

STATISTICAL ANALYSIS PLAN

A Phase 2, Multi-Center, Open-Label, Ascending Dose Study on the Efficacy, Safety and Tolerability of Perhexiline in Patients with Hypertrophic Cardiomyopathy and Moderate-to Severe Heart Failure with Preserved Left Ventricular Function

Investigational Product: Perhexiline

Protocol Number: HML-PHX-005 (Version 11.0, 02 December 2016)

Sponsor:

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SIGNATURE PAGE

A Phase 2, Multi-Center, Open-Label, Ascending Dose Study on the Efficacy, Safety and Tolerability of Perhexiline in Patients with Hypertrophic Cardiomyopathy and Moderate-to Severe Heart Failure with Preserved Left Ventricular Function
HML-PHX-005 (Version 10.0, 12 October 2016)

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TABLE OF CONTENTS

1	Introduction	8
2	Overview	8
	2.1 Objectives.....	8
	2.1.1 Primary Objective.....	8
	2.1.2 Secondary Objectives	8
	2.2 Study Design	8
3	Analysis Variables.....	13
	3.1 Efficacy Variables.....	13
	3.1.1 Primary efficacy variable	13
	3.1.2 Secondary efficacy variables.....	13
	3.2 Safety Variables	14
	3.2.1 Adverse Events.....	14
	3.2.2 Safety Laboratory Evaluations	15
	3.2.3 Pregnancy Testing	17
	3.2.4 Vital Signs	18
	3.2.5 12-Lead ECG.....	18
	3.2.6 Physical Examination.....	20
	3.3 Pharmacokinetic Variables.....	20
	3.3.1 Concentration Data.....	20
	3.4 Baseline Variables.....	20
	3.4.1 Prior and Concomitant Medication	20
	3.4.2 Demographic Data.....	21
	3.4.3 Medical History	21
	3.4.4 Coagulation Profile.....	21
	3.4.5 CYP2D6 Screening	21
	3.5 Study Medication	21
	3.5.1 Compliance and Exposure.....	21
	3.5.2 Dose Titration.....	22
4	Analysis Populations	23
	4.1.1 Safety Population	23
	4.1.2 Modified Intention to Treat Population.....	23
	4.1.3 Completer Population.....	23
	4.1.4 Pharmacokinetic Population.....	23
5	General Considerations for Data Analysis	23
	5.1 Evaluation of Center Effect.....	24
	5.2 Assessment Windows.....	24

5.3	Handling of Dropouts and Missing Data.....	24
5.4	Other Data Handling Approaches	24
6	Analysis of Disposition and Patient Characteristics.....	25
6.1	Disposition and Analysis Populations.....	25
6.2	Eligibility Criteria and Protocol Deviations.....	25
6.3	Demographics and Baseline Characteristics	25
6.4	Concomitant Medications	26
6.5	Study Medication	26
7	Analysis of Efficacy	26
7.1	Primary Efficacy Analysis	26
7.2	Secondary Efficacy Analyses.....	27
7.2.1	Difference between Period 2 and Period 1 Change from Baseline in VO ₂ MAX.....	27
7.2.2	Change from Baseline in VO ₂ MAX at the end of Period 1.....	27
7.2.3	Change from Baseline in 6MWT at the end of Period 2	27
7.2.4	Difference between Period 2 and Period 1 Change from Baseline in 6MWT	27
7.2.5	Change from Baseline in 6MWT at the end of Period 1	28
8	Analysis of Safety.....	28
8.1	Extent of Exposure.....	28
8.2	Adverse Events.....	28
8.3	Safety Laboratory Parameters	29
8.4	HbA1c	29
8.5	Vital Signs.....	29
8.6	ECG Parameters	30
8.7	Physical Examinations	30
8.8	Pharmacokinetic Analysis.....	30
9	Data Safety Monitoring Board	30
9.1	Study Monitoring Team	30
10	Interim Snapshot Analysis.....	31
11	Sample Size and Power Considerations	31
12	Changes from Protocol-Specified Statistical Analyses	31

LIST OF ABBREVIATIONS

6MWT	Six minute walk test
ADE	Adverse device effect
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
bpm	Beats per minute
BUN	Blood urea nitrogen
CIS	<i>cis</i> -Hydroxy-Perhexiline
CPEX	Cardiopulmonary Exercise
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPK	Creatine Phosphokinase
CRO	Contract Research Organization
CYP2D6	Cytochrome P450 2D6
CRF	Case Report Form(s)
CSR	Clinical Study Report
ECG	Electrocardiogram or electrocardiographic
EM	Extensive Metabolizer
HbA1c	Hemoglobin A1c or glycosylated hemoglobin
HCM	Hypertrophic Cardiomyopathy
IM	Intermediate metabolizer
INR	International Normalized Ratio
LDH	Lactate dehydrogenase
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention to Treat
msec	milliseconds
PEX	Perhexiline
PM	Poor metabolizer
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTc	Corrected QT interval
QTcF	QT corrected according to Fridericia's formula
RBC	Red Blood Cells

SAE	Serious adverse event
SAP	Statistical Analysis Plan
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Event
TRANS	<i>trans</i> -Hydroxy-Perhexiline
ULN	Upper limit of normal
UM	Ultra-rapid metabolizer
VO ₂ MAX	Maximal oxygen consumption

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 Heart Metabolics, HML-PHX-005. This document is based on protocol version 11, 02 December 2016. If circumstances arise during the study such that more appropriate analytic procedures become available, this 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

2.1.1 Primary Objective

The primary objective of the study is to evaluate the effect of PEX on the change from Baseline of maximal oxygen consumption (VO_{2MAX}) in patients with hypertrophic cardiomyopathy (HCM) and moderate-to-severe heart failure with preserved left ventricular (LV) function following repeat dosing with PEX for 112 days.

2.1.2 Secondary Objectives

The secondary objectives of the study are to evaluate:

- The ascending dose-response effect on the change from Baseline of VO_{2MAX} in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days.
- The electrocardiographic (ECG) response, tolerability and safety of orally administered PEX in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days.

2.2 Study Design

This Phase 2, open-label, single arm study aims to confirm the optimal dosing regimen of PEX for use in a future phase 3 study. The study had planned to enroll approximately 33 patients with HCM from approximately 7-10 study sites in the US.

In the 28 days before the planned start of study dosing, each patient was to be screened for eligibility. A complete list of all eligibility criteria is available in section 4.2 and 4.3 of the study protocol.

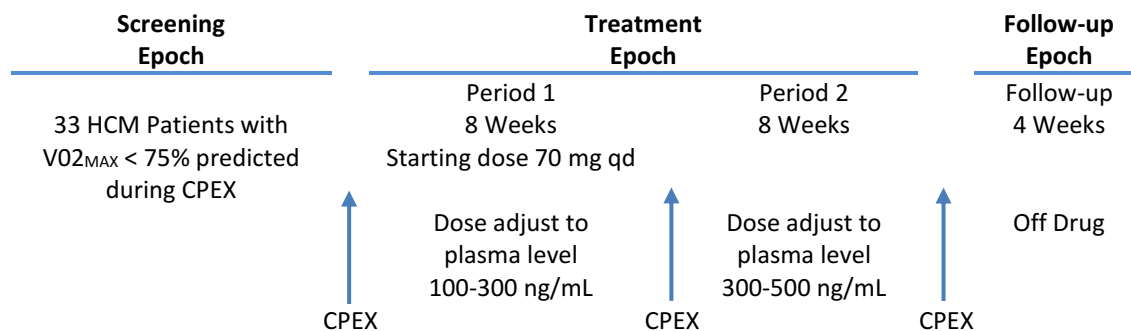
Following screening, a patient's suitability to enter the study was to be confirmed at the Baseline assessment. Confirmation would include an evaluation of the patient's Baseline 12-lead ECG by a central assessor from ECG Corelab. Study medication was only to be dispensed after confirmation of the patient's suitability to enter the study. Any delays in the central assessment of

the Baseline ECG could result in the patient having to return to the site for study drug dispensing and having a Baseline assessment split over more than one day. The day that study drug dosing commenced was to be regarded as Day 1.

Patients who met the study inclusion and exclusion criteria were to be admitted to the study on the morning of Day 1 when they were to start their open-label, study-drug dosing regimen with PEX. The first dose of study drug was to be administered under the supervision of the study-site staff. Subsequent daily dosing throughout the dosing period of 112 days was to be done in the evening (preferably between 8-11p.m.).

CPEX was to be completed at Baseline (before the start of study-drug dosing on Day 1), and again at the end of Periods 1 and 2. After completion of study drug dosing (end of Period 2) there was to be a follow-up safety observation period before patients completed the study.

Figure 1 Outline Study Design



If a patient chose to withdraw from the study during the dosing phase, the site was to attempt to complete the following assessments:

- CPEX Testing and 6-Minute Walk Test
- vital signs and 12-Lead ECG
- Blood sample for PEX, CIS and TRANS, full blood cell count, routine safety serum chemistry tests, serum pregnancy test and serum levels of hemoglobin A1c
- Concomitant Medications and AEs
- Study drug accountability and treatment compliance

The total study duration for safety and efficacy follow-up was to be 24 weeks.

Complete Schedule of Protocol Activities	Screening [A]	Baseline Week 1 (Day 1) [A]	After Completion of Week 1 (Day 8)	After Completion of Weeks 2, 4, 6, 8, 10, 12 & 14 (Days 15, 29, 43, 57, 71, 85 & 99)	End of Treatment After Completion of Week 16 (Day 113)	Final Visit Week 20 (Day 140)
Time window permitted	-28 days	n.a.	±1 Day	±1 Day for Week 2 ±3 Days for other timepoints	±3 Days	±3 Days
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X [B]				
Demographics, Medical Hist, Physical Exam	X					
12-lead ECG [C, D]	X	X [E]		X	X	X
CPEX Testing [D, F]	X	X [G]		After End of Week 8	X [H]	
Weight	X	X		After End of Week 8	X	X
Vital Signs [I]	X	X		X	X	X
Laboratory Procedures [J]						
Serum Pregnancy Test [K]	X					X
Urine Pregnancy Test [J, K]		X				
Serum Chemistry [L]	X			After End of Week 8	X	X
Complete Blood Count [M]	X				X	X
Coagulation Tests [N]	X					
CYP2D6 Screening [O]	X					
Plasma PEX, CIS & TRANS [P]			X	X	X	X
Biomarkers (Hemoglobin A1c)	X			After End of Week 8	X	X
Study Dosing & Dose Adjustment as per Guidelines & Algorithm [Q]		Start at 70 mg [R]	X	X		
Review of Dosing Instructions and Adherence to Dosing		X	X	X	X	
Adverse Event Assessment [S]	X	X	X	X	X	X
Adverse Device Effect Assessment [T]			X	X	X	X
Concomitant Medication Review [U]	X	X	X	X	X	X
6 Minute Walk Test (6MWT) [D]		X		After End of Week 8	X	

Footnotes:

- A. The Screening visit was to be performed within 28 days prior to dosing.
- B. Entry criteria was to be evaluated: Baseline CPEX compared to Screening CPEX, and ECG exclusion criteria
- C. ECGs were to be done in triplicate prior to blood draws when possible and obtained after the patient had been resting comfortably in a supine position for approximately 10 minutes.
- D. ECGs were to be performed first, the CPEX second, and the 6MWT last during any visit.
- E. The Baseline ECG were not to meet any of the exclusion criteria detailed in section 4.3.2; this was to be confirmed by the central ECG reader before study drug could be dispensed to the patient
- F.
 - i All CPEX test results were to be reviewed by the centralized CPEX assessor for compliance with prospectively defined CPEX test acceptance criteria
 - ii The Screening CPEX was to be performed to show that patient was able to perform exercise testing but unable to exceed 75% of the predicted age-adjusted maximum level (as determined by VO_{2MAX}).
- G.
 - i A valid Screening CPEX was to be confirmed by the centralized CPEX assessor before the Baseline CPEX was done
 - ii The Baseline VO_{2MAX} was not to vary from the screening VO_{2MAX} by more than $\pm 20\%$ (with the screening test being the reference); this was to be calculated by study-site staff in order to allow a decision on patient inclusion in the study during the Baseline site-visit
- H. If the centralized CPEX assessor deemed the EOT CPEX test to be invalid, the patient may be required to return for a repeat test.
- I. Heart rate and blood pressure assessed in the seated position after 5 minutes of rest.
- J. Samples for laboratory assays were to be sent to the central lab for analysis (with the exception of the urine pregnancy test at Baseline which were to be performed locally).
- K. Females of child bearing potential. (Eligible patients were to be advised to use an adequate contraceptive method.)
- L. Serum Chemistry: sodium, potassium, bicarbonate, chloride, calcium, phosphorus, glucose, creatinine, BUN, CPK, uric acid, albumin, total protein, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), LDH, total cholesterol
- M. CBC: hemoglobin, hematocrit, RBC, MCV, MCH, MCHC, RDW, WBC count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils), platelets.
- N. Coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- O. CYP2D6 Poor Metabolizer status as defined by the CPIC guidelines.
- P. All determinations of systemic blood levels of PEX, CIS, and TRANS were to be measured using the PEX-CIS assay. Blood sampling for determination of PEX, CIS and AS was to be scheduled approximately 12h after dosing on the previous study day. Results for PEX and CIS were to be reported to the study sites for confirmation of a patient's phenotypic status for PEX metabolism and for dose-adjustment decisions.
- Q. Patients were to be provided with up to 4 weeks' worth of study medication at the Baseline, Week 2, 4, 6, 8, 10, 12 and 14 study visits
- R. Study-drug was to be dispensed once the ECG Corelab confirmed that the Baseline ECG met the entry criteria. The first study-drug dose was to be administered under the supervision of the study-site staff once the study-site staff confirmed that the Baseline VO_{2MAX} was within $\pm 20\%$ of the Screening CPEX.

