MEDPACE
THE ADVANTAGE OF FOCUS

STATISTICAL ANALYSIS PLAN

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
Protocol Version: 4.0, 01 March 2019

Sponsor:
Eicos Sciences, Inc.
200 Four Falls Corporate Center, Suite 107
West Conshohocken, PA 19428-2958
USA
Telephone: 301-968-2390

SAP Version: 2.0, 26 June 2019

SIGNATURE PAGE

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

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature	Date
PPD Medpace, Inc.	
PPD Medpace, Inc.	
PPD Medpace, Inc.	
PPD Eicos Sciences, Inc.	
PPD Eicos Sciences, Inc.	

VERSION HISTORY

Version	Date	Description
1.0	25 MAR 2019	Original signed version
2.0	26 JUN 2019	1. Updated imputation method for primary endpoint; 2. Add imputation method for date of Systemic Sclerosis diagnosis and Raynaud's Phenomenon diagnosis.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ACE	Angiotensin-converting enzyme
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantification
BMI	Body mass index
CHFS	Cochin Hand Function Scale
ePRO	Electronic patient-reported outcomes
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NRS	Numeric Rating Scale
PGI-S	Patient Global Impression of Severity
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic
PT	Preferred Term
RP	Raynaud's Phenomenon
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SSc	Systemic sclerosis
TEAE	Treatment emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from Eicos Sciences, Inc. protocol number ES-201. If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report (CSR).

2 OVERVIEW

2.1 Objectives

The primary objectives are the following:

- To pilot the use of the electronic patient-reported outcomes (ePRO) diary for the evaluation of subject response to the treatment as well as the study drug infusion workflow for this multiday treatment.
- To assess whether there is a signal for efficacy of iloprost compared to placebo on the change in the weekly frequency of symptomatic Raynaud's phenomenon (RP) attacks from baseline in subjects with symptomatic RP secondary to systemic sclerosis (SSc).
- To provide an early assessment of intravenous iloprost safety

The exploratory objectives are to obtain preliminary evidence regarding the biological activity, efficacy, safety and tolerability of iloprost compared to placebo regarding the following measures:

- Severity of RP attack symptoms
- Raynaud's Condition Score
- Hand function as assessed by the Cochin Hand Function Scale (CHFS)
- Symptomatic RP attack duration
- Worst pain associated with symptomatic RP
- Patient assessment of overall improvement in symptomatic RP
- Pharmacokinetics (PK) of iloprost in subjects with symptomatic RP secondary to SSc

2.2 Trial Design

This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled study to evaluate the effect of iloprost on the relief of symptomatic RP attacks in subjects with SSc. The study will be piloting an initial evaluation of intravenous 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 study drug 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 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 a continous 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. Iloprost is associated with high rates (~>80%) of headaches during the daily infusions which is associated with reduced tolerability and may unmask subjects who are assigned to the active agent. Prior to study drug administration, subjects will be premedicated with a single dose of 2 acetaminophen extended-release tablets, 650 mg (each) to help maintain blinding and to improve study drug infusion tolerability.

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 study drug at the starting dose (ie, 0.5 ng/kg/min), the study drug 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 study drug 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 study drug 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 study drug 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 study drug infusion).

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

	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 the protocol 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 protocol 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.

3 STUDY ENDPOINTS

3.1 Efficacy Variables

3.1.1 Primary efficacy variable

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

A symptomatic RP 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.

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.

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, inclusive. 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).

If no data are reported on a particular day, the day will be excluded from the calculation of the mean. The weekly frequency is calculated by taking the sum of the attacks over the time period, divided by the number of days with data reported (including 0 attacks) in the time period, and multiplied by 7. For the double-blind weekly symptomatic RP attacks, as long as data are reported for at least one day on or between Days 8 to 21, the endpoint will be calculated in this way. For the baseline weekly frequency of symptomatic RP attacks, as long as data are reported for at least one day in the baseline ePRO completion period, the baseline will be calculated in this way.

3.1.2 Exploratory efficacy variables

Severity of RP Attack Symptoms

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

severity. If more than one symptom have the same value, the priority is pain > numbness > tingling > discomfort.

