titration is allowed to the Day 1 highest tolerated dose. A lower starting dose may be initiated on Days 3 to 5 (Visits 4 to 6) if the subject does not tolerate the previous days' highest tolerated dose as a starting dose.

Refer to Appendix C for the study drug IV infusion pump rate.

5.5.3.4 Common adverse events associated with iloprost intravenous infusion

Investigators should be aware that the following adverse events are commonly experienced with iloprost IV infusion: headache, flushing, jaw pain, myalgia, nausea, and vomiting. These adverse events may be dose-limiting, and Investigators should closely monitor subjects and reduce the dose in a stepwise manner as described in Table 1.

5.5.3.5 Decentralized visits

For sites that allow decentralized visits, please refer to Appendix E for additional details regarding study drug infusions occurring outside of the investigational site.

5.5.4 Treatment Compliance

Study drug will be administered at the site by a trained healthcare professional. Dosing compliance will be recorded by the Investigator or designee at the investigational site.

5.5.5 Storage and Accountability

The fully diluted study drug product, ready for use, can be used immediately, or stored at refrigerated temperatures (2°C to 8°C) for a maximum of 24 hours prior to use, or stored at room

temperature (20°C to 25°C) for 4 hours prior to administration as a 6-hour continuous infusion with an infusion pump per the conditions of use outlined in the Infusion and/or Pharmacy Manual.

Records will be maintained indicating the receipt and dispensation of all study drug supplies. At the conclusion of the study, the Clinical Research Associate (CRA) will conduct a review of the study drug inventory. Any unused drug will be returned to the Sponsor. If no study drug remains, this will be indicated in the Drug Accountability Log.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications are not permitted within 8 weeks of screening or during the study: any parenteral, inhaled, or oral prostacyclin or IP receptor agonists (eg, epoprostenol, treprostinil, iloprost, and selexipag).

5.6.2 Restricted/Allowed Medications and/or Procedures

Use of oral, topical, or IV vasodilators (eg, calcium channel blockers, PDE5 inhibitors [eg, sildenafil, tadalafil, or vardenafil], nitrates, and fluoxetine) is permitted only if the subject is currently receiving a stably medicated regimen (no dose adjustments for at least 2 weeks prior to screening). Initiation of any vasodilators within 2 weeks prior to screening is not permitted. After screening, any change to the subject's medication while on the study (new, stable, and/or discontinued) which is medically necessary should be documented in the subject's medical record and documented in concomitant medications.

Supportive medications to treat mild side effects of the study drug infusion (eg, headache) are allowed at the Investigator's discretion. All concomitant medications must be recorded on the eCRF.

5.6.3 Documentation of Prior and Concomitant Medication Use

All prior and concomitant medications and treatments received by the subject will be recorded on the appropriate eCRF as follows:

- For premedication with acetaminophen extended-release tablets (650 mg each)
- Within 8 weeks of screening and throughout the duration of the study for any parenteral, inhaled, or oral prostacyclin or IP receptor agonists
- Within 2 weeks of screening and throughout the duration of the study for oral, topical, or IV vasodilators
- Within 2 weeks of screening and throughout the duration of the study for all other medications

The medication name, route of administration, dose, frequency, indication, and duration of the treatment or procedure (start and stop dates) will be recorded.

6 STUDY PROCEDURES

6.1 Informed Consent (Any Day Prior to/Including Day -30)

Written informed consent for the study will be obtained from all subjects or legally authorized representative before any protocol-specific procedures are carried out. See Section 11.3 for details on informed consent. In situations where electronic consenting is permitted, consent can occur on or before Day-30 and the screening period will begin once the subject has been trained and begins to complete the ePRO diary.

6.2 Screening Period (Days -30 to -1)

The study consists of an up to 30-day screening period during which subjects will complete a daily ePRO diary to record information regarding all symptomatic RP attacks (eg, severity of symptoms and duration) and analgesic medication use (prescription and over-the-counter). The up to 30-day screening period consists of a 5-day eligibility period and an up to 25-day baseline ePRO diary completion period.

6.2.1 Eligibility Period (Days -30 to -26 [Visit 1])

During the 5-day eligibility period, eligible subjects will have a minimum of 10 symptomatic RP attacks, documented in the ePRO diary, occurring over at least 3 separate days of the 5-day eligibility period.

Subjects are allowed a 1-time rescreening at least 2 weeks from the last screening assessment. The following procedures will be performed at screening:

- Confirm that informed consent was obtained.
- Record demographics and medical/surgical history.
- Assess DUs as part of the subject's medical history.
  - Note: Investigator assessment of the DU will consist of location, status, and healing.
- Assess inclusion/exclusion criteria.
- Perform a physical examination.
- Obtain height and weight.
- Obtain vital signs (heart rate and blood pressure).
- Perform 12-lead electrocardiogram (ECG).
- Perform clinical laboratory assessments (chemistry and hematology).
- Draw blood samples for optional biomarker analysis.
- Perform a urine pregnancy test for women of childbearing potential only.
- Distribute the ePRO diary and train on its use.
- Complete the daily ePRO diary.
  - Note: Completion of the daily ePRO diary begins the same day that the ePRO training is completed.

- Assess adverse events.
- Record prior/concomitant medications.

6.2.2 Baseline Electronic Patient-Reported Outcomes Diary Completion Period (Days -25 to -1)

The baseline ePRO diary completion period is a minimum of 10 days and a maximum of 25 days prior to the day of randomization. While 10 days is the preferred baseline ePRO completion period, it may be necessary to extend the baseline ePRO diary completion period beyond 10 days in order to accommodate the preferred Monday to Friday dosing schedule. All eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period. The ePRO symptomatic RP attack data from this time period will be used for the calculation of the baseline frequency of symptomatic RP attacks.

6.3 Randomization (Day 1 [Visit 2] or up to 4 Days Prior)

Contact the IRT system to randomize the subject and obtain the study drug assignment.

6.4 Treatment Period (Days 1 to 5 [Visits 2 to 6])

Eligible subjects will be administered study drug infusions on 5 consecutive days.

6.4.1 Day 1 (Visit 2)

The following procedures will be performed at Day 1 (Visit 2):

- Assess inclusion/exclusion criteria.
  - Note: Eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period.
- Obtain weight.
- Obtain vital signs (heart rate and blood pressure).
  - Note: Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.
  - Note: The arm used for the study drug IV infusion should not be used for blood pressure monitoring.
  - Note: Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration.
- Perform a urine pregnancy test for women of childbearing potential only, prior to study drug administration.
- Unless a subject has taken an acetaminophen-containing prescription or nonprescription (over-the-counter) drug product within 4 hours prior to study drug administration, subjects will be premedicated with a single dose of 2 acetaminophen extended-release tablets (650 mg each), 30 minutes (±15 minutes) prior to study drug administration.

- Insert the NovaCath Integrated IV Catheter System or PICC.
    - Note: Prior to the first study drug infusion, the NovaCath Integrated IV Catheter System will be inserted into a small peripheral vein in the hand or arm using aseptic technique by a trained healthcare professional. If the subject's peripheral veins do not support the placement of a peripheral line, a trained healthcare professional will insert a PICC. When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment. The NovaCath Integrated IV Catheter System (peripheral catheter system) should be replaced when clinically indicated (eg, loss of line patency, signs of phlebitis, etc) or required by institutional policy. If peripheral venous access cannot be obtained in a subject during an infusion visit, the study drug infusion will be missed on that day. If no peripheral venous access is possible, a PICC should be considered.
- Confirm subject has completed the PGIS questionnaire of the ePRO diary prior to administration of the study drug.
- Prepare and administer the study drug infusion. See Section 5.5.3.
- Complete the ePRO diary.
- Assess adverse events.
- Record concomitant medications.

6.4.2 Days 2 to 5 (Visits 3 to 6)

The following procedures will be performed at Days 2 to 5 (Visits 3 to 6):

- Obtain vital signs (heart rate and blood pressure).
    - Note: Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.
    - Note: The arm used for the study drug IV infusion should not be used for blood pressure monitoring.
    - Note: Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration each day of study drug administration.
- Premedicate with a single dose of 2 acetaminophen extended-release tablets (650 mg each), 30 minutes (±15 minutes) prior to study drug administration. Verify the subject has not taken an acetaminophen-containing prescription or nonprescription (over-the-counter) drug product within 4 hours prior to study drug administration.
- Prepare and administer the study drug infusion. See Section 5.5.3.
- On Day 5 (Visit 6) only, perform clinical laboratory assessments (chemistry and hematology) 15 minutes (±15 minutes) postinfusion.
- On Day 5 (Visit 6) only, draw blood samples for optional biomarker analysis at **15 minutes (±15 minutes) prior to the end of the study drug infusion**. The arm used for the study drug IV infusion should not be used to draw blood samples.

- Complete the ePRO diary.
- Assess adverse events.
- Record concomitant medications.

6.5 Post-Treatment Period (Days 8 [+2 Days] and 22 [+2 Days] [Visits 7 and 8])

6.5.1 Day 8 (+2 Days) (Visit 7) – Telephone Call

The following procedures will be performed via a telephone call on Day 8 (+2 days) (Visit 7):

- Remind subjects to continue to complete the daily ePRO diary. Subjects will complete the ePRO diary through Day 21.
- Assess adverse events.
- Record concomitant medications.

6.5.2 Day 22 (+2 Days) (Visit 8) – Telephone Call

The following procedures will be performed via a telephone call on Day 22 (+2 days) (Visit 8):

- Confirm subject completed end of study questions (overall improvement, severity, and benefit).
- Confirm subject no longer needs to complete the ePRO diary.
- Assess adverse events.
- Record concomitant medications.

6.6 Follow-up Visit (Day 35 [+7 Days] [Visit 9])

The following procedures will be performed at the follow-up visit on Day 35 (+7 days) (Visit 9) 30 days after the last dose of study drug:

- Obtain vital signs (heart rate and blood pressure).
- Perform clinical laboratory assessments (chemistry and hematology).
- Draw blood samples for optional biomarker analysis.
- Assess DUs.
    - Note: Investigator assessment of the DU will consist of location, status, and healing.
- Assess adverse events.
- Record concomitant medications.
- Return ePRO tablet if used.

6.7 Early Termination Visit and Withdrawal Procedures

In circumstances where a subject discontinues the study prior to Day 35 (+7 days) (Visit 9), an ET visit will be performed. The following procedures will be performed at this visit:

- Obtain vital signs (heart rate and blood pressure).
- Perform clinical laboratory assessments (chemistry and hematology).
- Assess DUs.
    - Note: Investigator assessment of the DU will consist of location, status, and healing.
- Complete the daily ePRO diary.
- Assess adverse events.
- Record concomitant medications.
- Contact the IRT system to record the subject's withdrawal from the study.

7 EFFICACY ASSESSMENTS

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change of symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic RP attacks, from baseline to the end of the efficacy follow-up.

For the endpoint calculated using data from the ePRO diary, the baseline value will be the (weekly) average of the inputs during the 10- to 25-day baseline ePRO diary completion period, and the postbaseline value will be the (weekly) average of the inputs during Days 8 through 21.

7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include changes from baseline to the end of the efficacy follow-up in the following:

- Severity of RP attacks as determined by the overall severity of RP attack symptoms (using a Numeric Rating Scale [NRS]). The symptom (pain, numbness, discomfort, or tingling) with the worst average baseline value for each subject will be used for evaluating the subject's overall severity. If more than 1 symptom has the same value, the symptom used for analysis will be based on the following order of rank: pain>numbness>tingling>discomfort.
- Weekly total duration of symptomatic RP attacks.
- Proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline.

7.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include changes from baseline to the end of the efficacy follow-up in the following:

- Proportion of days without symptomatic RP attacks
- NRS for worst pain associated with symptomatic RP attacks
- NRS for worst numbness associated with symptomatic RP attacks
- NRS for worst tingling associated with symptomatic RP attacks
- NRS for worst discomfort associated with symptomatic RP attacks
- Proportion of pain responders, defined as subjects that have a 50% reduction in worst pain associated
- Proportion of numbness responders, defined as subjects that have a 50% reduction in worst numbness associated
- Proportion of tingling responders, defined as subjects that have a 50% reduction in worst tingling associated

- Proportion of discomfort responders, defined as subjects that have a 50% reduction in worst discomfort associated
- Proportion of total weekly duration responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic attacks
- Raynaud's Condition Score
- Duration of symptomatic RP attacks (average duration of an attack)
- Patient assessment of overall change in symptomatic Raynaud's attacks (PGIC)
- Patient assessment of overall severity in symptomatic Raynaud's attacks (PGIS)
- Patient assessment of overall benefit compared to side effects

Additionally, depending on the results of the primary and secondary efficacy analyses, the effect of iloprost on plasma biomarkers (eg, CXCL4, sE-selectin, VEGF, TPA, bFGF, sICAM-1, VCAM-1, PINP, MMP-2, endostatin, VWF, endothelin-1, angiopoietin-1, angiopoietin-2, thromboplastin, IL-10, IL-6, PDGF, vascular endothelial cadherin, and cAMP) and chemistry panel parameters (creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin) may be evaluated.

7.2 Efficacy Assessments

7.2.1 Raynaud's Phenomenon Attacks

A symptomatic Raynaud's attack for this study is defined as at least 1 color change of the subject's finger(s) (blue, white, or red) associated with at least 1 symptom (pain, numbness, tingling, and/or discomfort of the finger[s]). The attack is considered over when the color changes back to pre-attack color (normal) and the symptoms return to the subject's pre-attack level.

7.2.2 Electronic Patient-Reported Outcomes Diary

Subjects will be provided with an ePRO diary at Visit 1 and trained on its use. Subjects will be asked to complete the ePRO diary at the time points indicated in Appendix A. The ePRO diary allows for documentation of frequency, severity, and duration of symptomatic RP attacks and analgesic medication use (prescription and over-the-counter). Specific questionnaires include the severity of RP attack symptoms (using NRS), Raynaud's Condition Score, overall patient improvement, and overall patient severity.