Note:

- i. If for any reason the ECG Corelab was not able to immediately confirm the ECG outcome, the patient was to return home without receiving any dispensed study-drug. In such cases, once the ECG Corelab confirmation became available the patient was to return to the site to collect the study drug supply. The patient was then to commence study-drug dosing (defined as Day 1).
 - ii. All Baseline ECG confirmations were to be received by study sites from the ECG Corelab within a maximum of 48h.
 - iii. Before dosing commenced; if the centralized CPEX assessor confirmed the Baseline VO_{2MAX} was not within $\pm 20\%$ of the Screening CPEX then the patient was not to enter the study
 - iv. Before dosing commenced; if the centralized CPEX assessor confirms an invalid Baseline VO_{2MAX} the patient was to be invited to repeat the Baseline CPEX test within the 28-day period allowed between Screening and the start of study-drug dosing
 - v. After dosing commenced; if the centralized CPEX assessor deems the Baseline CPEX test to have been invalid or not within $\pm 20\%$ of the Screening CPEX then the patient was to remain in the study and the patient's Baseline CPEX result will be taken as the valid Baseline result
 - vi. All Baseline CPEX confirmations were to be received by study sites from the centralized CPEX assessor within a maximum of 48h.
- S. AEs were to be documented and recorded at each visit. All AEs (serious and non-serious, and related and non-related) were to be documented and recorded through the Follow-Up visit. Patients were to be followed for AEs until the final required protocol visit or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable).
- T. If an AE was determined to have been the result of a PEX-CIS Assay abnormality (e.g., false positive, false negative, measurement error), it will be deemed an ADE for the purpose of device reporting.
- U. Concomitant Medications was to be collected and recorded at each visit. All concomitant medications received up to and including 30 days prior to the start of study medication through the Follow-Up visit were to be recorded

3 ANALYSIS VARIABLES

3.1 Efficacy Variables

3.1.1 Primary efficacy variable

The primary endpoint of the study is the change from Baseline of VO₂MAX at the end of Period 2. Cardio-Pulmonary Exercise Testing (CPEX) was to be performed at Screening and repeated at Baseline (Day 1), at the end of Period 1 (Week 8) and the end of Period 2 (Week 16). Details of the exercise test performed and the resultant VO₂MAX evaluations were to be reported in the CRF. For entry into the study, the patient's VO₂MAX at Screening could not exceed 75% of the predicted age-adjusted value and the VO₂MAX at Baseline (Day 1) could not be outside $\pm 20\%$ of the Screening VO₂MAX value (if the centralized CPEX assessor deems the Baseline CPEX test is not within $\pm 20\%$ of the Screening CPEX after dosing with study medication has already commenced, the subject will remain in the study and the subject's Baseline CPEX result will be taken as the valid Baseline result, unless it is deemed invalid or if the CPEX test was administered after the start of study medication).

CPEX reports were to be validated by a centralized CPEX assessor.

The VO₂MAX at the Day 1 assessment will be regarded as Baseline unless the CPEX was reported to have been assessed after the start of study medication. If this situation arises, the VO₂MAX from Screening will be regarded as Baseline. Changes and percent changes from Baseline to the end of Period 2 VO₂MAX value will be derived:

$$\text{Change at Period 2} = \text{Period 2 VO}_{2\text{MAX}} - \text{Baseline VO}_{2\text{MAX}}$$

$$\text{Percent Change at Period 2} = (\text{Period 2 VO}_{2\text{MAX}} - \text{Baseline VO}_{2\text{MAX}}) / \text{Baseline VO}_{2\text{MAX}}$$

If the patient withdraws from the study early, but provides an unscheduled or early end-of-Period 2 VO₂MAX assessment then this VO₂MAX assessment will be used in the derivation of efficacy endpoints. Only if the unscheduled or early end-of-Period 2 VO₂MAX assessment is within ± 7 days of the intended target assessment (Period 2 target = Day 113), relative to Day 1, will the derived change in VO₂MAX be used in the primary analysis using the Completer Population (see section 7.1, below).

3.1.2 Secondary efficacy variables

Change from Baseline in VO₂MAX to end of Period 1 compared to Period 2 and Change from Baseline in VO₂MAX to end of Period 1

The change and percent change from Baseline in VO₂MAX to the end of study-drug dosing Period 1 and Period 2 will be derived:

Change at Period 1 = Period 1 VO₂MAX – Baseline VO₂MAX

Percent Change at Period 1 = (Period 1 VO₂MAX – Baseline VO₂MAX)/Baseline VO₂MAX

Change at Period 2 = Period 2 VO₂MAX – Baseline VO₂MAX

Percent Change at Period 2 = (Period 2 VO₂MAX – Baseline VO₂MAX)/Baseline VO₂MAX

As in the primary endpoint, the VO₂MAX at the Day 1 assessment will be regarded as Baseline.

In the same way as for the primary endpoint, if the patient withdraws from the study early, but provides an unscheduled or early end-of-Period 1 or end-of-Period 2 VO₂MAX assessment then this VO₂MAX assessment will be used in the derivation of efficacy endpoints. Only if the unscheduled or early end-of-Period 1 or end-of-Period 2 VO₂MAX assessment is within ±7 days of the intended target assessment (Period 1 target = Day 57; Period 2 target = Day 113), relative to Day 1, will the derived change in VO₂MAX values be used in the principal analysis of this endpoint using the Completer Population (see sections 7.2.1 and 7.2.2).