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.

The baseline and endpoint severity will be the average severity over the respective time periods.

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.

The baseline and endpoint Raynaud's Condition Score will be the average score over the respective time periods. If the score is not reported for a particular day, it will be excluded from the weekly mean derivation; no daily scores will be imputed.

Cochin Hand Function Scale

The CHFS is an 18-item self-administered instrument that assesses hand function as it relates to daily activities. Each item is scored on a 6-point Likert scale, where 0 = "Yes, without difficulty" and 5 = "Impossible". The total score is the sum of the scores from each item and ranges from 0 (without difficulty) to 90 (impossible). A higher score indicates more difficulty in hand function or greater disability. A total score will be calculated as long as 70% of the items (13 items) are completed. If any items are missing, the total score will be calculated as follows: 18 x (sum of the non-missing items) / (the number of non-missing items). Baseline will be the value collected at Day 1, and the endpoint will be the value collected at Day 21.

Duration of symptomatic RP Attacks

Subjects are asked to document the duration of each RP attack within their ePRO diaries. For each attack, the subject will record the duration in minutes. The average duration for baseline and endpoint will be calculated over the respective time periods.

Worst pain associated with symptomatic RP

Subjects will be asked to rate the severity of the worst pain using 11-point NRS within their ePRO diaries. The baseline and endpoint worst pain will be the average over the respective time periods.

Worst numbness, worst tingling and worst discomfort may also be explored in the same way.

Patient assessment of overall improvement in symptomatic RP

At Day -1, subjects will be asked to rate their overall RP in the last week using Patient Global Impression of Severity (PGI-S) score (0-10).
At Day 21, subjects will be asked to rate their overall RP compared to the start of the study, using Patient Global Impression of Change (PGI-C) score (Much worse, A little worse, No change, A little better, Much better).

3.2 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_{0-t}),
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}),
- Percentage of AUC obtained by extrapolation ($AUC_{extrap\%}$),
- Terminal elimination constant (λz),
- Plasma terminal elimination half-life ($t_{1/2}$),
- Plasma clearance (CL), calculated as Dose/AUC_{0-inf}, and
- Volume of distribution (V), calculated as Dose/(λz*AUC_{0-inf}).

3.3 Safety Variables

3.3.1 Adverse Events

Since RP attacks 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 an RP attack, that event is captured as an adverse event.

Adverse events, which include clinical laboratory test variables, are monitored and documented from the time of informed consent until Day 35.

Treatment-emergent adverse events (TEAEs) are defined as those AEs that have a start date on or after the first administration of study drug or occur prior to the first administration of study drug and worsen in severity/grade or relationship to study medication after the first administration of study drug.

Adverse events related to study drug will be those with a causality of possibly, probably, or definitely related.

Hypotension events will be considered as adverse events of special interest (AESI). Additionally, AESIs may be identified by the sponsor. AESIs will be recorded in the eCRF.

3.3.2 Safety Laboratory Evaluations

Chemistry and hematology will be assessed at Screening, Day 5, Day 35, and Early Termination Visit. A urine pregnancy test will be performed for women of childbearing potential at Screening and on Day 1 prior to study drug administration.

3.3.3 Vital Signs

Vital signs include heart rate and blood pressure and are assessed at each study visit except for Day 8.

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 study drug infusion. Additionally, vital signs will be monitored 15 minutes (±5 minutes) and 1 hour (±15 minutes) after completion of the study drug 6-hour infusion.

3.3.4 Other Safety Variables

A 12-lead ECG will be performed at screening.

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.

Height will be measured at screening only. Weight will be assessed at screening and the first in-clinic visit (Day 1).

4 ANALYSIS POPULATIONS

4.1.1 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.

4.1.2 Safety Population

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

4.1.3 Per-Protocol Population

The Per-Protocol (PP) Population will include subjects in the mITT Population who complete all scheduled study drug infusions and at least Day 21 follow-up without any major protocol deviations. The PP Population will be used for sensitivity analyses of the primary efficacy variable.

