CLINICAL STUDY PROTOCOL

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Pilot Study Evaluating Intravenous Iloprost in Subjects With Symptomatic Raynaud's Phenomenon Secondary to Systemic Sclerosis

Investigational Product: Iloprost Injection, for intravenous use
Protocol Number: ES-201

Sponsor:
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Version Number: 4.0
Original Protocol: 04 October 2018
Amendment 1: 05 December 2018
Amendment 2: 30 January 2019
Amendment 3: 01 March 2019

SIGNATURE PAGE

STUDY TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Pilot Study Evaluating Intravenous Iloprost in Subjects With Symptomatic Raynaud's Phenomenon Secondary to Systemic Sclerosis

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

Signature Date

PPD 01 Mar 2019

PPD

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

PPD 01 Mar 2019

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PPD 01 Mar 2019

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

PPD 02 Mar 2019

PPD

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

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 2 Pilot Study Evaluating Intravenous Iloprost in Subjects With Symptomatic Raynaud's Phenomenon Secondary to Systemic Sclerosis

PROTOCOL NUMBER: ES-201

INVESTIGATIONAL PRODUCT: Iloprost Injection, for intravenous use

PHASE: Phase 2

INDICATION(S): Symptomatic Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc)

OBJECTIVES:

The primary objective is to evaluate the efficacy of iloprost compared to placebo on the change in the weekly frequency of symptomatic RP attacks from baseline in subjects with symptomatic RP secondary to SSc.

The exploratory objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the severity of RP attack symptoms
- 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 hand function as assessed by the Cochin Hand Function Scale (CHFS)
- To evaluate the safety and tolerability of iloprost
- 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 worst pain associated with symptomatic RP
- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall improvement in symptomatic RP
- To evaluate the pharmacokinetics (PK) of iloprost in subjects with symptomatic RP secondary to 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. During the 5-day eligibility period, eligible subjects will 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.

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 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. 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.
6. Subjects must be willing and able to comply with the study requirements and give informed consent for participation in the study.

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.
2. Subjects with systolic blood pressure <85 mmHg (sitting position) at screening.
3. Subjects with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 at screening as determined by the Modification of Diet in Renal Disease equation.
4. Subjects with Child-Pugh Class B or Class C liver disease or an alanine aminotransferase and/or aspartate aminotransferase value >3 × the upper limit of normal at screening.
5. Subjects with gangrene, digital ulcer infection, or requirement of cervical or digital sympathectomy within 30 days of screening.
6. Subjects with intractable diarrhea or vomiting.
7. Subjects with a risk of clinically significant bleeding events including those with coagulation or platelet disorders.
8. Subjects with a history of major trauma or hemorrhage in the past 4 weeks.

9. Subjects with clinically significant chronic intermittent bleeding such as active gastric antral vascular ectasia or active peptic ulcer disease.
10. Subjects who have had any cerebrovascular events (eg, transient ischemic attack or stroke) within 6 months of screening.
11. 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.
12. Subjects with acute or chronic congestive heart failure (New York Heart Association Class III [moderate] or Class IV [severe]).
13. Subjects with a history of life-threatening cardiac arrhythmias.
14. Subjects with a history of hemodynamically significant aortic or mitral valve disease.
15. Subjects with more than mild restrictive or congestive cardiomyopathy uncontrolled by medication or implanted device.
16. Subjects with known pulmonary hypertension, pulmonary arterial hypertension, or pulmonary veno-occlusive disease.
17. 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).
18. Subjects with a history of cervical or digital sympathectomy within 6 months of screening.
19. Subjects with scleroderma renal crisis within 6 months of screening.
20. Subjects with a concomitant life-threatening disease with a life expectancy <12 months.
21. 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.
22. 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.
23. Subjects must not initiate dosing of oral, topical, or intravenous (IV) vasodilators (eg, calcium channel blockers, phosphodiesterase-5 inhibitors [eg, sildenafil, tadalafil, or vardenafil], nitrates, and fluoxetine), or if currently receiving any vasodilator, must have been stably medicated (no dose adjustments) for at least 2 weeks prior to screening.
24. Subjects with any history of acetaminophen intolerability (eg, allergic reaction to acetaminophen).
25. Subjects with any malignancy that requires treatment during the study period, that has required treatment within 1 year of screening, or that is currently not in remission.
26. Subjects who have used any investigational medication or device for any indication within 30 days or 5 half-lives (whichever is longer) of screening.

STUDY DESIGN AND DURATION:

This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate the effect of iloprost on the symptomatic relief of RP attacks in subjects with symptomatic RP secondary to SSc. The study will be piloting an initial evaluation of iloprost, testing the study endpoints and logistics of study operations that include, among other things, an ePRO diary for the evaluation of subject response to the treatment as well as the infusion workflow for this multiday treatment. 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 enroll up to a maximum of 40 subjects. 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, duration, and hand function). 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.
- During the baseline ePRO diary completion period, eligible subjects must complete the daily ePRO diary for a minimum of 10 days (up to a maximum of 25 days) until the day of randomization. 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. 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 given the option to participate in a PK substudy. Subjects who participate in the substudy will provide plasma samples for PK analysis. The samples will be analyzed for iloprost concentrations using validated liquid chromatography mass spectrometry methods.

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, and subjects will receive study drug for 5 consecutive days (eg, Monday through Friday) as an IV infusion over 6 hours each day via a peripheral line (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) prior to study drug administration each day of administration. On Day 1, 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 step wise 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 iloprost at the starting dose (ie, 0.5 ng/kg/min), the

infusion will be reduced to 0.25 ng/kg/min. If the dose of 0.25 ng/kg/min is not tolerated due to symptomatic hypotension or a dose-limiting adverse event occurs, the study drug will be discontinued and reinitiation of the infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be monitored 15 minutes (±5 minutes) prior to and after all dose changes. 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 infusion will be stopped until the symptoms resolve, at which point the study drug should 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 infusion period, the dose will be stopped. Subjects will be monitored for up to 1 hour after completion of study drug infusion (ie, vital signs will be obtained 15 minutes [±5 minutes] and 1 hour [±15 minutes] after completion of the infusion).

On Days 2 to 5, the infusion will be started using the highest infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in the dose. Vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion.

During the treatment period (Days 1 to 5), while subjects receive study drug, the ePRO diary will not be completed. No study assessments will be performed on the 2 days following the end of treatment (Days 6 and 7, eg, Saturday and Sunday) to allow the subject to rest and return to a schedule of normal daily living activity following the 5 days of infusions.

Subjects will be contacted via telephone on Day 8 to ensure they resume completion of the daily ePRO diary; subjects will complete the diary from Day 8 through Day 21. On Day 22, subjects will return to the clinic for post-treatment evaluations. A follow-up visit will occur 30 days after the last administration of study drug (Day 35).

Subjects who discontinue study drug early will remain in the study (unless the subject withdraws consent) and complete the daily ePRO diary from Day 8 to Day 21 including clinical laboratory assessments on the remaining missed infusion days 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:

Iloprost injection for IV use and matching placebo will be supplied in vials packaged in a blinded study drug kit (10 vials per kit). The iloprost and placebo vials will be identical, except 100 mcg of iloprost will be added to the active study drug vials. The 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 an IV infusion over 6 hours each day via a peripheral line (NovaCath Integrated IV Catheter System) or a PICC using an infusion pump. (Note: In some instances where the site chooses to use a PICC, it may be necessary to confirm placement of the PICC with an x-ray).

EFFICACY VARIABLES:

The primary efficacy parameter is the change in the weekly frequency of symptomatic RP attacks from baseline.

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

- Severity of RP attacks as determined by the severity of RP attack symptoms (pain, numbness, tingling, and/or discomfort) (using a Numeric Rating Scale [NRS])
- Raynaud's Condition Score
- Hand function as assessed by the CHFS
- Duration of symptomatic RP attacks
- NRS for worst pain associated with symptomatic RP
- Patient assessment of overall improvement in symptomatic RP

PHARMACOKINETIC VARIABLES:

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of iloprost:

- Steady state plasma concentration just before infusion is stopped
- Area under the plasma concentration versus time curve (AUC) from time of dosing to the last time point with measurable concentration
- AUC from time 0 extrapolated to infinity
- Percentage of AUC obtained by extrapolation
- Plasma terminal elimination half-life
- Plasma clearance
- Volume of distribution

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:

All efficacy analyses are intended to provide an initial description of the clinical profile of iloprost and to inform the design and logistics of future studies.

The modified Intent-to-Treat (mITT) Population is defined as all randomized subjects who initiate infusion of study drug. The mITT Population is the primary efficacy analysis population.

The Per-Protocol (PP) Population is defined as subjects in the mITT Population who complete at least Day 21 without any major protocol deviations. The PP Population will be used for sensitivity analyses of the primary efficacy variable.

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

Primary efficacy analysis

The baseline weekly frequency of symptomatic RP attacks is defined as the average number of weekly symptomatic RP attacks occurring during the 10- to 25-day baseline ePRO diary completion period. The double-blind weekly symptomatic RP attacks is defined as the average number of weekly symptomatic RP attacks during Days 8 to 21. The primary efficacy parameter is the change in the weekly frequency of symptomatic RP attacks from baseline (ie, the mean number of weekly symptomatic RP attacks during Days 8 to 21 compared to during the 10- to 25-day baseline ePRO diary completion period).

The primary analysis will be performed based on an analysis of covariance 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 site effect will be explored as necessary. For subjects in the mITT Population with intermittent missingness during the baseline or double-blind intervals, multiple imputation will be used assuming data are missing at random; for those subjects with truncated follow-up, methods will be used assuming missingness is not at random.

The primary analysis is formally based on a 3-category decision guideline for future clinical study evaluation of iloprost. Specifically, the decision guideline for this study is based on whether the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is less than X, is from X to Y, or is at least Y, where X is the threshold that would be exceeded with 90% probability when the true difference between iloprost and placebo in the change in the weekly frequency of symptomatic RP attacks from baseline is 6.65, and where Y is the threshold that would be exceeded with only 2.5% probability when the true difference between iloprost and placebo in the change in the weekly frequency of symptomatic RP attacks from baseline is 0.

Note that these categories based on the thresholds X and Y should not be interpreted as providing strict decision rules, but rather as guidelines that will be factored into a broader scientific and clinical assessment of the benefit-to-risk profile of IV iloprost. This broader assessment will include consideration of safety, supportive efficacy endpoints, and relevant information external to this study.

The decision guidelines for this study include the following:

- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is less than X, then iloprost is not plausibly more efficacious than placebo; its utility in this indication should be reconsidered unless the endpoints support further development.
- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is between X and Y, then iloprost is plausibly more efficacious than placebo.
- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is at least Y, then iloprost would be statistically significantly more effective than placebo, with the strength of evidence meeting the standard requirement of a 0.025 one-sided (0.05 two-sided) false-positive error rate.

Sample size determination

The study will enroll up to a maximum of 40 subjects.

If 12.0 is the standard deviation of the change from baseline in the weekly frequency of symptomatic Raynaud attacks, then with 20 patients per arm, X is 1.785 and Y is 7.438.

The operating characteristics for this 3-category decision guideline, when 12.0 is the standard deviation of the change from baseline in the weekly frequency of symptomatic Raynaud attacks and the sample size is 20 patients per arm, are as follows:

1. Regarding the false-positive error rate of the screening procedure, if IV iloprost truly provides no improvement in the change from baseline in the weekly frequency of symptomatic Raynaud attacks, then the probability of bringing IV iloprost forward to a Phase 3 study is 32%. However, there is only a 2.5% chance of reaching the false positive conclusion that IV iloprost provides a statistically significant improvement in efficacy relative to a placebo control.
2. The false-negative error rate is low. If the true difference between IV iloprost and the placebo control groups in the change from baseline in the weekly frequency of symptomatic Raynaud attacks is 6.65, then there is only a 10% chance that IV iloprost would be discarded, and thus a 90% chance that it would be evaluated in a subsequent confirmatory Phase 3 study; furthermore, the probability that IV iloprost will have a statistically significant improvement in efficacy (at one-sided $p<0.025$) relative to the placebo control is 21%.

Exploratory efficacy analysis

Descriptive analyses based on point estimates and confidence intervals will be used for exploratory endpoints.

Analysis of pharmacokinetics

The PK Population will include all subjects in the PK substudy who receive study drug and for whom at least 1 PK parameter can be determined and who have at least 1 value above the lower limit of quantification.

Descriptive statistics (sample size, mean, standard deviation, minimum, median, maximum, and coefficient of variation [CV]) will be used to summarize PK concentrations and parameters. Geometric mean and geometric CV will also be used to summarize specific parameters.

Additional PK/pharmacodynamic analysis may be performed as an exploratory analysis, if applicable.

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 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 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 signs parameters will be presented using descriptive statistics for observed values at each visit and changes from baseline, as appropriate.

DATA MONITORING COMMITTEE:

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

STEERING COMMITTEE:

The Steering Committee is 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 20 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
AUC	Area under the plasma concentration versus time curve
cAMP	Cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CHFS	Cochin Hand Function Scale
CRA	Clinical Research Associate
CV	Coefficient of variation
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
IP receptor	Prostacyclin receptor
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
mITT	Modified Intent-to-Treat
NRS	Numeric Rating Scale
PAH	Pulmonary arterial hypertension
PAOD	Peripheral arterial occlusive disease
PDE5	Phosphodiesterase-5
PICC	Peripherally inserted central catheter/line
PK	Pharmacokinetic(s)
PP	Per-Protocol
RP	Raynaud’s phenomenon
SAE	Serious adverse event
SOC	System organ class

Abbreviation	Definition
SSc	Systemic sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event

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 Raynaud's Phenomenon 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]

Raynaud's phenomenon (RP) is 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]

Raynaud's phenomenon is characterized by abnormal functioning of the cutaneous vessels involved in the thermal regulation of blood flow. The distinctive features of 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 secondary to SSc is also associated with significant disability and psychological impact.[12] In addition to pain, annoyance, and functional disability of 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 digital ulcers (DUs) and auto-amputation.

1.1.2 Digital Ulcers in Systemic Sclerosis

Digital ulcers are a frequent external manifestation of vasculopathy in SSc.[13] 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) leucocyte 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.[14]

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.[15] Ulcers can also occur over bony prominences such as proximal or metacarpophalangeal joints with well-demarcated borders and may be caused by traumatic and ischemic causes. 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.[16,17,18] A 30% annual incidence of SSc DUs has been reported in the literature, suggesting ~20,000 adult patients experience DUs secondary to SSc yearly in the United States (based on current United States Census data).[19] Of those patients who experience a DU, more than half have persistent or recurrent DUs for at least 6 months.[16,17,18,19]

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.[9,17,20,21]

1.1.3 Current Management of Raynaud's Phenomenon and Digital Ulcers in Systemic Sclerosis

Currently, there are no Food and Drug Administration (FDA) approved therapies to treat RP or DUs secondary to SSc. Management of RP 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.[22] None of these drugs are approved for SSc RP or DU in the United States.

In general, immunosuppressive therapies are not effective for vasculopathy associated with SSc, as highlighted in PAH and scleroderma renal crisis.[23]

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.[24] 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.[25,26] Iloprost is a potent prostacyclin receptor (IP receptor) agonist. Pharmacology studies have shown that iloprost increases the cyclic adenosine monophosphate

(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.[27,28,29,30,31,32]

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.[33,34] 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.[30,31] Iloprost is thought to have anti-inflammatory and immunomodulating effects. It reduces neutrophil adhesion and chemotaxis, and has been shown to down-regulate the intracellular expression of interleukin-6 and tumor necrosis factor-alpha in human monocytes.[35,36] 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.[28,32]

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.[37]

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 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.[25]

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.[38] This study demonstrated that the PK profile for iloprost in patients with renal failure, 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.[38,39]

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.[40]

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.[41,42]

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. [41]

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.[41]

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 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.[42]

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).[42]

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).[42]

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.[42]

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.[43,44,45,46,47,48]

1.3 Rationale

Intravenous iloprost has market authorization in Europe and Australia and is the standard of care treatment for RP and DUs 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 patients with symptomatic RP secondary to SSc. This Phase 2 pilot study will be piloting an initial evaluation of iloprost, testing the study endpoints and logistics of study operations that include, among other things, an electronic patient-reported outcomes (ePRO) diary for the evaluation of subject response to the treatment as well as the infusion workflow for this multiday treatment to prepare for a Phase 3 study. There are several significant feasibility challenges to studying symptomatic RP secondary to SSc. First, the population is very small,[2,49] estimated at ~70,000 adult patients with SSc in the United States (based on United States Census from 04 July 2016). For patients 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.[50] To ensure recruitment and limit the impact of seasonal variation in temperature on the incidence of attacks, this study will be conducted during the winter and spring months.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of iloprost compared to placebo on the change in the weekly frequency of symptomatic RP attacks from baseline in subjects with symptomatic RP secondary to SSc.

2.2 Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the efficacy of iloprost compared to placebo on the severity of RP attack symptoms
- 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 hand function as assessed by the Cochin Hand Function Scale (CHFS)
- To evaluate the safety and tolerability of iloprost
- 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 worst pain associated with symptomatic RP
- To evaluate the efficacy of iloprost compared to placebo on the patient assessment of overall improvement in symptomatic RP
- To evaluate the PK of iloprost in subjects with symptomatic RP secondary to SSc

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate the effect of iloprost on the symptomatic relief of RP attacks in subjects with symptomatic RP secondary to SSc. The study will be piloting an initial evaluation of iloprost, testing the study endpoints and logistics of study operations that include, among other things, an ePRO diary for the evaluation of subject response to the treatment as well as the infusion workflow for this multiday treatment. 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 enroll a maximum of 40 subjects. 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, duration, and hand function). 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.
- During the baseline ePRO diary completion period, eligible subjects must complete the daily ePRO diary for a minimum of 10 days (up to a maximum of 25 days) until the day of randomization. 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. 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 given the option to participate in a PK substudy. Subjects who participate in the substudy will provide plasma samples for PK analysis. The samples will be analyzed for iloprost concentrations using validated liquid chromatography mass spectrometry methods.

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, and subjects will receive study drug for 5 consecutive days (eg, Monday through Friday) as an IV infusion over 6 hours each day via a peripheral line (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) prior to study drug administration each day of administration. On Day 1, 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 step wise 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 iloprost at the starting dose (ie, 0.5 ng/kg/min), the infusion will be reduced to 0.25 ng/kg/min. If the dose of 0.25 ng/kg/min is not tolerated due to symptomatic hypotension or a dose-limiting adverse event occurs, the study drug will be discontinued and reinitiation of the infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be monitored 15 minutes (±5 minutes) prior to and after all dose changes. 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 infusion will be stopped until the symptoms resolve, at which point the study drug should 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 infusion period, the dose will be stopped. Subjects will be monitored for up to 1 hour after completion of study drug infusion (ie, vital signs will be obtained 15 minutes [±5 minutes] and 1 hour [±15 minutes] after completion of the infusion).

On Days 2 to 5, the infusion will be started using the highest infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in the dose. Vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion.

During the treatment period (Days 1 to 5), while subjects receive study drug, the ePRO diary will not be completed. No study assessments will be performed on the 2 days following the end of treatment (Days 6 and 7, eg, Saturday and Sunday) to allow the subject to rest and return to a schedule of normal daily living activity following the 5 days of infusions.

Subjects will be contacted via telephone on Day 8 to ensure they resume completion of the daily ePRO diary; subjects will complete the diary from Day 8 through Day 21. On Day 22, subjects will return to the clinic for post-treatment evaluations. A follow-up visit will occur 30 days after the last administration of study drug (Day 35).

Subjects who discontinue study drug early will remain in the study (unless the subject withdraws consent) and complete the daily ePRO diary from Day 8 to Day 21 including clinical laboratory assessments on the remaining missed infusion days 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 Section 9.2.6 for details.

3.2 Study Indication

The indication of this study is symptomatic RP secondary to SSc.

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. 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.
6. Subjects must be willing and able to comply with the study requirements and give informed consent for participation in the study.

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.
2. Subjects with systolic blood pressure <85 mmHg (sitting position) at screening.
3. Subjects with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 at screening as determined by the Modification of Diet in Renal Disease equation.
4. Subjects with Child-Pugh Class B or Class C liver disease or an alanine aminotransferase and/or aspartate aminotransferase value >3 × the upper limit of normal at screening.
5. Subjects with gangrene, DU infection, or requirement of cervical or digital sympathectomy within 30 days of screening.
6. Subjects with intractable diarrhea or vomiting.
7. Subjects with a risk of clinically significant bleeding events including those with coagulation or platelet disorders.
8. Subjects with a history of major trauma or hemorrhage in the past 4 weeks.

9. Subjects with clinically significant chronic intermittent bleeding such as active gastric antral vascular ectasia or active peptic ulcer disease.
10. Subjects who have had any cerebrovascular events (eg, transient ischemic attack or stroke) within 6 months of screening.
11. 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.
12. Subjects with acute or chronic congestive heart failure (New York Heart Association Class III [moderate] or Class IV [severe]).
13. Subjects with a history of life-threatening cardiac arrhythmias.
14. Subjects with a history of hemodynamically significant aortic or mitral valve disease.
15. Subjects with more than mild restrictive or congestive cardiomyopathy uncontrolled by medication or implanted device.
16. Subjects with known pulmonary hypertension, PAH, or pulmonary veno-occlusive disease.
17. 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).
18. Subjects with a history of cervical or digital sympathectomy within 6 months of screening.
19. Subjects with scleroderma renal crisis within 6 months of screening.
20. Subjects with a concomitant life-threatening disease with a life expectancy <12 months.
21. 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.
22. 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.
23. Subjects must not initiate dosing of oral, topical, or IV vasodilators (eg, calcium channel blockers, PDE5 inhibitors [eg, sildenafil, tadalafil, or vardenafil], nitrates, and fluoxetine), or if currently receiving any vasodilator, must have been stably medicated (no dose adjustments) for at least 2 weeks prior to screening.
24. Subjects with any history of acetaminophen intolerability (eg, allergic reaction to acetaminophen).
25. Subjects with any malignancy that requires treatment during the study period, that has required treatment within 1 year of screening, or that is currently not in remission.
26. Subjects who have used any investigational medication or device for any indication within 30 days or 5 half-lives (whichever is longer) of screening.

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 which 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

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 including clinical laboratory assessments on the remaining missed infusion days 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

In circumstances where a subject discontinues the study prior to Day 21, study staff should make every effort to complete the full panel of assessments scheduled for the early termination (ET) visit. The reason for subject withdrawal from the study must be documented in the eCRF.

5 STUDY TREATMENTS

5.1 Treatment Groups

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 [41,42,51] and current labeling outside the United States (Ilomedin).[26]

5.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. 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. Furthermore, adverse events due to iloprost typically resolve quickly once treatment with iloprost has been stopped. However, at all times, 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 should only occur 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 study blinding for the overall study.

If the blind is broken for a subject, the subject will be encouraged to continue his/her randomized intervention 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 intervention.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Iloprost injection for IV use and matching placebo will be supplied in vials packaged in a blinded study drug kit (10 vials per kit). The iloprost and placebo vials will be identical, except 100 mcg of iloprost will be added to the active study drug vials. The 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. Proof labels, detailing actual label text, will be available in the study files.

5.5.2 Study Drug Preparation and Dispensing

Dilution of drug product for use in the infusion pump is as follows: A total of 1 mL volume (0.5 mL withdrawn from 2 vials) should be withdrawn into a sterile syringe using aseptic technique. The iloprost in the sterile syringe should be transferred to a drug reservoir containing 99 mL of sodium chloride 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

Study drug will be administered at the site by personnel who are trained on how to prepare the study drug solution, how to prepare the IV site, and how to administer the IV infusion via a peripheral line or a PICC using an infusion pump. Prior to the first 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. (Note: In some instances where the site chooses to use a PICC, it may be necessary to confirm placement of the PICC with an x-ray). When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment. 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 an IV infusion over 6 hours each day via a peripheral line (NovaCath Integrated IV Catheter System) or a PICC using an infusion pump.

Prior to study drug administration, subjects will be premedicated with a single dose of 2 acetaminophen extended-release tablets, 650 mg (each).

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

<u>First infusion</u>

On Day 1, 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 step wise 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 iloprost at the starting dose (ie, 0.5 ng/kg/min), the infusion will be reduced to 0.25 ng/kg/min. If the dose of 0.25 ng/kg/min is not tolerated due to symptomatic hypotension or a dose-limiting adverse event occurs, the study drug will be discontinued and reinitiation of the infusion can be attempted after the event has resolved or been treated. Blood pressure and heart rate will be monitored 15 minutes (±5 minutes) prior to and after all dose changes. 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 infusion will be stopped until the symptoms resolve, at which point the study drug should 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 infusion period, the dose will be stopped. Subjects will be monitored for up to 1 hour after completion of study drug infusion (ie, vital signs will be obtained 15 minutes [±5 minutes] and 1 hour [±15 minutes] after completion of the infusion).

Infusions 2 to 5

On Days 2 to 5, the infusion will be started using the highest infusion rate tolerated on the previous day without up- or down-titration, unless the subject does not tolerate the infusion or adverse events occur that cannot be tolerated by the subject and necessitate a reduction in the dose. Vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion.

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	0.5 ng/kg/min	Reduce the dose to 0.25 ng/kg/min if the subject does not tolerate the 0.5 ng/kg/min starting dose.
Up-titration (±5 minutes)	30 min; Day 1	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	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	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 (Hours 2 to 6)	2.0 ng/kg/min, or highest tolerated dose	Reduce dose in a step-wise manner if the subject experiences dose-limiting adverse events.
Maintenance	Days 2 to 5	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 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 high tolerated dose. A lower starting dose may be initiated on Day 3 to Day 5 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.

5.5.3.1 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 step-wise manner as described in Table 1.

5.5.4 Treatment Compliance

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

5.5.5 Storage and Accountability

The fully diluted drug product, ready for use, can be used immediately as a 6-hour continuous infusion with an infusion pump per the conditions of use as outlined in the Infusion and/or Pharmacy Manual. The Day 1 dose preparation should not occur until randomization on Day 1.

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. 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 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.

5.6.3 Allowed 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.

5.6.4 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:

- Premedicated 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

Written informed consent for the study will be obtained from all subjects before any protocol-specific procedures are carried out. See Section 11.3 for details on informed consent.

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, duration, and hand function). 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:

- Obtain signed informed consent form (ICF).
- 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 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).
- Perform urine pregnancy test on women of childbearing potential.
- Distribute ePRO diary.
- Complete the daily ePRO diary.
  - Note: Completion of the daily ePRO diary begins the day after signing informed consent.
- Assess adverse events.
- Record prior/concomitant medications.

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

During the baseline ePRO diary completion period, eligible subjects must complete the daily ePRO diary for a minimum of 10 days (up to a maximum of 25 days) until the day of randomization. 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. 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 Treatment Period (Days 1 to 5 [Visits 2 to 6])

Eligible subjects will return to the site for study drug infusion on 5 consecutive days.

6.3.1 Day 1 (Visit 2)

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

- Assess inclusion/exclusion criteria.
  - Note: 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.
- Obtain weight.
- Obtain vital signs (heart rate and blood pressure).
  - Note: Vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion.
  - Note: The arm used for IV infusion should not be used for blood pressure monitoring.
  - Note: Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) prior to study drug administration.
- Perform urine pregnancy test on women of childbearing potential prior to study drug administration.
- Contact the IRT system to randomize the subject and obtain study drug assignment.
- Premedicate with a single dose of 2 acetaminophen extended-release tablets, 650 mg (each), 15 to 60 minutes prior to study drug administration.

- Insert NovaCath Integrated IV Catheter System or PICC.
    - Note: Prior to the first 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. (Note: In some instances where the site chooses to use a PICC, it may be necessary to confirm placement of the PICC with an x-ray.) When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment.
- Prepare and administer study drug infusion. See Section 5.5.3.
- Assess adverse events.
- Record concomitant medications.

6.3.2 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 measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion.
    - Note: The arm used for IV infusion should not be used for blood pressure monitoring.
    - Note: Subjects must have a systolic blood pressure ≥85 mmHg (sitting position) prior to study drug administration each day of study drug administration.
- Collect blood samples for PK analysis for subjects participating in the PK substudy on Day 2 only at the time points indicated in Section 7.3. The arm used for IV infusion should not be used to draw blood samples.
- On Day 5 only, perform clinical laboratory assessments (chemistry and hematology) 1 hour postinfusion (within 45 minutes to 3 hours postinfusion is allowed). The arm used for IV infusion should not be used to draw blood samples.
- Premedicate with a single dose of 2 acetaminophen extended-release tablets, 650 mg (each), 15 to 60 minutes prior to study drug administration.
- Administer study drug infusion. See Section 5.5.3.
- Assess adverse events.
- Record concomitant medications.

6.4 Post-Treatment Period (Days 8 and 22 [Visits 7 and 8])

6.4.1 Day 8 (Visit 7) – Telephone Call

The following procedures will be performed via the telephone call on Day 8 (Visit 7):

- Remind subjects to resume completion of the daily ePRO diary. Subjects will complete the diary from Day 8 to Day 21.
- Assess adverse events.
- Record concomitant medications.

6.4.2 Day 22 (Visit 8)

The following procedures will be performed at Day 22 (+5 days) (Visit 8):

- Obtain vital signs (heart rate and blood pressure).
- Assess DUs.
  - Note: Investigator assessment of the DU will consist of location, status, and healing.
- Assess adverse events.
- Record concomitant medications.

6.5 Follow-up Visit (Day 35 [Visit 9])

The following procedures will be performed at the follow-up visit (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).
- Assess DUs.
  - Note: Investigator assessment of the DU will consist of location, status, and healing.
- Assess adverse events.
- Record concomitant medications.

6.6 Early Termination Visit and Withdrawal Procedures

In circumstances where a subject discontinues the study prior to Day 21, 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 subject's withdrawal from the study.

7 EFFICACY AND PHARMACOKINETIC ASSESSMENTS

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoint

The primary efficacy parameter is the change in the weekly frequency of symptomatic RP attacks from baseline.

7.1.2 Exploratory Efficacy Endpoints

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

- Severity of RP attacks as determined by the severity of RP attack symptoms (pain, numbness, tingling, and/or discomfort) (using a Numeric Rating Scale [NRS])
- Raynaud's Condition Score
- Hand function as assessed by the CHFS
- Duration of symptomatic RP attacks
- NRS for worst pain associated with symptomatic RP
- Patient assessment of overall improvement in symptomatic RP

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. Questionnaires allow for documentation of frequency, severity, and duration of symptomatic RP attacks, as well as assessment of hand function. Specific questionnaires include the severity of RP attack symptoms (using NRS), Raynaud's Condition Score, CHFS, and overall patient improvement.

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 Cochin Hand Function Scale

Raynaud's phenomenon attacks have a significant impact on hand function.[12] The CHFS is an 18-item self-administered instrument that assesses hand function as it relates to daily activities. The CHFS has been validated for use in subjects with SSc.[21]

7.2.2.4 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.

7.2.2.5 Overall patient improvement

At Day -1, subjects will be asked to rate their overall symptomatic RP in the last week. At Day 21, subjects will be asked to rate their overall symptomatic RP compared to the start of the study.

7.3 Pharmacokinetic Assessments

Eligible subjects will be given the option to participate in a PK substudy. Subjects who participate in the substudy will provide plasma samples for PK analysis. The samples will be analyzed for iloprost concentrations using validated liquid chromatography mass spectrometry methods. The actual PK sampling times will be captured on the eCRF. The actual dosing time will also be captured on the eCRF.

The following PK parameters will be calculated whenever possible, based on the plasma concentrations of iloprost:

- Steady state plasma concentration just before infusion is stopped
- Area under the plasma concentration versus time curve (AUC) from time of dosing to the last time point with measurable concentration
- AUC from time 0 extrapolated to infinity
- Percentage of AUC obtained by extrapolation
- Plasma terminal elimination half-life
- Plasma clearance
- Volume of distribution

Plasma PK samples will not be obtained from the arm used for IV infusion. Plasma PK samples will be obtained only from subjects in the PK substudy at the following time points:

Day 2:

- Predose (±5 minutes)
- 6 hours (±5 minutes) postdose, just before infusion is stopped
- 6 hours and 15 minutes (±5 minutes) postdose
- 6 hours and 30 minutes (±5 minutes) postdose
- 6 hours and 45 minutes (±5 minutes) postdose
- 7 hours (±5 minutes) postdose

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. During study drug infusions (Day 1 to Day 5) treatment-emergent adverse events (TEAEs) are expected (see Section 5.5.3.1). 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 at screening until Day 35, 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 screening 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 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.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

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 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 error.
- **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 performed during this study is included in Appendix B. Samples for clinical laboratories will be collected at the visits indicated in Appendix A. The arm used for 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 IV infusion should not be used for blood pressure monitoring.

On dosing days (Days 1 to 5), vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour 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 and the first in-clinic visit (Day 1) and used with the dose rate card (Appendix C) 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/alcohol 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 the end of the study (Day 22, Day 35, or ET). Investigator assessment of the DU will consist of location, status, and healing.

9 STATISTICS

9.1 Analysis Populations

9.1.1 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) Population is defined as all randomized subjects who initiate infusion of study drug. The mITT 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 mITT Population who complete at least Day 21 without any major protocol deviations. The PP Population will be used for sensitivity analyses of the primary efficacy variable.

9.1.3 Safety Population

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

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

All efficacy analyses are intended to provide an initial description of the clinical profile of iloprost and to inform the design and logistics of future studies.

9.2.1.1 Primary efficacy analysis

The baseline weekly frequency of symptomatic RP attacks is defined as the average number of weekly symptomatic RP attacks occurring during the 10- to 25-day baseline ePRO diary completion period. The double-blind weekly symptomatic RP attacks is defined as the average number of weekly symptomatic RP attacks during Days 8 to 21. The primary efficacy parameter is the change in the weekly frequency of symptomatic RP attacks from baseline (ie, the mean number of weekly symptomatic RP attacks during Days 8 to 21 compared to during the 10- to 25-day baseline ePRO diary completion period).

The primary analysis will be performed based on an analysis of covariance 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 site effect will be explored as necessary. For subjects in the mITT Population with intermittent missingness during the baseline or double-blind intervals, multiple imputation will be used assuming data are missing at random; for those subjects with truncated follow-up, methods will be used assuming missingness is not at random.

The primary analysis will be performed on the mITT Population. Sensitivity analyses for the primary endpoint will include comparable analyses performed on the PP Population.

The primary analysis is formally based on a 3-category decision guideline for future clinical study evaluation of iloprost. Specifically, the decision guideline for this study is based on whether the difference between iloprost and placebo in the mean change in the weekly frequency of

symptomatic RP attacks from baseline is less than X, is from X to Y, or is at least Y, where X is the threshold that would be exceeded with 90% probability when the true difference between iloprost and placebo in the change in the weekly frequency of symptomatic RP attacks from baseline is 6.65, and where Y is the threshold that would be exceeded with only 2.5% probability when the true difference between iloprost and placebo in the change in the weekly frequency of symptomatic RP attacks from baseline is 0.

Note that these categories based on the thresholds X and Y should not be interpreted as providing strict decision rules, but rather as guidelines that will be factored into a broader scientific and clinical assessment of the benefit-to-risk profile of IV iloprost. This broader assessment will include consideration of safety, supportive efficacy endpoints, and relevant information external to this study.

The decision guidelines for this study include the following:

- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is less than X, then iloprost is not plausibly more efficacious than placebo; its utility in this indication should be reconsidered unless the endpoints support further development.
- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is between X and Y, then iloprost is plausibly more efficacious than placebo.
- If the difference between iloprost and placebo in the mean change in the weekly frequency of symptomatic RP attacks from baseline is at least Y, then iloprost would be statistically significantly more effective than placebo, with the strength of evidence meeting the standard requirement of a 0.025 one-sided (0.05 two-sided) false-positive error rate.

The study (and other information that emerges during the conduct of this study) will provide important insights through consideration of the following:

- Estimated benefit-to-risk profile of IV iloprost
- Possible refinements in the dose/schedule of IV iloprost
- Approaches to improve adherence to the IV iloprost regimen
- Modifications to defining eligibility criteria to enhance enrichment
- Approaches to achieving timely accrual of study participants at centers with the established ability to provide high quality implementation of the study
- Modifications to the use of an electronic diary to collect patient reported outcome data

9.2.1.2 Sample size determination

The study will enroll up to a maximum of 40 subjects. Subject enrollment may be halted by the Sponsor at any time for any reason.

If 12.0 is the standard deviation of the change from baseline in the weekly frequency of symptomatic Raynaud attacks, then with 20 patients per arm, X is 1.785 and Y is 7.438.

The operating characteristics for this 3-category decision guideline, when 12.0 is the standard deviation of the change from baseline in the weekly frequency of symptomatic Raynaud attacks and the sample size is 20 patients per arm, are as follows:

1. Regarding the false-positive error rate of the screening procedure, if IV iloprost truly provides no improvement in the change from baseline in the weekly frequency of symptomatic Raynaud attacks, then the probability of bringing IV iloprost forward to a Phase 3 trial is 32%. However, there is only a 2.5% chance of reaching the false positive conclusion that IV iloprost provides a statistically significant improvement in efficacy relative to a placebo control.
2. The false-negative error rate is low. If the true difference between IV iloprost and the placebo control groups in the change from baseline in the weekly frequency of symptomatic Raynaud attacks is 6.65, then there is only a 10% chance that IV iloprost would be discarded, and thus a 90% chance that it would be evaluated in a subsequent confirmatory Phase 3 study; furthermore, the probability that IV iloprost will have a statistically significant improvement in efficacy (at one-sided $p<0.025$) relative to the placebo control is 21%.

9.2.1.3 Exploratory efficacy analysis

Descriptive analyses based on point estimates and confidence intervals will be used for exploratory endpoints.

9.2.2 Analysis of Pharmacokinetics

The PK Population will include all subjects in the PK substudy who receive study drug and for whom at least 1 PK parameter can be determined and who have at least 1 value above the lower limit of quantification.

Descriptive statistics (sample size, mean, standard deviation, minimum, median, maximum, and coefficient of variation [CV]) will be used to summarize PK concentrations and parameters. Geometric mean and geometric CV will also be used to summarize specific parameters.

Additional PK/pharmacodynamic analysis may be performed as an exploratory analysis, if applicable.

9.2.3 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 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 signs 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.

9.2.4 Interim Analysis

No interim analysis is planned for the study.

9.2.5 Data Monitoring Committee

A DMC consisting of 3 members, including 1 SSc expert and 1 prostacyclin PAH expert, will be responsible for safeguarding the interests of study subjects and for enhancing the integrity and credibility of the study. To address this mission, the DMC will have ongoing access to efficacy and safety data, and to information regarding the quality of study conduct. A separate DMC Charter will be prepared.

9.2.6 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 Steering Committee Charter will be prepared.

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 Visit 35, 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 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 given to the subject.

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.

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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**	**9**	
Time point	**Days -30 to -26**	**Days -25 to -1**	**Day 1**	**Days 2 to 5**	**Day 8**	**Day 22**	**Day 35**	
Window						**+5 days**	**+7 days**	
Informed consent	X							
Demographics	X							
Medical/surgical history[f]	X							
Inclusion/exclusion criteria	X		X[g]					
Physical examination	X							
Height and weight[h]	X		X					
Vital signs (HR and BP)	X		X[i]	X[i]		X	X	X
12-lead ECG	X							
Clinical laboratory assessments[j]	X			X[k]			X	X
PK[l]				X[m]				
Urine pregnancy test[n]	X		X[o]					
Distribute ePRO diary[p]	X							
ePRO diary completion[q]	X	X			X			X
Randomization			X[r]					
Insertion of NovaCath™ Integrated IV Catheter System or PICC[s]			X					
Premedicate with acetaminophen[t]			X	X				
Administer study drug infusion[u]			X	X				
Digital ulcer assessment[f]	X					X	X	X
Adverse events[v]	X		X	X	X	X	X	X
Prior/concomitant medication	X		X	X	X	X	X	X

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, duration, and hand function). 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. During the baseline ePRO diary completion period, eligible subjects must complete the daily ePRO diary for a minimum of 10 days (up to a maximum of 25 days) until the day of randomization. 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. 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 21, 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 to ensure they resume completion of the daily ePRO diary; subjects will complete the diary from Day 8 through Day 21.
f. 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 the end of the study. Investigator assessment of the DU will consist of location, status, and healing.
g. 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.
h. Height will be collected at screening only.
i. Vital signs will be measured prior to study drug administration and at 15 minutes (±5 minutes) prior to and after all dose changes during the infusion. Additionally, vital signs will be monitored at 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the 6-hour infusion. Subjects must have a systolic BP ≥85 mmHg (sitting position) prior to study drug administration each day of administration. The arm used for IV infusion should not be used for blood pressure monitoring.
j. Includes chemistry and hematology. The arm used for IV infusion should not be used to draw blood samples.
k. On Day 5 only, perform clinical laboratory assessments (chemistry and hematology) 1 hour postinfusion (within 45 minutes to 3 hours postinfusion is allowed).
l. Eligible subjects will be given the option to participate in a PK substudy. Subjects who participate in the substudy will provide plasma samples for PK analysis on Day 2 at the time points indicated in Section 7.3. The arm used for IV infusion should not be used to draw blood samples.
m. Day 2 only.
n. For women of childbearing potential only.
o. Prior to study drug administration.
p. 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, CHFS, and overall patient improvement.
q. Subjects will complete the daily ePRO diary during the eligibility period and baseline ePRO diary completion period as outlined above. Subjects will not complete the ePRO diary during Days 1 to 7, but will resume reporting at Day 8 and continue until Day 21. The CHFS and overall patient improvement will only be completed on Day -1 and Day 21.
r. Contact the IRT system to randomize the subject and obtain study drug assignment.
s. Prior to the first 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. (Note: In some instances where the site chooses to use a PICC, it may be necessary to confirm placement of the PICC with an x-ray). When possible, the same NovaCath Integrated IV Catheter System or PICC will be used for the 5 days of treatment.
t. Subjects will be premedicated with a single dose of 2 acetaminophen extended-release tablets, 650 mg (each), 15 to 60 minutes prior to study drug administration.
u. To be administered for 5 consecutive days (eg, Monday through Friday) as an 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. Refer to Section 5.5.3 for further details.
v. All adverse events will be collected from the time of informed consent until Day 35.

BP = blood pressure; CHFS = Cochin Hand Function Scale; DU = digital ulcer; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes; ET = early termination; HR = heart rate; IRT = Interactive Response Technology; IV = intravenous; NRS = Numeric Rating Scale; PICC = peripherally inserted central catheter/line; PK = pharmacokinetic(s); RP = Raynaud's phenomenon; SAE = serious adverse event.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	Mean corpuscular volume

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)				
	0.25 ng/kg/min	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	0.45	0.9	1.8	2.7	3.6
40 to 49.9 kg	0.6	1.2	2.4	3.6	4.8
50 to 59.9 kg	0.75	1.5	3.0	4.5	6.0
60 to 69.9 kg	0.9	1.8	3.6	5.4	7.2
70 to 79.9 kg	1.05	2.1	4.2	6.3	8.4
80 to 89.9 kg	1.2	2.4	4.8	7.2	9.6
90 to 99.9 kg	1.35	2.7	5.4	8.1	10.8
100 to 109.9 kg	1.5	3.0	6.0	9.0	12.0
If the subject weight ≥110 kg, contact the Medical Monitor to discuss the dosing strategy.					