6 Minute Walk Test

A 6-minute walk test (6MWT) was to be performed at the Baseline (Day 1) assessment and repeated at the end of Period 1 (Week 8) and the end of Period 2 (Week 16).

The change and percent change from Baseline at the end of study-drug dosing Period 2 and the change and percent change from Baseline at the end of study-drug dosing Period 1 will be derived, taking the Day 1 assessment as Baseline.

If a patient withdraws from the study early, but provides an end-of-Period 1 or end-of-Period 2 assessment then this assessment will be used in the derivation of the efficacy endpoints. As in the analysis of the primary endpoint, only if the unscheduled or early end-of-Period 1 or end-of-Period 2 6MWT assessment is within ±7 days of the intended target assessment (Period 1 target = Day 57; Period 2 target = Day 113), relative to Day 1, will the derived change in 6MWT values be used in the principal analysis of this endpoint using the Completer Population (see section 7.2.3 and 7.2.4).

3.2 Safety Variables

3.2.1 Adverse Events

Adverse events (AEs) were to be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. The protocol (section 7.1) defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

The following information was to be captured for all AEs:

- Start date

- End date (or ongoing status, if ongoing at the end of study)
- Outcome (Recovered/Resolved; Recovered/Resolved with Sequelae; Recovering/Resolving; Not Recovered/Not Resolved; Fatal; Unknown)
- Relationship to study treatment (Definitely Related; Probably Related; Possibly Related; Unrelated)
- Action taken with study treatment (Drug Withdrawn; Drug Interrupted; Dose Reduced; Dose Not Changed; Dose Increased; Other; Not Applicable)
- Any other action taken (No; Yes)
- Caused study discontinuation (No; Yes)
- Severity (Mild; Moderate; Severe)
- Seriousness (No; Yes)
- Adverse Device Effects (No; Yes)
- Is the event an overdose (No; Yes)
- Is the event a cancer event (No; Yes)

If the investigator deemed the AE to be serious, the reason(s) for being considered serious would be recorded in the eCRF.

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

A treatment-emergent adverse event (TEAE) is defined as any AE with a recorded start date on or after the date of the first dose of study medication. Treatment emergent (TE) status of AEs with a partial start date will be determined using available incomplete date information. For example, if the AE has a missing day field but the non-missing month and year fields place the start of the AE after the start of study medication, then the AE will be designated TE. For AEs where the available partial date information is inconclusive (for example, missing day but available month and year are equal to the month and year of start of study medication) then the AE will be classified as TE. In particular, AEs with a completely missing start date will be assumed to be TE (unless the AE stop date places the AE prior to starting treatment).

TEAEs will be split further according to whether the AE start date occurred during Period 1 or Period 2 of the Treatment Epoch, or during the Follow-up Epoch.

3.2.2 Safety Laboratory Evaluations

Serum Chemistry

Blood samples were to be obtained for routine serum chemistry safety tests at Screening, and repeated at the end of Period 1 (Week 8), at the end of Period 2 (Week 16) and at Follow-up (planned for Week 20) visit. The following safety chemistry parameters levels were to be assessed by a central laboratory:

- Sodium [mmol/L]
- Potassium [mmol/L]
- Bicarbonate [mmol/L]
- Chloride [mmol/L]
- Calcium [mmol/L]
- Phosphorus [mmol/L]
- Glucose [mmol/L]
- Creatinine [μ mol/L]
- BUN [mmol/L]
- Creatine Kinase [U/L]
- Uric acid [μ mol/L]
- Albumin [g/L]
- Total protein [g/L]
- AST (SGOT) [U/L]
- ALT (SGPT) [U/L]
- Alkaline phosphatase [U/L]
- Total bilirubin [μ mol/L]
- Lactate dehydrogenase (LDH) [U/L]
- Total cholesterol [mmol/L]

The Baseline value for each parameter will be identified as the last assessment value taken prior to the start of study medication. For most parameters and most patients, this will be taken as the Screening assessment, however, if any patients have an unscheduled assessment after their Screening assessment and before starting study medication, this will be used.

The change and percentage change from Baseline to the end of Period 1 (Week 8), end of Period 2 (Week 16) and Follow-up (Week 20) assessment will also be derived.

For transaminases, any assessments that are outside the following upper limit of normal (ULN) threshold multiples will be identified electronically in the analysis dataset:

AST (SGOT) [U/L]	> 3 x ULN
ALT (SGPT) [U/L]	> 3 x ULN
Alkaline phosphatase [U/L]	> 2.5 x ULN
Total bilirubin [mg/dL]	> 2 x ULN

Complete Blood Count

Blood samples were to be obtained for complete blood count at Screening, and repeated at the end of the study, Period 2 (Week 16), and Follow-up (Week 20) assessment. The following parameters levels were to be assessed by a central laboratory:

- Hemoglobin [g/L]
- Hematocrit [%]
- Red blood cells (RBC) [$10^{12}/L$]
- MCV [fL]
- MCH [pg]
- MCHC [g/L]
- White blood cells [$10^9/L$]
- Neutrophils [$10^9/L$ and %]
- Lymphocytes [$10^9/L$ and %]
- Monocytes [$10^9/L$ and %]
- Eosinophils [$10^9/L$ and %]
- Basophils [$10^9/L$ and %]
- Platelets [$10^9/L$]

The Baseline value for each parameter will be identified as the last assessment value taken prior to the start of study medication. For most parameters and most patients, this will be taken as the Screening assessment, however, if any patients have an unscheduled assessment after their Screening assessment and before starting study medication, this will be used. The change and percentage change from Baseline to the end of Period 1 (Week 8), end of Period 2 (Week 16), and Follow-up (Week 20) assessment will also be derived.

Biomarker Hemoglobin A1c Testing

Sampling for biomarker levels of hemoglobin A1c was to be performed at Screening, and repeated at the end of the Period 1 (Week 8), at the end of Period 2 (Week 16), and at the Follow-up (Week 20) assessment.

- Hemoglobin A1c (HbA1c) [%]

The Baseline HbA1c value will be identified as the last assessment value taken prior to the start of study medication. For most patients, this will be taken as the Screening assessment, however, if any patients have an unscheduled assessment after their Screening assessment and before starting study medication, this will be used. The change and percentage change from Baseline to the end of Period 1 (Week 8), end of Period 2 (Week 16) and Follow-up (Week 20) assessment will also be derived.

3.2.3 Pregnancy Testing

A serum pregnancy test was to be performed at Screening and Week 20, and a urine pregnancy test was to be performed at Baseline (Day 1).

3.2.4 Vital Signs

Vital signs were to be recorded at Screening and repeated at Baseline (Day 1), and at the study visit at Week 2, 4, 6, and 8 during Period 1 and at Week 10, 12, 14, and 16 during Period 2 and at the Follow-up (Week 20) assessment. Vital signs assessments would include: height (at Screening only), weight (at Screening, Week 8, 16, and 20 only), systolic and diastolic blood pressure, heart rate and temperature (all assessments).

The screening weight value will be taken as Baseline. The Baseline value for each of the remaining recurring vital signs parameters will be identified as the last assessment value taken prior to the start of study medication. For most parameters and most patients, this will be taken as the Baseline (Day 1) assessment, however, if any patients have an unscheduled assessment after their Day 1 assessment and before starting study medication, this will be used; or if a patient has a missing Day 1 value, then their Screening value will be used. The change and percentage change from Baseline to each post-Baseline assessment will be derived for each vital signs parameter.

Values from each assessment or changes from Baseline that are outside the thresholds presented below will be identified in an analysis dataset by electronic programming for reporting purposes.

	Threshold
Systolic BP (mmHg)	≥ 160
Diastolic BP (mmHg)	≥ 100
Heart Rate (bpm)	≤ 50
Heart Rate (bpm)	≥ 120
Change in Systolic BP (mmHg)	≥ 30
Change in Diastolic BP (mmHg)	≥ 30
Change in Heart Rate (bpm)	≥ 30

3.2.5 12-Lead ECG

A 12-lead ECG was to be performed at Screening, and repeated at Baseline (Day 1), and at the scheduled visits at Week 2, 4, 6, and 8 during Period 1 and at Week 10, 12, 14, and 16 during Period 2, and the Follow-up (Week 20) assessment.

At each ECG assessment, three traces were to be performed, each containing three complexes (of a single beat). From each complex, the following ECG parameters were to be reported by the ECG Corelab:

- RR [ms]
- PR [ms]
- QRS [ms]
- QT [ms]
- T-Peak (TP) [ms]
- T-wave amplitude (Tamp) [mV]
- J-Tpeak
- Tpeak-Tend

From the exported parameters listed above, the following additional parameters will be derived by statistical programming for each available complex:

$$QTcF = QT / \sqrt[3]{RR}$$

$$JTcF = QTcF - QRS$$

For each ECG parameter (RR, PR, QRS, QT, TP, T-wave, QTcF, JTcF) within each trace, a mean of the three complexes was to be derived. A mean of the three traces was then to be derived from the mean of the three complexes. This mean (of traces) of the mean (of complexes) will be presented in the ECG listings and used in the ECG descriptive statistics and analyses. Individual complexes will be available in the SDTM and ADaM datasets only and will not be presented in study listings.

ECG Corelab will also provide a Global RR value for the whole ECG trace. From this Global RR, statistical programming will derive ECG heart rate:

$$HR = 60 / [Global\ RR / 1000]$$

In addition to the above measurements, ECG Corelab was to provide an overall interpretation of the ECG. ECG traces were also to be made available to the study site Investigator, who would provide their overall interpretation and an indication of the clinical significance of any findings.

Changes in each of the ECG parameters from Baseline to each post-Baseline will be derived. The last ECG assessment prior to starting study medication will be regarded as Baseline (this will usually be the Day 1 assessment).

Assessment values or changes from Baseline that are outside the thresholds presented below will be identified in an analysis dataset by electronic programming for reporting purposes.

	Thresholds
QT (msec)	>450 >480 >500
Changes in QT (msec)	>30 >60
QTcF (msec)	>450 >480 >500
Changes in QTcF (msec)	>30 >60

3.2.6 Physical Examination

A physical examination was to be performed at Screening.

3.3 Pharmacokinetic Variables

3.3.1 Concentration Data

A plasma sample for analysis of PEX, CIS and TRANS was to be obtained approximately 12 hours after dosing on the previous study day at scheduled visits at Week 1, 2, 4, 6, 8 from Period 1 and at Week 10, 12, 14, 16 from Period 2 and at Week 20, Final visit.

On the morning of Week 1 (after completion of a minimum of 6 days of dosing), patients were to provide a blood sample for the measurement of PEX, CIS and TRANS. These will be used to identify phenotypic Poor Metabolizer (PM), ie a patient whose CIS:PEX ratio is <0.4. Based on these results, PM patients will be immediately withdrawn from study-drug dosing.

On the morning of Week 2 (after completion of a minimum of 13 days of dosing), patients were to provide a blood sample for PEX, CIS and TRANS evaluation. Patients with a CIS:PEX ratio <0.4 will be discussed with the Medical Monitor.

At all assessments from Week 2 onwards, dose adjustment will be considered based on determination of plasma PEX levels.

3.4 Baseline Variables

3.4.1 Prior and Concomitant Medication

Prior medications, received up to and including 30 days prior to the start of study medication, and concomitant medications received at any point during the study were to be recorded in the CRF.

Some medications or drug classes are known to have potential for adverse interactions with PEX. Although, their use was permitted in the protocol, they were to be considered with caution. A list of these agents is included in Appendix A of the protocol.

The original terms recorded on the patient's eCRF for concomitant medications will be standardized by assigning preferred terms from the International Non-Proprietary Name drug terms and procedures dictionary for treatments and surgical and medical procedures.

Medication start and stop dates, recorded on the eCRF, will be used to determine programmatically whether the medications were (i) started and stopped prior to the study period or (ii) used during the study period. To implement this, any medication with a reported stop date that is before the first dose of any study medication will be regarded as a (i) Prior medication. Medications that start before the first dose of any study medication and are continued into the study or start on or after the first dose of any study medication or will be regarded as (ii) Concomitant medication.

3.4.2 Demographic Data

Demographic data, including date of birth, age, sex, race, ethnicity and child bearing potential, were to be recorded at Screening.

3.4.3 Medical History

Medical history, including event or diagnosis description, start and stop dates or ongoing status were to be recorded at Screening. All terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

3.4.4 Coagulation Profile

A coagulation profile was to be performed at Screening only:

- prothrombin time (PT) [Sec]
- partial thromboplastin time (PTT) [Sec]
- international normalized ratio (INR) [None]

3.4.5 CYP2D6 Screening

CYP2D6 was to be assessed at Screening to identify Poor Metabolizer (PM) status, which was to be defined according to the CPIC guidelines.

Any incidences of polymorphisms will be identified and reported under the header CYP2D6 Genotype.

3.5 Study Medication

3.5.1 Compliance and Exposure

Patients were to complete two sequential, 8-week study drug-dosing periods. At the start of Period 1, patients were to commence treatment on 70 mg PEX daily with subsequent dose titration to a plasma level of 100-300 ng/ml (or ug/L) over 8 weeks. During the 8-weeks of Period 2, the dose was to be titrated further to a plasma level of 300-500 ng/ml.

For each of the following study medication accounting periods, the number of tablets dispensed and returned was to be recorded on the CRF and used to derive the number of tablets taken:

Period 1: Day 1 to Week 1
Period 1: Week 1 to Week 2
Period 1: Week 2 to Week 4
Period 1: Week 4 to Week 6
Period 1: Week 6 to Week 8
Period 2: Week 8 to Week 10
Period 2: Week 10 to Week 12
Period 2: Week 12 to Week 14
Period 2: Week 14 to Week 16

For each study medication accounting period an estimate of the total dose and daily dose will be derived from the number of tablets taken. Due to the potential for dose titrations, study medication compliance will not be derived by comparing the number of tablets taken with the intended dose.

Study medication exposure will be derived as the number of days that the patient remained on study medication. Exposure in days will be classified into one of the following categories:

1- 8 days (Week 1)
9- 29 days (Week 4)
30- 43 days (Week 6)
44- 57 days (Week 8)
58- 71 days (Week 10)
72- 85 days (Week 12)
86- 99 days (Week 14)
100-113 days (Week 16)
>113 days

3.5.2 Dose Titration

The dose titration algorithm was to be based on the systemic plasma levels of PEX throughout the dosing regimens in Periods 1 and 2. On the morning of Day 8 (± 1 day) (after completion of a minimum of 6 days of dosing) patients were to provide a blood sample for the measurement of PEX, CIS and TRANS. The analytical results were to be available within 3-5 days of the blood sampling and results for PEX and CIS reported to the study sites and used to determine the following:

- Patients deemed to be phenotypic PMs based on these results were to be immediately withdrawn from study-drug dosing. A phenotypic PM is defined as a patient whose CIS:PEX ratio is <0.4

On the morning of Day 15 (± 1 day) (after completion of a minimum of 13 days of dosing) patients were to provide a blood sample for the measurement of PEX, CIS and TRANS. The analytical results were to be available within 3-5 days of the blood sampling and results for PEX and CIS reported to the study sites and used to determine the following:

- The CIS:PEX ratio will be evaluated and patients with a ratio <0.4 will be further evaluated and the patient status will be discussed with the Medical Monitor.
- Dose adjustment will be decided according to the dose-adjustment algorithm presented in section 4.4.3 and Table 4.1 below.

Subsequent blood samples were to be obtained and plasma levels of PEX, CIS and TRANS determined at the end of Week 4, 6, and 8 in Period 1, and Week 10, 12 and 14 in Period 2.

The following doses were expected to produce therapeutic concentrations in the majority of patients included in the study.

Intermediate Metabolizers (IM)	70 to 140 mg daily
Extensive Metabolizers (EM)	140 to 210 mg daily
Ultra-rapid Metabolizers (UM)	May require maximum doses of: 210 (Period 1) or 280 (Period 2) mg daily.

4 ANALYSIS POPULATIONS

4.1.1 *Safety Population*

The Safety Population will include all patients who receive study drug.

4.1.2 *Modified Intention to Treat Population*

The Modified Intention to Treat Population (MITT) will include all patients who receive study drug and have at least one post-Baseline efficacy assessment.

4.1.3 *Completer Population*

The Completer Population will include all patients who receive study drug and complete all study procedures at Baseline, end of Period 1 and end of Period 2 and have their Period 2 CPEX assessment within 7 days of the target day of 113.

4.1.4 *Pharmacokinetic Population*

The Pharmacokinetic Population will include all patients who receive study drug and had at least one plasma sample collected.

5 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.3 or above.

All available data will be presented in patient data listings, which will be sorted by site number, unique patient identifier and where appropriate, visit number and visit/assessment date.

5.1 Evaluation of Center Effect

This is a single arm open-label study that will be reported using descriptive stats and a one-sample t-test. Therefore, no adjustments for center effects will be implemented.

5.2 Assessment Windows

No visit windowing required.

5.3 Handling of Dropouts and Missing Data

If the patient withdraws from the study early, but provides an unscheduled or early end-of-Period 1 or end-of-Period 2 VO_{2MAX} assessment then this VO_{2MAX} assessment will be used in the derivation of efficacy endpoints. Only if the unscheduled or early VO_{2MAX} assessment is within ± 7 days of the intended target assessment relative to Day 1, will the derived change in VO_{2MAX} be used in the primary analysis using the Completer Population (see section 7.1, below), but will be used in the supportive analysis, based on the MITT.

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 patients are output as “NA”, unless otherwise specified.

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 month.

5.4 Other Data Handling Approaches

The programming specification, including the mock-up analysis tables, figures, and data listings, as well as the derived database specification, will be prepared in stand-alone documents. The programming specification document will be finalized prior to the database lock.

Descriptive statistics (n, mean, standard deviation, median, maximum, and minimum) will be used to summarize the continuous data. Unless otherwise stated, descriptive statistics showing the mean or median will be displayed to one more decimal place than the original data; the standard deviation will be displayed to two decimal places more than the original data; minimum and maximum will be displayed to the same number of decimal places as the original data.

Discrete measures will be summarized using counts and percentages. Percentages will be displayed with 1 decimal place and percentages for zero counts will be omitted from the presented results.

P-values will be presented to 4 decimals. When a p-value is less than 0.0001, '<0.0001' will be displayed.

6 ANALYSIS OF DISPOSITION AND PATIENT CHARACTERISTICS

6.1 Disposition and Analysis Populations

The reason given for each screen failure (did not satisfy all inclusion/exclusion criteria, withdrawal by patient, physician decision, adverse event, lost to follow-up, other) will be listed and summarized.

A data listing will be presented to indicate which patients satisfied the criteria for inclusion in the Safety, Modified Intention to Treat, Completer and Pharmacokinetic Populations. The number of patients included in each population will be summarized using counts and percentages, with percentages based on Safety Population as denominator.

Patient disposition will be presented for all patients in the Safety Population. The number and percentage of patients in each of the following disposition categories will be presented, with percentages based on Safety Population as denominator:

- Patients who completed screening (number of patients only)
- Patients who started study treatment
- Patients who completed Period 1 treatment
- Patients who completed Period 2 treatment
- Patients who completed the study as planned to the follow up visit

For patients in the Safety Population who withdraw early from the study treatment or withdrew from the study before the follow up visit, the primary reason for the early withdrawal will be listed and summarized.

6.2 Eligibility Criteria and Protocol Deviations

A list of any inclusion or exclusion criteria failures will be presented in data listings and summarized to show the number and percent of patients failing each criterion for the Safety Population.

Any additional CSR-reportable deviations, drawn from the monitoring reports, will be listed for the Safety Population.

6.3 Demographics and Baseline Characteristics

Demographics characteristics will be presented as data listings and summary statistics using the Safety Population.

Medical history findings reported at Screening will be presented in data listings and summarized to show the number and percent of patients within each Preferred Term within each System Organ Class term for the Safety Population.

6.4 Concomitant Medications

Prior and concomitant medications will be listed by patient for the Safety Population, with an indication of whether the medication was regarded as Prior or Concomitant (see section 3.4.1). Concomitant medications will be summarized by Therapeutic Class and Preferred Term, showing the number and percentage of patients from the Safety Population taking each medication.

6.5 Study Medication

Study medication, in terms of number of tablets dispensed, returned and assumed taken during each study medication accounting period (see section 3.5.1) will be listed for the Safety Population along with the derived estimated total and daily dose.

7 ANALYSIS OF EFFICACY

7.1 Primary Efficacy Analysis

The primary endpoint is the change from Baseline of VO_{2MAX} at the end of Period 2. This will be analyzed using an Analysis of Covariance (ANCOVA) with covariates of baseline VO_{2MAX} and the mean plasma PEX level, with the mean taken from all available Period 2 assessments (> Week 8 to Week 16). The primary analysis population will be the Completer Population and will include an efficacy endpoint from all patients with an assessment within ± 7 days of the planned assessment. The estimated mean change in VO_{2MAX} from Baseline to Period 2 will be presented along with a 95% confidence interval of the change and the p-value. This analysis will be repeated for the percent change from Baseline of VO_{2MAX} at the end of Period 2, including the same covariates.

Descriptive statistics of the Baseline value, VO_{2MAX} at the end of Period 2 and the change and percent change from Baseline to end of Period 2 will be presented for the Completer Population.

The primary analysis and descriptive statistics table will be repeated for the MITT, and will include any imputed change in VO_{2MAX} values for patients who did not complete the study to the end of Period 2 but provided an end of Period 2 VO_{2MAX} assessment (see section 3.1.1).

Example SAS code is shown below:

```
proc mixed data=dataP2;
  class Period;
  model CHG=BASE PEXALL Period/ solution cl;
  lsmeans Period/ cl;
run;
```

7.2 Secondary Efficacy Analyses

7.2.1 *Difference between Period 2 and Period 1 Change from Baseline in VO₂MAX*

The first secondary efficacy endpoint is the change from Baseline of VO₂MAX at the end of Period 1 compared to the change from Baseline at the end of Period 2. This will be analyzed using an ANCOVA with covariates of baseline VO₂MAX and the Period-mean plasma PEX level for the Completer Population. The estimated mean change in VO₂MAX from Baseline to Period 1 and to Period 2 and the difference between Period 1 and Period 2 will be presented along with a 95% confidence interval and the p-value. This analysis will be repeated for the MITT, and will include any imputed change in VO₂MAX as in the primary analysis.

Example SAS code is shown below:

```
proc mixed data=dataP1P2;  
  class Period;  
  model CHG=BASE PEXP1P2 Period/ solution cl;  
  lsmeans Period/ cl diffs;  
  estimate "Period 2 vs. Period 1" Period -1 1/ cl;  
run;
```

7.2.2 *Change from Baseline in VO₂MAX at the end of Period 1*

The second secondary efficacy endpoint is the change from Baseline of VO₂MAX at the end of Period 1. Similar to the primary efficacy endpoint, this will be analyzed using an ANCOVA with covariates of baseline VO₂MAX and the Period 1 mean plasma PEX level for the Completer Population. This will be repeated for the MITT, including any imputed change in VO₂MAX values for patients who did not complete the study to the end of Period 1. Descriptive statistics of the Baseline value, VO₂MAX at the end of Period 1 and the change from Baseline to end of Period 1 will be presented for the Completer Population and the MITT Population.

7.2.3 *Change from Baseline in 6MWT at the end of Period 2*

The change from Baseline in the 6MWT at the end of Period 2 will be analyzed using an ANCOVA with covariates of baseline VO₂MAX and the Period 2 mean plasma PEX level. This will be presented for the Completer Population and repeated for the MITT including any imputed change from Baseline values for patients who did not complete the study to the end of Period 2.

7.2.4 *Difference between Period 2 and Period 1 Change from Baseline in 6MWT*

The change from Baseline in the 6MWT at the end of Period 1 compared to the change from Baseline at the end of Period 2 will be analyzed using an ANCOVA with covariates of baseline VO₂MAX and the Period-mean plasma PEX level Completer Population and repeated for the MITT.

7.2.5 *Change from Baseline in 6MWT at the end of Period 1*

The change from Baseline in the 6MWT at the end of Period 1 will be analyzed using an ANCOVA with covariates of baseline VO_{2MAX} and the Period 1 mean plasma PEX level. This will be presented for the Completer Population and repeated for the MITT including any imputed change from Baseline values for patients who did not complete the study to the end of Period 1.

8 ANALYSIS OF SAFETY

8.1 Extent of Exposure

The number of days of exposure to study medication will be listed and summarized using descriptive statistics and using counts and percentages of the number of patients in each exposure category listed in section 3.5.1.

8.2 Adverse Events

Treatment-emergent AEs (TEAEs) occurring in patients from the Safety Population will be presented in data listings with an indication of whether the AE start date occurred during Period 1, Period 2, or the Follow-up Period. Any AEs that were recorded in the CRF from patients who were not included in the Safety Population will be listed separately and will not be included in any subsequent listings or tables.

A summary overview of TEAEs will be provided, which will present the number and percentage of patients satisfying each of the following categories. This table will be presented for Period 1 and Period 2 (see 3.2.1 for derivation) separately and for Period 1 and Period 2 combined and for the Follow-up Period, using the Safety Population.

- Any TEAEs
- Maximum severity of TEAEs
- Study drug-related TEAEs
- All TE SAEs
- All TE study drug-related TE SAEs
- TEAEs leading to death
- TEAEs leading to withdrawal of study medication

The number and percentage of patients with TEAEs will be summarized by their MedDRA preferred term within system organ class. This will be presented for Period 1 and Period 2 separately and for Period 1 and Period 2 combined and for the Follow-up Period, using the Safety Population. In this summary, any patients reporting multiple episodes of the same TEAE (i.e. same preferred term) within a single period, will be counted once. It is acknowledged that any conclusions that arise from a comparison of AEs reported during Period 1 and Period 2 may be limited due to the consecutive nature of the periods. A similar summary will be provided for study drug-related TEAEs.

The number and percentage of patients with TEAEs will be summarized by reported severity (*Severity = 'Mild', 'Moderate', 'Severe'*) within each MedDRA preferred term within system organ class. This will be presented for Period 1 and Period 2 separately and for Period 1 and Period 2 combined and for the Follow-up Period, using the Safety Population. In this summary, any patients reporting multiple episodes of the same TEAE (i.e. same preferred term) within a single period, will be counted once against the most severely reported category.

8.3 Safety Laboratory Parameters

Laboratory chemistry and hematology data will be listed for each subject in the Safety Population with values outside the normal reference ranges flagged as low or high.

Descriptive statistics of each chemistry and hematology parameter will be presented for the Safety Population, showing the observed visit and change from Baseline to each visit value.

The number of patients with reported transaminases (AST, ALT, Alkaline phosphatase, total bilirubin) that are outside the defined ULN threshold multiples (see section 3.2.2) will be summarized showing the counts and percentages for Period 1 and Period 2 separately and for Period 1 and Period 2 combined, using the Safety Population.

Pharmacogenetic data (CYP2D6 genotyping at screening) will be listed for each subject in the Safety Population. Any incidences of polymorphisms (see section 3.4.5) will be summarized for the Safety Population.

A cross-tabulation will be displayed to show the agreement between the CYP2D6 genotyping status (PM, IM, EM, UM) and the phenotype status defined from the ratio of the CIS:PEX ratio (<0.4 , ≥ 0.4) from the Week 1 plasma levels (see section 3.3.1).

8.4 HbA1c

HbA1c data will be listed for each subject in the Safety Population with values outside the normal reference ranges flagged as low or high.

The change from Baseline to the end of Period 2 will be analyzed using an ANCOVA with a covariate of baseline HbA1c for the Completer Population.

The difference between the change from Baseline at the end of Period 1 compared to the change from Baseline at the end of Period 2 will be analyzed using an ANCOVA with a covariate of baseline HbA1c for the Completer Population.

The change from Baseline to the end of Period 1 will be analyzed using an ANCOVA with a covariate of baseline HbA1c for the Completer Population.

8.5 Vital Signs

Vital signs data from patients in the Safety Population will be presented in a data listing. The listing will identify the Baseline value, and present the visit value and change from Baseline to

each visit value, for each parameter. Values outside the thresholds indicated in section 3.2.4 will be identified on the listing.

Descriptive statistics of each vital signs parameter will be presented for the Safety Population, showing the observed visit and change from Baseline to each visit value. The number of patients who report a vital signs parameter outside the thresholds at any visit during Period 1, or Period 2 will be summarized using counts and percentages for the Safety Population.

Shift tables will be used to indicate the number of patients with systolic or diastolic blood pressure or heart rate values that changed status relative to the thresholds identified above (section 3.2.4) between Baseline and any vital signs assessment during each period.

8.6 ECG Parameters

All ECG data from patients in the Safety Population will be presented in a data listing. The listing will identify the Baseline value, and present the visit value and change from Baseline to each visit value, for each parameter. Each ECG parameter will be summarized using descriptive statistics for each assessment visit using the Safety Population.

The number of patients experiencing visit values or changes from Baseline within the ranges specified in section 3.2.5 will be summarized by counts and percentages for patients in the Safety Population.

Shift tables will be used to indicate the number of patients with QT or QTcF values or changes from Baseline values that changed status relative to the thresholds identified above (section 3.2.5) between Baseline and any ECG during each period.

The change from Baseline of the QTcF interval at the end of study-drug dosing Period 1 compared to the change from Baseline at the end of study-drug dosing Period 2 will be analyzed using an ANCOVA for the Safety Population.

8.7 Physical Examinations

Physical examination information will be listed for the Safety Population.

8.8 Pharmacokinetic Analysis

Pharmacokinetic data for PEX, CIS and TRANS, will be listed by patient and summarized for each sampling time point.

9 DATA SAFETY MONITORING BOARD

9.1 Study Monitoring Team

A Study Monitoring Team will be established to review and discuss the available study data as patients are enrolled. The Study Monitoring Team will include at a minimum an independent

cardiologist, the Medical Monitor (CRO), the study biostatistician (CRO), and the Sponsor Chief Medical Officer or Chief Operating Officer and a Sponsor Representative.

The team will evaluate all available data listings every two months (until the study is completed) following 25% enrollment in the study. The review will include observed outcomes related to patient safety and tolerance (i.e., AEs, adverse device effects [ADEs], vital signs measurements, ECGs, laboratory assessments, and concomitant medications). These listings will be reviewed by the Study Monitoring Team to determine whether the dosing regimen should be altered during the course of the study or whether any other protocol modifications should be instituted to ensure the safety of the patients.

10 INTERIM SNAPSHOT ANALYSIS

An interim analysis (referred to as a snapshot in the protocol) will be performed on the CPEX data (listings and summary statistics) from Period 1 when all patients have completed Week 8. A two-sided, one-sample t-test will be performed for the comparison of VO_{2MAX} at the end of Period 1 compared to Baseline.

11 SAMPLE SIZE AND POWER CONSIDERATIONS

The sample size was based on a two-sided, one-sample t-test of the change from Baseline for the end of Period 2 with the following assumptions:

- Mean change from Baseline for Period 1 is 1.2mL O₂/kg/min
- Mean change from Baseline for Period 2 is 2.0mL O₂/kg/min
- Standard deviation of change from Baseline is 2.5mL O₂/kg/min for both periods
- Significance level (alpha) of 0.05

With these assumptions, a power of > 95% is anticipated for the primary outcome, and 72% for the first secondary outcome is expected for a sample size of 30 patients.

12 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

1. Added Modified Intention to Treat Population as a sensitivity analysis population for efficacy analyses.
2. Added inclusion of early withdrawal efficacy assessments in efficacy analyses that use the MITT Population.
3. The protocol specified that each analysis would be performed using a t-test. During preparation of the statistical analysis plan, it was decided to change this to analysis of covariance (ANCOVA). The intention was to allow covariate adjustment for a Baseline value, to adjust for baseline severity, and in some analyses the plasma PEX level, to adjust for some measure of study medication intake level.