Subject data will be reviewed by the clinical team to identify exclusions from the PP Population. The list of subjects to be excluded from the PP Population will be finalized prior to database unblinding.

4.1.4 PK Population

The PK Population will include all subjects in the PK substudy who received study drug and who had at least 1 value above the lower limit of quantification.

5 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

5.1 Baseline Determination

For efficacy measurements, baselines are defined in section 3.1.

For safety measurements, unless otherwise stated, baseline will be the Day 1 value. If the Day 1 value is missing, the last measurement prior to the first administration of study drug will be the baseline value. Baseline for clinical laboratory assessments will be the value at the Screening Visit.

5.2 Evaluation of Site Effect

The site effect will be explored using a pooled site. Pooled site will be generated using the following procedure:

- Sites are sorted by the total number of mITT subjects and site ID in ascending order.
- If the first (smallest) site has less than 6 mITT subjects, it will be pooled with the next site on the sorted list (i.e., the smallest of other sites) until the pooled site has at least 6 mITT subjects.
- The previous steps are repeated for the rest of the sites until all pooled sites have at least 6 mITT subjects. If the total number of mITT subjects in the rest of the site(s) is less than 6, they will then be included in the previous pooled sites.

5.3 Handling of Dropouts and Missing Data

5.3.1 Missing or Incomplete Dates

Dates will be printed in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are missing because they are not applicable for the subjects will be output as "NA", unless otherwise specified.

For diagnosis/onset dates for Systemic Sclerosis diagnosis and Raynaud's Phenomenon diagnosis, the following imputation rules for partial dates will be used for summary (if the imputed date is later than the date of screening, the date of screening will be used instead):

- If month and year available but day missing, day will be imputed to the 15th (e.g. 06/UNK/2009 will be imputed as 06/15/2009)
- If year available but day and month missing, month and day will be imputed to July 1 (e.g. UNK/UNK/2010 will be imputed as 07/01/2010).

Adverse events with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility, e.g. the adverse event month is prior to the treatment infusion month. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months. If the causality for an adverse event is missing, the adverse event will be assumed to be related.

5.3.2 Multiple Imputation for Efficacy Endpoints

Day 8 to Day 21

An imputation model will impute missing values between Day 8 and Day 21 as follows:

- For subjects who permanently discontinue before or during Days 8 through 21, missing data after their discontinuation will be imputed. The missing data imputation method will use data from subjects in the placebo arm.
- For subjects who have only intermittent missingness of Days 8 through 21 values, no imputation will be needed.

Missing data will be imputed 100 times to generate 100 complete data sets using the regression method. For each of the 100 imputed datasets, the corresponding endpoint will be constructed, and the estimates from the 100 fitted models will be combined.

5.3.3 Missing or Incomplete PK Data

For PK substudy, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged and the scheduled time point may be used for the calculation of PK variables.

In cases of missing pre-dose, the missing components will be assumed as zero. For the other cases, the missing data will not be imputed.

If one or more below limit of quantification (BLQ) values occur before the first measurable concentration, they will be assigned a value of zero. For the BLQ values occur between measurable concentrations, they may be assigned a value of lower limit of quantification (LLOQ).

If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing) in the derivation of PK variables, statistical analysis, and the individual subject plots.

6 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

6.1 Disposition and Analysis Populations

Subject disposition will be provided for all randomized subjects. The number and percentage of subjects in each of the following disposition categories will be presented by treatment and in total:

- Subjects who are randomized,
- Subjects who received at least one infusion of study drug,
- Subjects who completed treatment per protocol and
- Subjects who completed the study.

For subjects who did not complete the study, a summary will be provided for the reason of discontinuation.

The reason for screen failure will be summarized and listed.

The number and percent of subjects in each of the analysis populations will also be provided.

The reason for exclusion from the PP population will be listed.

6.2 Protocol Deviations

Protocol deviations as defined in the Medpace Protocol Deviation Plan will be summarized for all subjects in the Randomized Population. The number and percentage of subjects with a protocol deviation will be summarized for each deviation and overall, by treatment group and total, as well as by study site. The deviations will also be listed by site and subject.