7.2.2.1 Severity of Raynaud's phenomenon attack symptoms (using a Numeric Rating Scale)

Raynaud's phenomenon attacks are associated with significant discomfort (pain, numbness, tingling, and/or discomfort). Subjects will be asked to rate the severity of RP attack symptoms (pain, numbness, tingling, and/or discomfort) using an 11-point NRS.

Intensity will be assessed as follows: 0 = no pain/numbness/tingling/discomfort, 1 to 3 = mild pain/numbness/tingling/discomfort, 4 to 6 = moderate pain/numbness/tingling/discomfort, and 7 to 10 = severe pain/numbness/tingling/discomfort.

7.2.2.2 Raynaud's Condition Score

The Raynaud's Condition Score asks subjects to rate their difficulty with Raynaud's condition on a given day from "No difficulty (0)" to "Extreme difficulty (10)." Subjects will be asked to consider the number of attacks they have had on that day and how long each attack lasted. Subjects will also be asked to consider how much pain, numbness, or other symptoms the Raynaud's caused in their fingers (including painful sores) and how much the Raynaud's alone affected the use of their hands that day.

7.2.2.3 Worst pain associated with Raynaud's phenomenon attacks (using a Numeric Rating Scale)

Raynaud's phenomenon attacks are associated with significant pain. Subjects will be asked to rate the worst pain associated with RP attacks using an 11-point NRS.

Intensity will be assessed as follows: 0 = no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain, and 7 to 10 = severe pain.

7.2.2.4 Weekly total duration of symptomatic Raynaud's phenomenon attacks

Subjects will be asked to document the duration of each symptomatic RP attack within their ePRO diaries. For each attack, the subject will record the duration in minutes. Refer to Section 7.2.1 for the definition of a symptomatic RP attack. The weekly total duration of symptomatic RP attacks is the cumulative duration of all attacks calculated on weekly basis.

7.2.2.5 Duration of Raynaud's phenomenon attacks

Subjects will be asked to document the duration of each symptomatic RP attack within their ePRO diaries. For each attack, the subject will record the duration in minutes. Refer to Section 7.2.1 for the definition of a symptomatic RP attack. The weekly total duration of symptomatic RP attacks is the cumulative duration of all attacks calculated on weekly basis.

7.2.2.6 Overall patient improvement

At Day 21, subjects will be asked to rate their overall improvement in symptomatic Raynaud's attacks compared to the start of the study. Overall improvement in symptomatic Raynaud's attacks will be assessed on a 7-point scale from very much better to very much worse.

7.2.2.7 Overall patient severity

At Day 1 (Visit 2) (prior to initiating study drug), subjects will be asked to rate their overall severity in symptomatic Raynaud's attacks in the last week. At Day 21, subjects will be asked to rate their overall severity in symptomatic Raynaud's attacks. Overall severity of symptomatic Raynaud's attacks will be assessed on a 5-point scale from none to very severe.

7.2.2.8 Patient benefit

At Day 21, subjects will be asked if the study drug provided a meaningful benefit: Did the study drug provide a meaningful benefit compared to any side effects? Yes/No

7.2.3 Optional Biomarker Assessments

Blood samples will be collected at the time points indicated in Appendix A for optional biomarker analysis.

The biomarker analysis is an optional assessment for the subject and is not required for study completion. Subjects are not required to allow their blood samples collected at the time points indicated in Appendix A to be used for analysis of their biomarkers.

All biomarker samples will be de-identified at the time of sample collection. These samples may be stored for up to 10 years for testing to evaluate the effect of iloprost compared to placebo on biomarkers of SSc. These biomarkers include CXCL4, sE-selectin, VEGF, TPA, bFGF, sICAM-1, VCAM-1, PINP, MMP-2, endostatin, VWF, endothelin-1, angiopoietin-1, angiopoietin-2, thromboplastin, IL-10, IL-6, PDGF, vascular endothelial cadherin, cAMP, and chemistry panel parameters (creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin).

Samples will not be used for the research and development of any diagnostics, no cell lines will be generated and no genetic testing will be performed.

Subjects who consent to the optional biomarker assessments will not have these assessments completed if decentralized study visits are performed for these subjects.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

Since symptomatic RP attacks (as defined in Section 7.2.1) are recorded as efficacy assessments, these will not be treated as adverse events. However, if an event results in hospitalization or amputation, the event will then be reported as an SAE. If subjects have non-RP-related pain during a symptomatic RP attack, that event will be captured as an adverse event.

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

All adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until Day 35 (+7 days) (Visit 9). During study drug infusions (Days 1 to 5 [Visits 2 to 6]) treatment-emergent adverse events (TEAEs) are expected (see Section 5.5.3.4). Treatment-emergent adverse events should be captured in relation to the dose, dose rate, and/or need for dose reduction. Subjects should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning from the time of informed consent until Day 35 (+7 days) (Visit 9), Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an adverse event, unless the medical condition or signs or symptoms present at baseline change in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at the date of informed consent and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event.

Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "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.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of severity

Mild – An event that is easily tolerated, causing minimal discomfort, and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to the event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug-

  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each subject for clinical and laboratory evidence for predefined adverse events of special interest (AESIs) throughout the subject's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an adverse event form which must be submitted within 24 hours of awareness of the event.

For this study, hypotension will be considered an AESI.

During the course of the study, additional AESIs may be identified by the Sponsor.

Adverse events of special interest must be recorded in the eCRF.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalization.

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email.

If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

A pregnancy is not considered to be an adverse event or SAE. However, if a subject becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male subject becomes pregnant while the subject is receiving study drug or within the safety follow-up period defined in the protocol (30 days after last study drug infusion), the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed (up to 1 year) until the outcome of the pregnancy is known, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should also follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to an investigational medicinal product.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the subject has taken an additional dose(s) or the Investigator has reason to suspect that the subject has taken an additional dose(s).

- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information, and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional, excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is defined as any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, subject, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of an investigational product are not considered reportable as medication errors.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation Reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE eCRF. Details of the signs and symptoms, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.7 Clinical Laboratory Evaluations

A detailed list of clinical laboratory analytes assessed during this study is included in Appendix B. Samples for clinical laboratory evaluations will be collected at the visits indicated in Appendix A. The arm used for the study drug IV infusion should not be used to draw blood samples.

A urine pregnancy test for female subjects of childbearing potential only will be performed at the visits indicated in Appendix A.

8.8 Vital Signs

Vital signs include heart rate and blood pressure and will be assessed at the visits indicated in Appendix A. A resting blood pressure and heart rate will be measured indirectly by using an oscillometric device on the same arm. The arm used for the study drug IV infusion should not be used for blood pressure monitoring.

On dosing days (Days 1 to 5 [Visits 2 to 6]), vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the

study drug infusion. Additionally, vital signs will be obtained 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion.

8.9 Electrocardiograms

A 12-lead ECG will be performed at screening.

8.10 Physical Examinations

A complete physical examination will be performed at screening. The physical examination will consist of an examination of the following systems: general appearance, skin, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart (including any auscultated cardiac murmurs), abdomen, extremities, and neurologic.

8.11 Height and Weight

Height will be measured at screening only. Weight will be assessed at screening (Visit 1) and Day 1 (Visit 2) and used with the dose rate card (Appendix C or Appendix D) to determine the starting flow rate for each subject.

8.12 Demographics and Medical/Surgical History

Demographic information, including day, month, and year of birth; race; ethnicity; and gender will be collected for all subjects at screening.

Medical history information, including relevant details regarding illness and allergies, date(s) of onset, status of current condition, and smoking use, will be collected at screening. Additional information to be collected includes past surgical and medical procedures.

8.13 Digital Ulcers

Digital ulcers will be assessed at screening and captured as part of the medical history at this visit. New DUs will be captured as an adverse event/SAE. In all cases, subjects that present with DUs will be followed until Day 35 (+7 days) (Visit 9) or the ET visit. Investigator assessment of the DU will consist of location, status, and healing.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all randomized subjects who initiate study drug infusion on Day 1. The ITT Population is the primary efficacy analysis population.

9.1.2 Per-Protocol Population

The Per-Protocol (PP) Population is defined as all subjects in the ITT Population who complete at least Day 21 without any major protocol deviations. The primary analysis will be repeated on the PP Population.

9.1.3 Safety Population

The Safety Population is defined as all randomized subjects who initiate study drug infusion. The Safety Population will be used for all safety analyses.

9.2 Statistical Methods

A separate Statistical Analysis Plan provides further detail on the analysis of the study.

9.2.1 Analysis of Efficacy

All available efficacy data (weekly frequency of symptomatic RP attacks, severity of symptomatic RP attacks, Raynaud's Condition Score, weekly total duration of symptomatic RP attacks, the duration of symptomatic RP attacks [average duration of an attack], overall change in symptomatic RP, overall patient severity in symptomatic RP attack) will be listed for the ITT Population. Efficacy measurements will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group (iloprost injection for IV use and placebo). Baseline, change from baseline, and percent change from baseline to endpoint will be presented for each efficacy measurement for the ITT Population.

A fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 2-sided 0.05 level first, followed by testing the secondary efficacy endpoints at the 2-sided 0.05 level in the following hierarchical manner: (1) overall severity of RP attack symptoms, (2) weekly total duration of symptomatic RP attacks, and (3) proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline. Inferential conclusions about these efficacy endpoints will require statistical significance of the previous endpoints and the primary efficacy endpoint.

9.2.1.1 Primary efficacy analyses

The primary efficacy endpoint is the change in symptomatic digital ischemic episodes, as measured by the weekly frequency of symptomatic RP attacks from baseline to the end of the efficacy follow-up. The baseline weekly frequency of symptomatic RP attacks is defined as the average weekly number of symptomatic RP attacks that occur during the 10- to 25-day baseline ePRO diary completion period. The double-blind weekly frequency of symptomatic RP attacks is defined as the average weekly number of symptomatic RP attacks that occur during Days 8

through 21. The weekly frequency is calculated by taking the sum of the number of attacks over the time period, divided by the number of days with data reported (including 0 attacks) in the time period, and multiplied by 7.

The primary efficacy analysis on the primary efficacy endpoint will be performed based on an analysis of covariance (ANCOVA) model, including randomized treatment group and randomized stratification (ie, use of phosphodiesterase inhibitors at screening) as factors and baseline weekly frequency of symptomatic RP attacks as a covariate. The treatment comparisons will be estimated together with the 95% confidence interval and p-value. The primary analysis will be performed on the ITT Population.

For subjects in the ITT Population with a missing primary efficacy endpoint, the following imputation rule will be used: if there are values available for fewer than 7 days between Day 8 and Day 21, the missing daily values between Day 8 and Day 21 (inclusive) required to total 7 days values will be imputed by (1) the average value of the subjects in the same treatment group on the same study day if it is intermittent missing daily values, or (2) the average value of the subjects in the placebo group on the same study day if the subject has discontinued (early termination) from the study.

The primary efficacy analysis will also be repeated for the PP Population.

Primary efficacy measurements will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group (iloprost injection for IV use and placebo). Baseline, change from baseline, and percent change from baseline to endpoint will be presented for each efficacy measurement for the ITT Population.

9.2.1.2 Secondary efficacy analyses

The secondary efficacy analyses will be performed on the ITT Population. Secondary efficacy endpoints in the hierarchical step-down testing procedure include changes from baseline to the end of the efficacy follow-up in the following: (1) overall severity of RP attack symptoms, (2) weekly total duration of symptomatic RP attacks, and (3) the proportion of responders, defined as subjects that have a 50% reduction in weekly total duration of symptomatic RP attacks and 50% reduction in overall severity from baseline.

For subjects in the ITT Population with a missing secondary efficacy endpoint, the same imputation method as used for the primary efficacy analysis will be used. Overall severity will be derived after the imputation for each symptom. Responders will be derived after the imputation of the missing weekly total duration of symptomatic RP attacks and overall severity.

The ANCOVA model will be used to analyze the change from baseline to the end of the efficacy follow-up in overall severity of RP attack symptoms and weekly total duration of symptomatic RP attacks. A logistic regression model will be used to estimate the proportion of responders within each treatment group. These analyses will include randomized treatment group and randomized stratification as factors and baseline value as a covariate.

9.2.1.3 Sample size determination

The study will target randomizing approximately 180 subjects. Subject enrollment may be halted by the Sponsor at any time for any reason.

The study will be stratified based on the current use of oral PDE5 inhibitors. Eighty-six subjects per arm, at the end of the efficacy evaluation time point, will provide ≥85% power to detect a 5.5 improvement between iloprost and the placebo group for the mean change from baseline to the end of the efficacy follow-up in the weekly frequency of symptomatic RP attacks, assuming a common standard deviation of 12 and use of a traditional 2-sided 0.05 level test. Assuming a rate of missingness of 5% before Day 8, 90 subjects in each treatment group are planned.

9.2.1.4 Exploratory efficacy analyses

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided by treatment group for the exploratory endpoints on the ITT Population.

The ANCOVA model will be used to analyze the continuous efficacy endpoints and will include randomized treatment group and randomized stratification as factors and baseline value as a covariate. The treatment comparisons will be estimated together with the 95% confidence interval. P-values will be provided. The ANCOVA model for PGIC will include only randomized treatment group and randomized stratification as factors since there is no PGIC value at baseline.

The same logistic model for the secondary efficacy analysis will be used for the exploratory categorical endpoints on the ITT Population. The odds ratio between iloprost and placebo will be provided together with the p-value.

Subjects with missing values will be excluded. No imputation is needed.

9.2.2 Analysis of Safety

All safety analyses will be performed on the Safety Population. Subjects will be analyzed by the treatment received.

Safety measures will be summarized descriptively. Qualitative variables will be summarized using counts and percentages by treatment group at each study visit. A TEAE is defined as an adverse event with a start date and time on or after the administration of study drug. Treatment-emergent adverse events will be summarized by the Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term. Tables will be provided for overall incidence and incidence by SOC and preferred term for TEAEs, drug-related TEAEs, TEAEs by maximum severity, SAEs, and TEAEs leading to treatment discontinuation.

Laboratory and vital sign parameters will be presented using descriptive statistics for observed values at each visit and changes from baseline, as appropriate. Abnormal physical examination findings will be presented in a by-subject data listing. Descriptive statistics will be provided for ECG data. Details of any abnormalities will be included in subject listings.

9.2.3 Data Monitoring Committee and Interim Analyses

The DMC will be responsible for safeguarding the interests of clinical study subjects and for enhancing the integrity of the study. To address this mission, the DMC will have ongoing access to efficacy and safety data, and information regarding the quality of study conduct. The DMC will review safety information on a monthly basis. The DMC will also have a planned formal interim analysis meeting, where available efficacy data will be reviewed to enable the interpretation of safety in the context of this emerging efficacy data, and to assess the quality of its capture. The

meeting will occur when approximately 80 to 90 subjects have completed the Day 22 Visit (+2 days) (Visit 8). In addition, the DMC will hold ad hoc teleconference meetings to discuss safety or study conduct information as needed. Based on its insights from emerging evidence, the DMC will provide recommendations to the study Sponsor, including a recommendation regarding study continuation. Given the very short timeframe for the study and the importance of robust evidence, there will not be formal statistical boundaries for early termination for efficacy. In assessing the acceptability of the safety profile, the DMC will consider the totality of information regarding benefits and risks. To contribute to enhancing the integrity of the study, the DMC may also formulate recommendations relating to the rates of recruitment and eligibility of subjects, improving adherence to protocol-specified regimens (eg, ePRO adherence, study drug infusions, etc), retention of subjects, and the timeliness of data capture and adjudication of study endpoints.

The DMC will be advisory to the study Sponsor (and/or the clinical study leadership group, hereafter referred to as the Steering Committee). The Sponsor and/or the Steering Committee will be responsible for promptly reviewing the DMC recommendations, discussing them with the DMC, and making decisions about their implementation.

The DMC will consist of 3 members, including an SSc expert, a prostacyclin PAH expert, and a biostatistician.

A separate charter further describes the DMC role.

9.2.4 Steering Committee

The purpose of the Steering Committee is to provide objective and independent scientific and medical input on the design, execution, analysis, and reporting of the study. The Steering Committee will consist of members with medical specialties or scientific expertise (eg, statisticians) pertinent to the population under study. There will be 7 voting external members of the Steering Committee who are independent of Eicos Sciences, Inc. The Steering Committee statisticians and Sponsor representatives will be nonvoting members. A separate charter describes the Steering Committee role.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- World Health Organization Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. For this study, the end of study will be Day 35 (+7 days) (Visit 9), unless the subject terminates early.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements. The ICF will be provided to the subject in his/her native language, as necessary.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject or a legally authorized representative before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be provided to the subject. Electronic consenting of subjects will be available in this study.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well organized, and easily retrievable data.

Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor and share their proposed publication with Medpace and the Sponsor at least 60 days prior to submitting for publication, upon which, the Sponsor has 60 days to review and propose edits or additional delay.

The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13 REFERENCES

1. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum.* 2013;65(11):2737-2747.
2. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol.* 2012;24(2):165-170.
3. Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2008;78(8):961-968.
4. Campbell PM, LeRoy EC. Pathogenesis of systemic sclerosis: a vascular hypothesis. *Semin Arthritis Rheum*. 1975;4(4):351-368.
5. Khanna D, Denton CP, Merkel PA, et al. Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis DUAL-1 and DUAL-2 Randomized Clinical Trials. *JAMA*. 2016;315(18):1975-1988.
6. LeRoy EC. Systemic sclerosis. A vascular perspective. *Rheum Dis Clin North Am*. 1996;22(4):675-694.
7. Matucci-Cerinic M, Seibold JR. Digital ulcers and outcomes assessment in scleroderma. *Rheumatology (Oxford)*. 2008;47(Suppl5):v46-47.
8. Matucci-Cerininc M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum*. 2013;65(8):1953-1962.
9. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. *Autoimmun Rev*. 2006;5(2):125-128.
10. Wigley FM. Raynaud's phenomenon and other features of scleroderma, including pulmonary hypertension. *Curr Opin Rheumatol.* 1996;8(6):561-568.
11. Denton CP, Korn JH. Digital ulceration and critical digital ischemia in scleroderma. *Scleroderma Care Res*. 2003;1:12-16.
12 Wigley FM. Clinical practice. Raynaud's phenomenon. *N Engl J Med*. 2002;347(13):1001-1008.
13. Merkel PA, Herlyn K, Martin RW, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's Phenomenon. *Arthritis Rheum*. 2002;46(9):2410-2420.
14. Nihtyanova SI, Brough GM, Black CM, et al. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis*. 2008;67(1):120-123.
15. Tsou PS, Rabquer BJ, Ohara RA, et al. Scleroderma dermal microvascular endothelial cells exhibit defective response to pro-angiogenic chemokines. *Rheumatology (Oxford).* 2016;55(4):745-754.
16. Baron M, Chung L, Gyger G, et al. Consensus opinion of a North American Working Group regarding the classification of digital ulcers in systemic sclerosis. *Clin Rheumatol*. 2014;33(2):207-214.
17. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)*. 2002;81(2):139-153.
18. Matucci-Cerinic M, Krieg T, Guillevin L, et al. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. *Ann Rheum Dis*. 2016;75(10):1770-1776.

19. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis.* 2007;66(6):754-763.
20. Steen V, Denton CP, Pope JE, et al. Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology (Oxford)*. 2009;48(Suppl 3):iii19-24.
21. Hachulla E, Clerson P, Launay D, et al. Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. *J Rheumatol.* 2007;34(12):2423-2430.
22. Mouthon L, Mestre-Stanislas C, Bérézne A, et al. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. *Ann Rheum Dis*. 2010;69(1):214-217.
23. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327-1339.
24. Sanchez O, Sitbon O, Jaïs X, et al. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest*. 2006;130(1):182-189.
25. Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. *Rheumatology (Oxford)*. 2017;56(1):14-25.
26. Ventavis (iloprost). [inhalation solution prescribing information]. San Francisco, CA. Actelion Pharmaceuticals US, Inc. 2017.
27. Ilomedin (iloprost). [data sheet]. Hillcrest, North Shore, Auckland. Bayer New Zealand Limited. 19 March 2012.
28. D'Amelio P, Cristofaro MA, D'Amico L, et al. Iloprost modulates the immune response in systemic sclerosis. *BMC Immunol*. 2010;11:62.
29. Gomez-Arroyo J, Sakagami M, Syed AA, et al. Iloprost reverses established fibrosis in experimental right ventricular failure. *Eur Respir J.* 2015;45(2):449-462.
30. Grant SM, Goa KL. Iloprost. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. *Drugs*. 1992;43(6):889-924.
31. Modesti PA, Fortini A, Poggesi L, et al. Acute reversible reduction of PGI2 platelet receptors after iloprost infusion in man. *Thromb Res.* 1987;48(6):663-669.
32. Tremoli E, Colli S, Paoletti R. Mode of action of PGI2 and of its stable derivative iloprost on platelets and leukocytes. *Throm Res Suppl.* 1990;11:33-42.
33. Zhu Y, Liu Y, Zhou W, et al. A prostacyclin analogue, iloprost, protects from bleomycin-induced pulmonary fibrosis in mice. *Respir Res*. 2010;11:34.
34. Ercan ZS, Türker RK. The relaxing activity of iloprost and prostaglandin E2 in the isolated various smooth muscle strips of the rabbit. *Pharmacology*. 1985;31(2):61-66.
35. Ioannou P, Talesnik J. Platelet antiaggregatory substances inhibit arachidonic acid induced coronary constriction. *Can J Physiol Pharmacol*. 1986;64(4):398-405.
36. Nicolini FA, Mehta JL. Inhibitory effect of unstimulated neutrophils on platelet aggregation by release of a factor similar to endothelium-derived relaxing factor (EDRF). *Biochem Pharmacol.* 1990;40(10):2265-2269.
37. Czeslick EG, Simm A, Grond S, et al. Inhibition of intracellular tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 production in human monocytes by iloprost. *Eur J Clin Inves*. 2003;33(11):1013-1017.
38. Krause W, Krais T. Pharmacokinetics and pharmacodynamics of the prostacyclin analogue iloprost in man. *Eur J Clin Pharmacol*. 1986;30(1):61-68.

39. Hildebrand M, Krause W, Fabian H, et al. Pharmacokinetics of iloprost in patients with chronic renal failure and on maintenance haemodialysis. *Int J Clin Pharmacol Res.* 1990;10(5):285-292.
40. Hildebrand M, Krause W, Oberender HA, et al. Pharmacokinetics of iloprost in patients with severe peripheral arterial occlusive disease. *Eicosanoids.* 1990;3(3):145-148.
41. Hildebrand M, Krause W, Angeli P, et al. Pharmacokinetics of iloprost in patients with hepatic dysfunction. *Int J Clin Pharmacol Ther Toxicol*. 1990;28(10):430-434.
42. Wigley FM, Seibold JR, Wise RA, et al. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. *J Rhematol.* 1992;19(9):1407-1414.
43. Wigley FM, Wise RA, Seibold JR, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med*. 1994;120(3):199-206.
44. Foti R, Visalli E, Amato G, et al. Long-term clinical stabilization of scleroderma patients treated with a chronic and intensive IV iloprost regimen. *Rhematol Int.* 2017;37(2):245-249.
45. Garcia de la Peña Lefebvre P, Nishishinya MB, Pereda CA, et al. Efficacy of Raynaud's Phenomenon and digital ulcer pharmacological treatment in systemic sclerosis patients: a systematic literature review. *Rheumatol Int.* 2015;35(9):1447-1459.
46. Casigliani Rabl S, Della Rossa A, Pepe P, et al. Long-term cyclic intravenous iloprost in systemic sclerosis: clinical experience from a single center. *Reumatismo.* 2012;64(3):158-165.
47. Kawald A, Burmester GR, Huscher D, et al. Low versus high-dose iloprost therapy over 21 days in patients with secondary Raynaud's phenomenon and systemic sclerosis: a randomized, open, single-center study. *J Rheumatol*. 2008;35(9):1830-1837.
48. Zachariae H, Halkier-Sørensen L, Bjerring P, et al. Treatment of ischaemic digital ulcers and prevention of gangrene with intravenous iloprost in systemic sclerosis. *Acta Derm Venereol.* 1996;76(3):236-238.
49. Caramaschi P, Biasi D, Canestrini S, et al. Evaluation of finger skin temperature in scleroderma patients cyclically treated with iloprost. *Joint Bone Spine*. 2006;73(1):57-61.
50. Mayes MD. Endothelin and endothelin receptor antagonists in systemic rheumatic disease. *Arthritis and Rheum*. 2003;48(5):1190-1199.
51. Watson HR, Robb R, Belcher G, et al. Seasonal variation of Raynaud's Phenomenon secondary to systemic sclerosis. *J Rheumatol*. 1999;26(8):1734-1737.
52. Torley HI, Madhok R, Capell HA, et al. A double blind, randomised, multicentre comparison of two doses of intravenous iloprost in the treatment of Raynaud's phenomenon secondary to connective tissue diseases. *Ann Rheum Dis.* 1991;50(11):800-804.

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening Period[a]		Treatment Visits		Post-Treatment Visits		Follow-up Visit	ET Visit[d]
	Eligibility Period[b]	Baseline ePRO Completion Period[c]						
Visit	**1**	**NA**	**2**	**3, 4, 5, 6**	**7[e]**	**8[f]**	**9**	
Time Point	**Days -30 to -26**	**Days -25 to -1**	**Day 1**	**Days 2 to 5**	**Day 8**	**Day 22**	**Day 35**	
Window					**+2 days**	**+2 days**	**+7 days**	
Informed consent	X[g]							
Demographics	X							
Medical/surgical history[h]	X							
Inclusion/exclusion criteria	X		X[i]					
Physical examination	X							
Height and weight[j]	X		X					
Vital signs (HR and BP)	X		X[k]	X[k]			X	X
12-lead ECG	X							
Clinical laboratory assessments[l]	X			X[m]			X	X
Optional biomarkers[n]	X			X[o]			X	
Urine pregnancy test[p]	X		X[q]					
Distribute ePRO diary[r]	X							
ePRO diary completion[s]	X[t]	X	X	X	X	X[u]		X
Randomization			X[v]					
Insertion of NovaCath™ Integrated IV Catheter System or PICC[w]			X					
Premedicate with acetaminophen[x]			X	X				
Administer study drug infusion[y]			X[z]	X				
Digital ulcer assessment[h]	X						X	X
Return ePRO tablet							X	
Adverse events[aa]	X		X	X	X	X	X	X
Prior/concomitant medication	X		X	X	X	X	X	X

See footnotes on the following page.

a. The study consists of an up to 30-day screening period during which subjects will complete a daily ePRO diary to record information regarding all symptomatic RP attacks (eg, severity of symptoms and duration) and analgesic medication use (prescription and over-the-counter). The up to 30-day screening period consists of a 5-day eligibility period and an up to 25-day baseline ePRO diary completion period. Subjects are allowed a 1-time rescreening at least 2 weeks from the last screening assessment.
b. During the 5-day eligibility period, eligible subjects will have a minimum of 10 symptomatic RP attacks, documented in the ePRO diary, occurring over at least 3 separate days of the 5-day eligibility period.
c. The baseline ePRO diary completion period is a minimum of 10 days and a maximum of 25 days prior to the day of randomization. While 10 days is the preferred baseline ePRO completion period, it may be necessary to extend the baseline ePRO diary completion period beyond 10 days in order to accommodate the preferred Monday to Friday dosing schedule. All eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period. The ePRO symptomatic RP attack data from this time period will be used for the calculation of the baseline frequency of symptomatic RP attacks.
d. In circumstances where a subject discontinues the study prior to Day 35 (+7 days) (Visit 9), an ET visit will be performed. Contact the IRT system to record the subject's withdrawal from the study.
e. Subjects will be contacted via telephone on Day 8 (+2 days) (Visit 7) to remind subjects to continue to complete the daily ePRO diary; subjects will complete the ePRO diary through Day 21.
f. Subjects will be contacted via telephone on Day 22 (+2 days) (Visit 8) to confirm they completed end of study questions (overall improvement, severity, and benefit) and to confirm they no longer need to complete the ePRO diary.
g. Written informed consent for the study will be obtained from all subjects or legally authorized representative before any protocol-specific procedures are carried out. In situations where electronic consenting is permitted, consent can occur on or before Day-30 and the screening period will begin once the subject has been trained and begins to complete the ePRO diary.
h. Digital ulcers will be assessed at screening and captured as part of the medical history at this visit. New DUs will be captured as an adverse event/SAE. In all cases, subjects that present with DUs will be followed until Day 35 (+7 days) (Visit 9) or the ET visit. Investigator assessment of the DU will consist of location, status, and healing.
i. Eligible subjects must complete a minimum of 80% of the daily ePRO diary entry during the baseline period.
j. Height will be measured at screening only.
k. Vital signs will be obtained 15 minutes (±15 minutes) prior to study drug administration and at 15 minutes (±5 minutes) after all up-titrations during the study drug infusion. Additionally, vital signs will be obtained at 15 minutes (±5 minutes) after completion of the 6-hour study drug infusion. Subjects must have a systolic BP ≥85 mmHg (sitting position) 15 minutes (±15 minutes) prior to study drug administration each day of administration. The arm used for the study drug IV infusion should not be used for blood pressure monitoring.
l. Includes chemistry and hematology.
m. On Day 5 (Visit 6) only, perform clinical laboratory assessments (chemistry and hematology) 15 minutes (±15 minutes) postinfusion.
n. Blood samples for optional biomarker analysis will be collected during the 5-day eligibility period, Day 5 (Visit 6) (15 minutes [±15 minutes] prior to the end of the study drug infusion), and Day 35 (+7 days) (Visit 9). The arm used for the study drug IV infusion on Day 5 (Visit 6) should not be used to draw blood samples. Subjects who consent to the optional biomarker assessments will not have these assessments completed if decentralized study visits are performed for these subjects.
o. Day 5 (Visit 6) only.
p. For women of childbearing potential only.
q. Prior to study drug administration.
r. Subjects will be provided with an ePRO diary at Visit 1 and trained on its use. Subjects will start the daily ePRO diary the day after signing informed consent. Specific questionnaires include the severity of RP attack symptoms (using NRS), Raynaud's Condition Score, overall patient improvement, and overall patient severity.
s. Subjects will complete the daily ePRO diary during the eligibility period and baseline ePRO diary completion period. Subjects randomized will complete the ePRO diary during the treatment and post-treatment period Days 1 (Visit 2) to 21. Overall patient improvement and patient benefit will be completed on Day 21. Overall patient severity will be completed on Day 1 (Visit 2) (prior to initiating study drug) and Day 21.
t. Completion of the daily ePRO diary begins the same day that the ePRO training is completed.
u. Day 21 is the last day of diary entry. Subjects will be contacted via telephone on Day 22 (+2 days) (Visit 8) to confirm they completed end of study questions (overall improvement, severity, and benefit) and to confirm they no longer need to complete the ePRO diary.
v. Contact the IRT system to randomize the subject and obtain study drug assignment. Randomization may take place on Day 1 (Visit 2) or up to 4 days prior.

w. Prior to the first study drug infusion, the NovaCath™ Integrated IV Catheter System will be inserted into a small peripheral vein in the hand or arm using aseptic technique by a trained healthcare professional. If the subject's peripheral veins do not support the placement of a peripheral line, a trained healthcare professional will insert a PICC. When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment. The NovaCath Integrated IV Catheter System (peripheral catheter system) should be replaced when clinically indicated (eg, loss of line patency, signs of phlebitis, etc) or required by institutional policy. If peripheral venous access cannot be obtained in a subject during an infusion visit, the study drug infusion will be missed on that day. If no peripheral venous access is possible, a PICC should be considered.
x. Unless a subject has taken an acetaminophen-containing prescription or nonprescription (over-the-counter) drug product within 4 hours prior to study drug administration, subjects will be premedicated with a single dose of 2 acetaminophen extended-release tablets (650 mg each), 30 minutes (±15 minutes) prior to study drug administration.
y. To be administered for 5 consecutive days (eg, Monday through Friday) as a continuous IV infusion over 6 hours each day via a peripheral line or a PICC using an infusion pump. Study drug will be initiated at a dose of 0.5 ng/kg/min and will be increased every 30 minutes (±5 minutes) in increments of 0.5 ng/kg/min to 2.0 ng/kg/min or the individual tolerated dose. The weight of the subject at screening may be used with the dose rate card (Appendix C or Appendix D) to determine the starting flow rate for each subject. If the weight of the subject at screening is used, it should be confirmed on Day 1 (Visit 2). Subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease) will require a starting a reduced starting dose and modified dose titration. Refer to Section 5.5.3 for further details.
z. Prior to study drug administration, subjects must complete the Patient Global Impression in Severity questionnaire of the ePRO diary.
aa. All adverse events will be collected from the time of informed consent until Day 35 (+7 days) (Visit 9).

BP = blood pressure; DU = digital ulcer; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; ET = early termination; HR = heart rate; IRT = Interactive Response Technology; IV = intravenous; NA = not applicable; NRS = Numeric Rating Scale; PICC = peripherally inserted central catheter; RP = Raynaud's phenomenon; SAE = serious adverse event.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatinine	Estimated glomerular filtration rate
Glucose	Potassium
Sodium	Total bilirubin
Total protein	

Hematology

Hematocrit	Hemoglobin
Mean corpuscular volume	Platelets
Red blood cell count	

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Pregnancy Test

Urine pregnancy test (for women of childbearing potential only)

APPENDIX C: STUDY DRUG INTRAVENOUS INFUSION PUMP RATE

Subject Weight	Study Drug Intravenous Infusion Pump Rate (mL/hr)			
	0.5 ng/kg/min (Starting Dose)	1.0 ng/kg/min	1.5 ng/kg/min	2.0 ng/kg/min
30 to 39.9 kg	0.9	1.8	2.7	3.6
40 to 49.9 kg	1.2	2.4	3.6	4.8
50 to 59.9 kg	1.5	3.0	4.5	6.0
60 to 69.9 kg	1.8	3.6	5.4	7.2
70 to 79.9 kg	2.1	4.2	6.3	8.4
80 to 89.9 kg	2.4	4.8	7.2	9.6
90 to 99.9 kg	2.7	5.4	8.1	10.8
100 to 109.9 kg	3.0	6.0	9.0	12.0
If the subject weighs <30 kg or ≥110 kg, contact the Medical Monitor to discuss the dosing strategy. A more precise dose can be used if the infusion rate is calculated based on the subject's weight. The weight of the subject at screening may be used with the dose rate card to determine the starting flow rate for each subject. If the weight of the subject at screening is used, it should be confirmed on Day 1 (Visit 2).				

APPENDIX D: STUDY DRUG DOSE TITRATION AND INTRAVENOUS INFUSION PUMP RATE FOR SUBJECTS WITH HEPATIC DYSFUNCTION (CHILD-PUGH CLASS B AND CLASS C LIVER DISEASE)

The following table lists study drug dose titration for subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease).

Titration and Maintenance	Time Point	Dose	Instructions
Starting dose	0 min; Day 1 (Visit 2)	0.25 ng/kg/min	Discontinue and attempt to reinitiate the study drug infusion if the subject does not tolerate 0.25 ng/kg/min starting dose.
Up-titration (±5 min)	30 min; Day 1 (Visit 2)	0.5 ng/kg/min	Reduce the dose to 0.25 ng/kg/min (starting dose) if the subject does not tolerate the 0.5 ng/kg/min dose.
	60 min; Day 1 (Visit 2)	0.75 ng/kg/min	Reduce the dose to 0.5 ng/kg/min if the subject does not tolerate the 0.75 ng/kg/min dose.
	90 min; Day 1 (Visit 2)	1.0 ng/kg/min	Reduce the dose to 0.75 ng/kg/min if the subject does not tolerate the 1.0 ng/kg/min dose.
	120 min; Day 1 (Visit 2) (Hours 2 to 6)	1.0 ng/kg/min, or highest tolerated dose	Reduce dose in a stepwise manner if the subject experiences dose-limiting adverse events.
Maintenance	Days 2 to 5 (Visits 3 to 6)	1.0 ng/kg/min, or highest dose tolerated on previous day	The highest tolerated dose will be administered for the remaining days without up- or down-titration, unless the subject does not tolerate the study drug infusion or adverse events occur that necessitate a reduction in dose (in 0.25 ng/kg/min increments) and subsequent up-titration is allowed to the Day 1 highest tolerated dose. A lower starting dose may be initiated on Days 3 to 5 (Visits 4 to 6) if the subject does not tolerate the previous days' highest tolerated dose as a starting dose.

The following table lists study drug infusion pump rate for subjects with hepatic dysfunction (Child-Pugh Class B and Class C liver disease).

	Study Drug Intravenous Infusion Pump Rate (mL/hr)			
Subject Weight	0.25 ng/kg/min (Starting Dose)	0.5 ng/kg/min	0.75 ng/kg/min	1.0 ng/kg/min
30 to 39.9 kg	0.5	0.9	1.4	1.8
40 to 49.9 kg	0.6	1.2	1.8	2.4
50 to 59.9 kg	0.8	1.5	2.3	3.0
60 to 69.9 kg	0.9	1.8	2.7	3.6
70 to 79.9 kg	1.1	2.1	3.2	4.2
80 to 89.9 kg	1.2	2.4	3.6	4.8
90 to 99.9 kg	1.4	2.7	4.1	5.4
100 to 109.9 kg	1.5	3.0	4.5	6.0
If the subject weighs <30 kg or ≥110 kg, contact the Medical Monitor to discuss the dosing strategy. A more precise dose can be used if the infusion rate is calculated based on the subject's weight. The weight of the subject at screening may be used with the dose rate card to determine the starting flow rate for each subject. If the weight of the subject at screening is used, it should be confirmed on Day 1 (Visit 2).				

APPENDIX E: DECENTRALIZED VISITS

For institutions who have Institutional Review Board approval for decentralized visits that can occur outside of the institutional site, the Investigator will determine, per subject, which visits (if any) will occur outside of the institutional site. An additional consent will be obtained for subjects who have any visits outside of the institutional site. The location for the study visit (ie, subject's home or off-site ambulatory infusion suite) will be documented per visit, supported by the home care nurses, and overseen by the Investigator or designee. Refer to the Decentralized Visit Manual and Infusion Manual for Decentralized Infusions for additional details.

Home care nurses

For home care nursing or alternative clinical site visits, home care nurses will be qualified and trained on all study-related activities and procedures. The home care nurses will provide one-on-one nursing for subjects at home and/or alternative clinical sites. The home care nurses will provide clinical sites with, at a minimum, the following onboarding documentation prior to performing any study-related visits or procedures:

- Curriculum vitae/resume
- Nursing license (copy or online verification)
- Basic Life Support/Advanced Cardiac Life Support certification
- Good Clinical Practice training module certificate and assessment
- Home Care Nurse Training Form (signed/dated)

Visit schedule

The visits that may be conducted outside of the institutional site include:

- Screening (Visit 1)
- Infusions (Days 1 to 5 [Visits 2 to 6])
- Day 35 (+7 days) (Visit 9)

Optional biomarker samples will not be obtained for any visits that occur outside of the institutional site.

Decentralized infusions and Investigator oversight

In the event of disruption from coronavirus disease 2019 or any other local, regional, or nation-wide crisis, intravenous study drug infusions can be administered in a decentralized setting (ie, home or off-site ambulatory infusion suite) with one-on-one care from a registered nurse. The study drug infusion nurse must have appropriate equipment for physiological monitoring (blood pressure and heart rate), be adequately trained and qualified, and capable of managing drug adverse events and providing supportive care under the direction of the Investigator via telehealth. The infusion nurses are certified in Basic Life Support and Advanced Cardiac Life Support. During dose initiation and titration, study drug dose-limiting pharmacological effects are expected to occur and dose reduction is required per the protocol. Treatment may require dose adjustment to manage the pharmacological effects (eg, headache, flushing, jaw pain, myalgia, nausea, or vomiting) during the study drug infusion initiation and titration period as directed by the Investigator. Blood

pressure and heart rate will be measured prior to study drug administration and monitored 15 minutes (±5 minutes) after study drug initiation, all up-titrations, completion of the 6-hour study drug infusion, and with all adverse events. All vital signs and adverse events will be reported to the Investigator and study coordinator in real time via telehealth.

The Investigator is required to be accessible via telehealth during the decentralized (home or off-site ambulatory infusion suite) infusions to assess adverse events and vital signs (blood pressure and heart rate). All dose adjustments will be directed by the Investigator after assessment of adverse events and vital signs (blood pressure and heart rate).

If dose-limiting prostacyclin-associated adverse events (eg, headache, flushing, jaw pain, myalgia, nausea, or vomiting) occur that cannot be tolerated by the subject, then the dose/infusion rate will be reduced in a stepwise manner by 0.5 ng/kg/min every 30 minutes (±5 minutes), until a tolerated dose is determined. If a dose/infusion rate cannot be tolerated by the subject, the study drug infusion will be interrupted and re-initiation of the study drug infusion can be attempted after the event has resolved or been treated. If the study infusion is stopped at any point for a dose-limiting adverse event, the study drug can be reinitiated at a previously tolerated dose/infusion rate once the adverse event has resolved or subsided and in the medical judgment of the Investigator the subject is able to resume the study drug infusion. All adverse events will be collected and reported in real time to the Investigator and study coordinator via telehealth.

Infusion nursing guidelines for immediate interruption of the infusion will include symptomatic hypotension, a systolic blood pressure <80 mmHg, or intolerable adverse events (eg, vomiting). Once the Investigator determines that the symptoms have subsided or resolved, the study drug can be reinitiated at a previously tolerated dose/infusion rate per protocol.

If a subject experiences a systolic blood pressure drop more than 10 mmHg from their pre-infusion measurement during the administration of study drug, the nurse will immediately contact the Investigator. If the Investigator is not available, the infusion will be interrupted until the Investigator determines if the infusion should be re-initiated.

Please refer to the Infusion Manual for Decentralized Infusions for detailed instructions.