6.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be provided for the Safety Population.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for age, baseline weight, baseline body mass index (BMI), and height at Screening will be provided for each treatment group and in total. Counts and percentages of subjects for sex, ethnicity, race, smoking/alcohol use, and phosphodiesterase inhibitor use at screening will also be presented.

Medical and surgical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) by treatment group and total. Medical and surgical history will also be listed.

Digital ulcers assessed at screening will be listed and will include the location, status, and healing.

6.4 Concomitant Medications

Medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary version. Prior medications are any medications stopped prior to the first dose of study medication. Concomitant medications are any medications taken on or after the first dose of study medication. The number and percentage of subjects taking each concomitant medication will be summarized by preferred term within each anatomical therapeutic chemical (ATC) classification for the Safety Population.

Prior and concomitant medications will be listed.

6.5 Study and Drug Exposure

Study exposure will be calculated as the date of last visit – date of first dose + 1. Study exposure will be summarized with descriptive statistics by treatment group and in total.

The count and percentage of subjects receiving a study drug infusion will be summarized by day (Day 1 through Day 5) for each treatment group and in total. Additionally, the count and percentage of subjects will be summarized by the highest study drug infusion dose by day for each treatment group and in total.

7 ANALYSIS OF EFFICACY

All available efficacy data (weekly frequency of symptomatic RP attacks, severity of symptomatic RP attacks, Raynaud's Condition Score, hand function as assessed by the CHFS, the duration of symptomatic RP attacks, worst pain associated with symptomatic RP, overall improvement in symptomatic RP on a Likert scale) will be listed for the mITT Population. Efficacy measurements will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group (iloprost injection for IV use and placebo). Baseline, change from baseline, and percent change from baseline to endpoint will be presented for each efficacy measurement for the mITT Population.

7.1 Primary Efficacy Analysis

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

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

For subjects in the mITT Population with a missing primary efficacy endpoint, multiple imputation will be used.

Normality assumption of the ANCOVA model will be checked and nonparametric model may be explored if the assumption is violated.

Site effect

Pooled site will be added into the previous ANCOVA model as a factor. The treatment comparisons will be estimated with the 95% confidence interval. The patients with missing efficacy measurement will be excluded. No imputation will be used.

7.2 Exploratory Efficacy Analyses

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 overall severity of RP attack symptoms (using a Numeric Rating Scale [NRS]). The symptom (pain, numbness, discomfort or tingling) with the worst average baseline value for each patient will be used for evaluating the patient's overall severity. If more than one symptom have the same value, the priority is pain > numbness > tingling > discomfort
- 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

Descriptive statistics (n, mean, standard deviation, median, minimum, maximum) will be provided by treatment group for the exploratory endpoints on mITT Population. The same ANCOVA model utilized in the primary efficacy analyses will be used to analyze the exploratory endpoints on mITT Population. The treatment comparisons will be estimated together with the 95% confidence interval. No imputation will be needed in the exploratory efficacy analyses.

7.3 Subgroup Analysis

The primary efficacy endpoint will be summarized for the mITT population by gender (male, female). The ANCOVA model in the primary analysis will be used for each subgroup by gender Corresponding forest plot for treatment effect by gender will be provided.

Stratification factor (ie, use of phosphodiesterase inhibitors at screening) will also be explored for subgroup effects. Age and race may be also explored.

7.4 Sensitivity Analyses

The primary analysis will be repeated on the PP Population. No other sensitivity analysis will be performed.

8 PHARMACOKINETIC ANALYSIS

The PK parameters of iloprost will be calculated by standard non-compartmental methods (NCA) for PK Population. The actual collection times will be used for evaluation of PK data. The AUC before end-of-infusion will be calculated as the multiplication of the concentration just before end-of-infusion and the corresponding infusion time. AUC after end-of-infusion will be calculated using the Linear Up Log Down method (equivalent to the Linear Up/Log Down option in WinNonlin® Professional). The total AUC will be sum of the AUC before end-of-infusion and AUC after end-of-infusion.

In order to estimate first-order terminal elimination constant, λz, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points. Uniform weighting will be selected to perform the regression analysis to estimate λz. The λz will not be presented for subjects who do not exhibit a terminal elimination phase in their concentration-time profiles.

The constant λz will not be assigned if one of the following happens:

1. T_{max} is one of the 3 last data points,
2. The adjusted regression coefficient (R-squared) is less than 0.8,
3. The estimated elimination rate indicates a positive slope, or
4. The terminal elimination phase is not linear (as appears in a semi-logarithmic scale) based on visual inspection.

In the case where the percent of $AUC_{0\text{-}inf}$ extrapolated exceeds 20%, the λz will be assigned to the subject(s) but the corresponding λ_Z-related PK parameters (i.e., $t_{1/2}$, $AUC_{0\text{-}inf}$, CL, and V) will be flagged but still included to the calculation of summary statistics with an explanatory footnote. In cases where the constant λz is not assigned, the values of associated variables (i.e., $t_{1/2}$, $AUC_{0\text{-}inf}$, $AUC_{extrap\%}$, CL, and V) will not be calculated.

Descriptive statistics (n, mean, standard deviation, median, minimum, 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. The maximum plasma concentration and AUCs after dose administration for each cohort will be evaluated using a power model for dose proportionality. The power model is described below as:

$y = \alpha \times Dose^{\beta}$,

where y denotes the PK variables. Dose proportionality implies that β=1 and will be assessed by estimating β along with its 90% confidence interval. The exponent, β, in the power model will be estimated by regressing the ln-transformed PK variable on ln-transformed dose.

The power model will be fitted by restricted maximum likelihood (REML) using SAS® Proc Mixed. Both the intercept and slope will be fitted as fixed effects. The mean slope will be estimated from the power model and the corresponding 90% confidence interval calculated.

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

9 ANALYSIS OF SAFETY

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

9.1 Adverse Events

An overview of adverse events will be provided that includes the number and percentage of subjects from the Safety Population by treatment group and in total for the following categories:

- Any TEAEs,
- Maximum severity/grade of TEAEs,
- Study drug-related TEAEs,
- Maximum severity/grade of study drug-related TEAEs,
- SAEs,
- TE-SAEs,
- Study drug-related TE-SAEs,
- AESI,
- TEAEs leading to study drug discontinuation
- Study drug-related TEAEs leading to study drug discontinuation, and
- TEAEs leading to death.

Adverse events will be coded using the latest version of MedDRA. The number and percentage of subjects with AEs will be summarized by SOC and PT for each treatment group and in total for the following:

- TEAEs,
- Study drug-related TEAEs,
- SAEs,
- TE-SAEs,
- Study drug-related TE-SAEs, and
- TEAEs leading to study drug discontinuation.

The number and percentage of subjects with TEAEs will be summarized by reported maximum severity/grade for each MedDRA preferred term within system organ class for each treatment group and in total.

The number and percentage of subjects with AESIs will be summarized by preferred term within system organ class for each treatment group and in total.

All SAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death will be listed.

9.2 Clinical Laboratory Evaluations

Descriptive statistics for each chemistry and hematology parameter will be presented by treatment group for baseline, each visit, and the change from baseline.

9.3 Vital Signs

Vital signs include heart rate and blood pressure. Vital signs parameters will be summarized using descriptive statistics for each visit and time point for each treatment group. The change from baseline will also be summarized.

9.4 ECG Parameters

The overall interpretation of the ECG at Screening will be summarized with counts and percentages for each treatment group and in total. All ECG parameters will be listed.

9.5 Physical Examination

Physical examination data will be listed.

10 DATA MONITORING COMMITTEE

A DMC consisting of 3 members including an independent biostatistician, 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.

11 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.

12 INTERIM ANALYSIS

No interim analysis is planned for the study.

13 SAMPLE SIZE AND POWER CONSIDERATIONS

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

The operating characteristics for this 3-category decision guideline (please refer to the protocol), 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%.

14 PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.3 or above. All available data will be presented in subject data listings, which will be sorted by site number, unique subject identifier and where appropriate, visit number and visit/assessment date.

The programming specifications, including the mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents.