Title	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
Study Number	HML-PHX-005
Indication	Treatment of Moderate-to-Severe Symptomatic Hypertrophic Cardiomyopathy
Study Phase	Phase 2
Sponsor	Heart Metabolics, Ltd.
US IND	118,826
Study Sites	Multicenter
Protocol Physician	Mark Midei, M.D.
Study Dates	Anticipated Initiation: Q3 2016 Anticipated Completion: Q1 2017
Version and Date:	Version 11.0, 02 December 2016

APPROVED BY:

Mark G Midei 12|5|2016

Mark Midei, M.D. Date

Heart Metabolics Ltd.

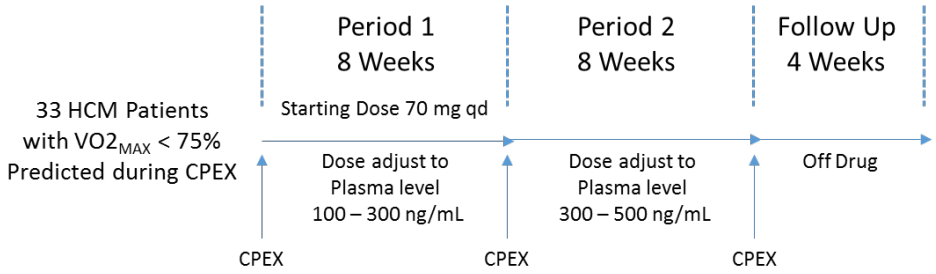
Table of Contents

List of Tables

List of Figures

1 CLINICAL PROTOCOL SYNOPSIS

Title	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
Protocol Number	HML-PHX-005
Phase	2
Sponsor	Heart Metabolics Ltd.
Investigational Product	Perhexiline
Indication	Treatment of moderate-to-severe symptomatic hypertrophic cardiomyopathy (HCM)
Study Centers	Approximately 10 US sites
Objectives	**Primary:** • To evaluate the effect of perhexiline (PEX) on the change from baseline of a functional status measure ($VO2_{MAX}$) in patients with HCM and moderate-to-severe heart failure with preserved left ventricular (LV) function following repeat dosing with PEX for 112 days **Secondary:** • To evaluate the ascending dose-response effect on the change from baseline of $VO2_{MAX}$ in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days • To evaluate 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
Endpoints	**Primary:** • Change from baseline of $VO2_{MAX}$ at the end of Period 2 **Secondary Endpoints:** • The change from baseline of VO2MAX at the end of study-drug dosing Period 1 compared to the change from baseline at the end of Period 2. • An evaluation of the change in VO2MAX at the end of study-drug dosing Period 1 compared to baseline will be performed • 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 Period 2 • The change from baseline at the end of study-drug dosing Period 2 in the Six-Minute Walk Test (6MWT) and change from baseline at the end of study-drug dosing Period 1 compared to the change from baseline at the end of Period 2 • Safety data (adverse events [AE], routine laboratory safety test of blood, ECG abnormalities, vital signs, and concomitant medication and patient withdrawals) during study-drug dosing Period 1 compared to Period 2

	Exploratory endpoints: • Change from baseline of other ECG variables at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2 • Change from baseline of HbA1c at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2
Study Design	This is a Phase 2, open label study that will enroll approximately 33 patients with HCM who are unable to exercise more than 75% of their maximum predicted capacity during Cardio-Pulmonary Exercise Testing (CPEX) at Screening (Figure 1.1). They will then be started on 70 mg PEX daily and dose titrated to a plasma level of 100-300 ng/ml over 8 weeks (Period 1). CPEX will be repeated, and then the dose will be titrated up to a plasma level of 300-500 ng/ml PEX for a further 8 weeks (Period 2). CPEX will be assessed at the end of Period 2. The patients will then complete a 4-week safety observation period before study termination. Approximately 30 patients are projected to complete the study. **Figure 1.1** Study design for Periods 1 and 2 
Number of Patients	Approximately 33; anticipate 30 to complete full 16 weeks of dosing
Target Population	Patients with HCM and moderate to severe heart failure with preserved LV function
Length of Study	Approximately 24 weeks as follows: • Screening: 4 weeks • Period 1: 8 weeks • Period 2: 8 weeks • Follow-up: 4 weeks
Investiga-tional Drug	PEX is available as 35 mg tablets
Study Drug Dosing	All patients will receive 70 mg daily during weeks one and two in Period 1. Formal dose adjustments will not be done during this time, although the PEX dose may be decreased at any time for suspected elevated PEX levels or related AE. Patients should take study drug in the evening, preferably between 8 and 11p.m (with the exception of the first dose of study drug, which will be administered under the supervision of the study-site staff). On the morning of day 8 (±1 Day), a blood sample to determine the levels of PEX and *cis*- and *trans*-hydroxy-perhexiline (CIS, TRANS) will be obtained. Results for PEX and CIS will be reported to the study sites in order to: • Withdraw phenotypic poor metabolizers (PMs) from the study On the morning of day 15 (±1 Day), a blood sample to determine the levels of PEX, CIS, and TRANS will be obtained. Results for PEX and CIS will be reported to the study sites to:

<table>
<tr><td></td><td>

Evaluate the CIS:PEX ratio. Patients with a ratio <0.4 will be further evaluated and the patient status will be discussed with the Medical Monitor.
Determine dose adjustment starting after completion of a minimum of 13 days of study-drug dosing.

PEX, CIS, and TRANS Levels will continue to be measured every other week (Weeks 4, 6, 8, 10, 12 and 14) in order to guide dose adjustment according to Table 1.1 (below) and to evaluate the CIS:PEX ratio. At the conclusion of Period 2 (end of Week 16), an additional blood sample will be obtained to determine the levels of PEX, CIS, and TRANS.

A final blood sample will be obtained at the conclusion of the 4-week safety follow-up period (end of week 20) and plasma levels of PEX, CIS and TRANS determined.
</td></tr>
<tr><td>Dose Adjustment Guidelines and Algorithm</td><td>
1. All patients will receive 70mg/day for the first 14 days. Formal dose-adjustments will start at the end of Week 2 / Start of Week 3 in Period 1. However, the dose may be decreased at any time for suspected elevated PEX levels or related AE.
2. Available dose levels will include:
a. Period 1: 35, 70, 105, 140, 175, and 210 mg (tablet strength is 35 mg)
b. Period 2: 35, 70, 105, 140, 175, 210, 245, & 280 mg (tablet strength is 35 mg)
3. In general, only one dose adjustment should be made per two-week period. If the PI thinks an additional dose adjustment should be made, the PI should contact the Medical Monitor.
4. Upon notification of a dose adjustment the site should contact the patient as soon as possible to initiate dose adjustment according to Table 1.1, below.
5. To achieve the higher target range for PEX in Period 2, the dose will initially be adjusted based on the plasma PEX level measured at Week 6 in Period 1. This dose adjustment will be performed at the Week 8 visit (start of Period 2) in accordance with the Period 2 column in Table 1.1, below. Important: Any change made at Week 6 will need to be accounted for when adjusting the dose at Week 8.

Table 1.1 Dose-adjustments from Week 2, Period 1 and throughout Period 2
<table>
<tr><th>Systemic Perhexiline Level (PEX) (ng/mL)**</th><th>Period 1 (Weeks 2 – 8)
Target Range 100-300 ng/mL

Start Dose of 70 mg/day, 2 tablets per day

(Tablets to be taken orally in the evening)

Maximum Dose 210 mg (6 tablets)</th><th>Period 2 (Weeks 9 – 16)
Target Range 300-500 ng/mL

Start dose will be the dose-adjustment decision based on the Period 1, Week 6 level of PEX†

(Tablets to be taken orally in the evening)

Maximum Dose 280 mg (8 tablets)</th></tr>
<tr><td>< 50</td><td>+2 tablets per day#</td><td>+2 tablets per day#</td></tr>
<tr><td>50 to 100</td><td>+1 tablet per day#</td><td>+2 tablets per day#</td></tr>
<tr><td>101 to 200</td><td>No change</td><td>+1 tablet per day#</td></tr>
<tr><td>201 – 300</td><td>No change</td><td>+1 tablet per day#</td></tr>
<tr><td>301 – 400</td><td>-1 tablet per day*</td><td>No change</td></tr>
<tr><td>401 – 500</td><td>-2 tablets per day*</td><td>No change</td></tr>
<tr><td>501 – 600</td><td>-3 tablets per day*</td><td>-1 tablet per day*</td></tr>
<tr><td>601 – 700</td><td>Discontinue for 1 day, and -3 tablets per day*</td><td>Discontinue for 1 day, and -2 tablets per day*</td></tr>
</table>
</td></tr>
</table>

	701 - 900	**Discontinue for 3 days**, and -4 tablets per day*	**Discontinue for 1 day**, and -3 tablets per day*
	901 - 1200	**Discontinue for 7 days**, and -5 tablets per day*	**Discontinue for 3 days**, and -4 tablets per day*
	> 1200	**Discontinue for 7 days**, and -5 tablets per day*	**Discontinue for 7 days**, and -5 tablets per day*

Unless the patient has already reached the highest daily dose of six (6) tablets or 210 mg in Period 1 and eight (8) tablets or 280 mg in Period 2
* The lowest daily dose is one (1) tablet per day or 35 mg.
** Blood sampling for plasma PEX, CIS and TRANS measurement should be obtained approximately 12 hours following dosing on the previous day. Results for systemic PEX and CIS levels will be reported to the study sites.
† Any change made at Week 6 will need to be accounted for when adjusting the dose at Week 8.

6. Dose adjustment for QTcF/JTcF prolongation (regardless of PEX levels reported, unless the PEX levels and dose adjustment algorithm result in a dose reduction or discontinuation of a greater magnitude) will proceed as follows for EITHER:

   a. Patients with a QRS interval ≤ 100 msec WITH;

   - A prolonged QTcF > 540 msec OR,
   - An increase in QTcF > 75 msec over baseline AND QTcF > 500 msec

   b. Patients with a baseline OR any on-study QRS interval > 100 msec WITH:

   - An increase in the JTcF > 75 msec over baseline AND the JTcF > 410 msec OR
   - An on-study JTcF interval > 450 msec

   The dose of study drug will be stopped for 2 days and the daily dose subsequently reduced by 35 mg (for patients receiving ≤ 105 mg) or 70 mg (for patients receiving ≥ 140 mg) and restarted only if the QTcF/JTcF measurement has fallen back into the acceptable range for continued dosing. If the QTcF/JTcF measurement has NOT fallen back into the acceptable range after stopping drug for 2 days, the process of holding study drug and rechecking the ECG every 2 to 3 days will continue until the QTcF or JTcF limits are not exceeded and at which time study drug may be restarted at the reduced dose. The dose of study drug will not be increased any further during either Period 1 or Period 2 if a dose reduction for QTcF or JTcF prolongation is required.

Safety Assessment	A Study Monitoring Team will be established to review all available data in listings approximately every 2 months (until the study is completed) following 25% enrollment in the study with an emphasis on observed outcomes related to patient safety and tolerance (*i.e.*, AEs, adverse device effects (ADE), 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. The Study Monitoring Team will include at a minimum an independent cardiologist, the Medical Monitor (Contract Research Organization [CRO]), the study biostatistician (CRO), and a Sponsor representative.

Inclusion Criteria	**1. General Criteria** a. Adult, at least 18 years of age b. Able and willing to give written informed consent **2. Cardiomyopathy-related Criteria** a. Hypertrophic cardiomyopathy with moderate-to-severe heart failure meeting all of the 2011 American College of Cardiology Foundation/American Heart Association Criteria for the Diagnosis of Hypertrophic Cardiomyopathy [Gersh *et al.*, 2011]. b. Left ventricular hypertrophy (LVH) with maximum LV wall thickness ≥ 15 mm measured within the past 12 months without an alternative explanation. c. Left ventricular ejection fraction ≥ 50% d. Able to perform exercise testing but unable to exceed 75% of the predicted age-adjusted maximum level (as determined by $VO2_{MAX}$ measured during Screening CPEX). $VO2_{MAX}$ will be determined again at Baseline and must not exceed ±20% of the Screening $VO2_{MAX}$. e. Normal sinus rhythm at Screening and Baseline (atrial fibrillation pattern acceptable for patients with chronic atrial fibrillation and controlled ventricular response) f. If taking any medications for the treatment of HCM (including beta-blockers, calcium channel blockers, diuretics), the medication has been taken at a stable dose for at least 60 days prior to screening and will be continued at the same dose throughout the study
Exclusion Criteria	**1. General Exclusion Criteria:** a. Pregnant women, women who intend to become pregnant, or woman who are not practicing contraception, either pharmacologically or with a barrier method b. Lactating women c. CYP2D6 Poor Metabolizer (PM) status, based on genotype known prior to Screening, or as determined by genotype assessed at Screening. CYP2D6 Poor Metabolizer status will be reported by the central laboratory in the screening report according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [Crews *et al.*, 2014]. d. Any patient who regularly takes a medication known to be a strong inhibitor of CYP2D6 (bupropion, fluoxetine, paroxetine, quinidine, or ritonavir) e. Any concomitant disease, condition, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator or sponsor, pose an unacceptable risk to patients and/or interfere with the interpretation of study data. f. History of a known toxic or inflammatory peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, drug-related neuropathy or neuritis, or diabetic neuropathy (history of a compression neuropathy, such as carpal tunnel syndrome, is acceptable) g. Poorly controlled diabetes mellitus (*e.g.*, HbA1c > 9.0%) h. Clinically severe chronic obstructive pulmonary disease (*i.e.*, Chronic Obstructive Pulmonary Disease requiring home oxygen or history of intra-venous or oral steroid use)

	i. History of a known chronic liver disease including cirrhosis of any cause, or chronic hepatitis B or hepatitis C j. History of porphyria k. History of recurrent hypoglycemia l. Active infection requiring antibiotics m. Life expectancy of less than 2 years n. Evidence of an active or suspected cancer or systemic treatment within the previous 5 years for a malignancy, except for skin squamous cell or basal cell carcinomas that did not require systemic therapy and are considered to be cured o. History of substance abuse, including alcohol or illicit drugs within the past 12 months **2. <u>QT Interval-Related Exclusion Criteria:</u>** a. Personal history of congenital long QT syndrome, Torsade de Pointes (TdP), or drug-induced long QT b. On the basis of the mean of triplicate ECGs at screening or baseline: i. QTcF > 500 msec if QRS ≤ 100 msec ii. JTcF > 410 msec if QRS > 100 msec c. Serum potassium < 3.8 mEq/L (may be repeated up to two times during screening after attempts at medical management) d. Currently taking a medication with known risk of QT prolongation and TdP as listed in the "Known Risk of TdP" Risk Category on www.crediblemeds.org [Woosley and Romero]. e. If possessing a pacemaker or Implantable Cardioverter Defibrillator (ICD), ventricular pacing > 10% of the time **3. <u>Other Exclusion Criteria:</u>** a. Abnormal safety studies of clinical significance at Screening such as: i. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or lactate dehydrogenase (LDH) > 1.5 x upper limit of normal ii. Total Bilirubin > 2.0 x upper limit of normal (unless subject is known to have Gilbert's syndrome) b. Known hypersensitivity to perhexiline c. Unable or unwilling to comply with the protocol d. Enrolled in another therapeutic trial for HCM **4. <u>Cardiomyopathy-Related Exclusion Criteria</u>** a. Asymptomatic patients or patients whose symptoms are controlled with medications b. Resting Left Ventricular Outflow Tract (LVOT) gradient > 50 mmHg or exercise-induced LVOT gradient > 80 mmHg c. Absence of an operational implantable cardioverter defibrillator device if there is a history of non-sustained ventricular tachycardia (> 5 beats), or an immediate family history of sudden cardiac death or arrest d. Known coronary artery disease (> 50% arterial luminal narrowing of a major epicardial vessel)

	e. History of cardiac transplantation f. Cardiac surgery or septal reduction surgery planned in the next 6 months or having occurred within the past 6 months g. HCM believed to be caused by infiltrative disorders, glycogen storage disorders, and/or hypertensive heart disease (including genotypic or phenotypic evidence of Fabry's Disease)
Study Procedures	Dosing will be initiated at the Baseline Visit after successful completion of the Protocol Activities during this visit. Study medication will be taken once daily in the evening (preferably 8-11p.m., with the exception of the first dose of study drug, which will be administered under the supervision of the study-site staff) on an outpatient basis for 112 consecutive days. Patients should take the study medication with a glass of water or other non-alcoholic beverage, regardless of food intake. All patients will be started at an initial dose of 70 mg (2 tablets) per day. After two weeks, dose level adjustment will be made every second week according to plasma level measurements for Period 1 according to the Dose Adjustment Guidelines and Algorithm (Table 1.1). At the end of Period 1 (end of Week 8), all patients will undergo CPEX examination. Following the successful completion of Period 1, patients will undergo dose adjustment every second week according to the higher target therapeutic range for plasma levels defined for Period 2 (Table 1.1). At the end of Period 2 (end of Week 16), all patients will undergo CPEX testing.
Statistical Analysis	A two-sided, one-sample t-test of the change from baseline for the end of Period 2 is planned for $VO2_{MAX}$; a power of at least 72% is expected for a sample size of 30 patients for at least a mean change from baseline of 1.2mL O_2/kg/min.

2 INTRODUCTION

2.1 HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic Cardiomyopathy (HCM) is an inherited disease in which defective production of contractile proteins in the cardiac sarcomere leads to excessive growth of heart muscle tissue. Only a small percentage of patients with the genetic propensity for the disease develop any signs or symptoms for which medical treatment is necessary. Response to medical therapy is often incomplete, and typically temporary. Once a patient has recognizable symptoms, the patient's condition may become rapidly and progressively worse, and the risk that the patient experiences sudden death is increased [Krikler *et al.*, 1980, McKenna and Camm 1989].

Symptoms in HCM are ultimately due to LV dysfunction consequent to associated cellular energy deficit and ischemia. Patients with heart failure with preserved LV systolic function have reduced myocardial energy reserve which leads to a dynamic impairment in active relaxation during exercise [Phan *et al.*, 2009a] especially in HCM, where the energy demands may be greater than most any other cardiac condition [Jung *et al.*, 1998]. Impaired cardiac energetics have been demonstrated in patients with HCM, and are associated with abnormal cardiac muscle cell function [Crilley *et al.*, 2003, Morimoto 2008, Phan *et al.*, 2009a].

2.2 UNMET CLINICAL NEED IN SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY

There are no drugs approved in the United States for the treatment of HCM. Off-label use of drugs for other, more common, forms of cardiomyopathy is unpredictable and occasionally dangerous because of the different underlying pathology and pathophysiology of HCM [Gersh *et al.*, 2011]. None of the drugs the US Food and Drug Administration has approved for the treatment of either systolic heart failure or angina have been tested in clinical trials of HCM patients. Current HCM therapy consists of negatively inotropic agents that reduce myocardial oxygen demand by reducing heart muscle contractility but variable patient response and their limited anti-ischemic potential in HCM results in unpredictable benefit.

Recognition of HCM as a disease of disordered metabolism by an NHLBI Working Group highlighted this as an opportunity for further study of potential therapies [Force *et al.*, 2010].

2.3 PERHEXILINE

Perhexiline (PEX) was developed as an anti-ischemic drug for treatment of angina pectoris but interest in its use was tempered by its poorly understood side effects, most notably liver and nerve toxicity in a small proportion of patients. Understanding of PEX's metabolism has allowed its continued safe usage in tandem with accurate and vigilant monitoring of blood levels and dose adjustment. It has been in continuous use in Australia and New Zealand for more than 30 years with over 100,000 patient-years of exposure. More recently, PEX has been used in randomized controlled trials and in open label studies in the United Kingdom [Phan *et al.*, 2009b].

PEX is an inhibitor of carnitine palmitoyltransferase (CPT), the enzyme responsible for mitochondrial uptake of long-chain fatty acids. This results in a greater cellular dependence on carbohydrate utilization for energy production which is inherently more efficient that fatty acid oxidation. The shift in cardiac metabolism to carbohydrates in the presence of PEX explains its potent beneficial effects on coronary ischemia and symptoms of angina [Ashrafian *et al.*, 2007, Essop and Opie 2004, Lee *et al.*, 2004]. By inhibiting CPT in HCM patients, PEX may improve the balance of myocardial oxygen demand by shifting metabolic utilization from free fatty acids to carbohydrates thereby improving efficiency of cardiac energy production. PEX is known to correct the energy deficit seen in HCM [Horowitz and Chirkov 2010, Ashrafian *et al.*, 2011] leading to significant improvements in multiple metabolic and clinical parameters in HCM.

In 46 patients with HCM and symptomatic exercise limitation, PEX increased maximal oxygen output (VO_{2MAX}) on CPEX, improved diastolic filling, restored depleted myocardial energy

stores more quickly and improved New York Heart Association class of heart failure symptoms versus placebo [Abozguia *et al.*, 2010].

2.4 MIXED ION CHANNEL EFFECTS OF PERHEXILINE

PEX is known to alter myocellular electrical activity through blockade of voltage gated L-type calcium [Barry *et al.*, 1985] and sodium channels [Grima *et al.*, 1988]. PEX is also known to block the voltage-dependent Kv1.5 potassium channel in human embryonic kidney cells (IC50 = 1.5 μM) and also inhibits the ultra-rapidly activating K+ channel (IKur), encoded by Kv1.5, in human atrial myocytes [Rampe *et al.*, 1995]. At the ventricular level PEX causes voltage-dependent block of the human ether-a-go-go-related gene (hERG) channel (IC50 7.8 μM) [Walker *et al.*, 1999].

PEX inhibits major cardiac ion channels with IC50 in the low micromolar range. Ventricular therapeutic concentrations of PEX in humans are in the range of 17.45 to 76.8μM [Drury *et al.*, 2014, Drury *et al.*, 2013] and therefore the cardiac ion channel blocking properties of PEX are likely to play a role in the cardiac effects of the drug. This is especially true for hERG, calcium channel and late sodium current inhibition.

The effects of PEX on late sodium current (late hNav1.5 or INaL) and the L-type calcium current (hCav1.2) may reduce the potential pro-arrhythmic effects associated with IKr block (as measured by the hERG current). Most drugs that have been shown to prolong the QTcF interval in humans and induce Torsade de Pointes (TdP) inhibit the rapid component of the delayed rectifier potassium current (IKr) in cardiac cells, as does PEX. However, the reverse is not true, *i.e.*, drugs that decrease IKr do not necessarily cause TdP. Examples include verapamil (L-type calcium channel block), ranolazine and amiodarone (late INa inhibition). It is recognized that a balanced multiple ion-channel effect (MICE), especially inhibition of Cav1.2 and late INa, can result in no or a reduced pro-arrhythmic potential [Eichenbaum *et al.*, 2012, Shantsilla *et al.*, 2007; Sager *et al.*, 2014].

2.5 PERHEXILINE THOROUGH QT STUDY

PEX has MICE which might also predict a potential QT prolongation effect. Nevertheless, pro-arrhythmic effects have not been seen to any significant extent in its > 30 year clinical experience. The Australian Therapeutic Goods Administration label notes that the drug may be associated with QT prolongation and has been associated with a single report of TdP.

A thorough QT (TQT) study was done to establish the frequency and degree of PEX effects on the QT/QTcF interval. In that study PEX caused QT prolongation (ΔΔ QTcF of 15.3 and 22.8 msec at mean Cmax of 278.6 and 677.9 ng/mL, respectively) within the plasma concentration ranges tested in this study. Most of the QTcF prolongation was the result of the ΔΔTpeak-Tendc at all timepoints up to and including 8 hours post-dosing. Subsequently the QTcF prolongation was the product of similar, combined effects of the ΔΔTpeak-Tendc and ΔΔJ-Tpeakc. This suggests that PEX has mixed ion channel effects at relevant plasma levels, reducing the effect of hERG inhibition. PEX also had a mild effect on heart rate and AV nodal conduction indicating possible late sodium channel effect. PEX was well tolerated with few AEs and no serious adverse events (SAE); there were no pro-arrhythmic events seen during the study. In view of the QTcF prolongation, enhanced cardiac screening and monitoring for QT prolongation and arrhythmias will be included in this clinical study.

2.6 PERHEXILINE SUMMARY

The mechanism of action of PEX in HCM is likely two-fold, one metabolic, the other through its inhibitory MICE, especially Calcium and INaL:

- By inhibiting CPT, PEX improves oxygen consumption and therefore decreases the levels of oxygen free radicals that contribute to the development of INaL and intracellular calcium overload.

- By its MICE, especially by inhibiting Ca and INaL, PEX protects and perhaps reverses the development of intracellular calcium overload, thereby improving the electromechanical properties of the left ventricle. Furthermore, its Ca channel properties (hCav1.2 IC50 = 0.068 μM) may further protect cardiac myocytes from calcium overload and cell death as well as counteract the IKr inhibition and its attendant cardiac arrhythmias.

2.7 PEX-CIS ASSAY

2.7.1 Description of PEX-CIS Assay

The PEX-CIS assay is a straightforward protein precipitation assay. It extracts perhexiline (PEX), *cis*-hydroxy perhexiline (CIS) and two internal standards (referred to as IS-PEX and IS-CIS) from human plasma. The internal standards were designed specifically to enhance the performance of the PEX-CIS assay. The analytes are separated by HPLC on a XBP-C8(L) column, and the eluates are monitored by an API4000 MS/MS detector in positive MRM mode. The extract is then assayed against a calibration curve. The data are acquired by the data acquisition system Analyst® (Sciex) and processed in Watson LIMS. The method range is from 10.0 to 1500 ng/ml for PEX and CIS, and requires 50 μL aliquot of human plasma. The method has a run time of approximately 4.5 minutes per sample.

The test has been validated using an independent laboratory following principles of Good Laboratory Practice (GLP), International Organization for Standardization and the International Electrotechnical Commission 17025 as well as FDA's Guidance documents for Bioanalytical method validation. The test method selectivity, accuracy, precision, recovery, linearity, sensitivity, dilution and stability during processing were investigated and consideration was given to batch sizes during sample analysis.

2.7.2 Use of the PEX-CIS Assay in This Study

The test is not required for enrollment in this study. However, there is a 1% incidence of what is known as phenotypic poor metabolizers (PMs) that the test will be used to identify around day 8, based on a metabolic ratio of CIS to parent PEX, which are determined from the assay.

In addition to identifying phenotypic PMs, the assay will also be used for dose adjustments throughout the study.

2.8 STUDY RATIONALE

This is an open-label, phase II study to confirm the optimal dosing regimen of PEX for use in a future phase III study in patients with HCM. The previous study [Abozguia, 2010] in HCM patients demonstrated that a safe and effective plasma concentration for PEX was 150-600 ng/mL. However, a more refined dosing study to evaluate safety and efficacy at low (100-300 ng/mL) and high (300-500 ng/mL) plasma PEX levels has not yet been performed. Potentially, equal efficacy with improved safety could be achieved at lower concentrations of PEX.

A population pharmacokinetic (PK) evaluation of the PK data from the PEX-TQT study was done to identify and characterize patient factors influencing PEX PK and the magnitude of unexplained PK variability [Mould, 2016]. Application of this newly developed model compared to a previously published model [Hussein *et al*., 2001] showed the new model better describes PEX PK, particularly in extensive metabolizer (EM) and intermediate metabolizer (IM) groups.

The 2-compartment PK model developed from this exercise was used to predict drug exposures after single and multiple doses of PEX 70, 140, and 280 mg in all CYP2D6 genotypes [Mould, 2016]. Simulations of multiple dose administrations demonstrated that therapeutic levels of PEX in the range of 150-600 ng/mL for all the CYP2D6 genotypes eligible could be achieved in this study with doses of 70 to 280 mg daily. Figure 2.1 shows the initial response to 70 mg daily in IM, EM, and PM subjects, and clearly shows that all subjects, including phenotypic PM subjects can be safely dosed through two weeks without reaching

excessive PEX levels. However, conservatively, a blood sample to measure PEX and CIS levels will be obtained at day 8 to withdraw phenotypic PMs from the study. Then starting on day 15, PEX levels will continue to be measured every other week (Weeks 2, 4, 6, 8, 10, 12 and 14) in order to guide dose adjustment and to achieve the desired plasma concentrations. The following doses are expected to produce therapeutic concentrations in the majority of patients (PMs are being excluded from 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. These subjects may not reach the target therapeutic level.

2.8.1 Therapeutic Window Rationale

The therapeutic window of PEX has been established as a range from 150ng/mL to 600ng/mL [Pexsig Product Information, 2000]. Regular monitoring of systemic levels of PEX is recommended to inform dose-adjustment decisions to maintain systemic levels within the therapeutic window.

2.8.2 Primary Endpoint Rationale

HCM patients suffer from significant exercise limitation [Abozguia, 2010]. CPEX testing provides a noninvasive method for assessing the cardiovascular, pulmonary, and skeletal muscle components of exercise performance [Balady *et al.*, 2012]. Patients with HCM routinely undergo CPEX testing where $\dot{V}O_{2MAX}$ is used as the primary measure of exercise performance. CPEX testing provides prognostic information in patients with hypertrophic cardiomyopathy where sub-maximal exercise parameters predict death from heart failure [Coats *et al.*, 2014].

2.8.3 Mitigation of Potential QT Prolongation

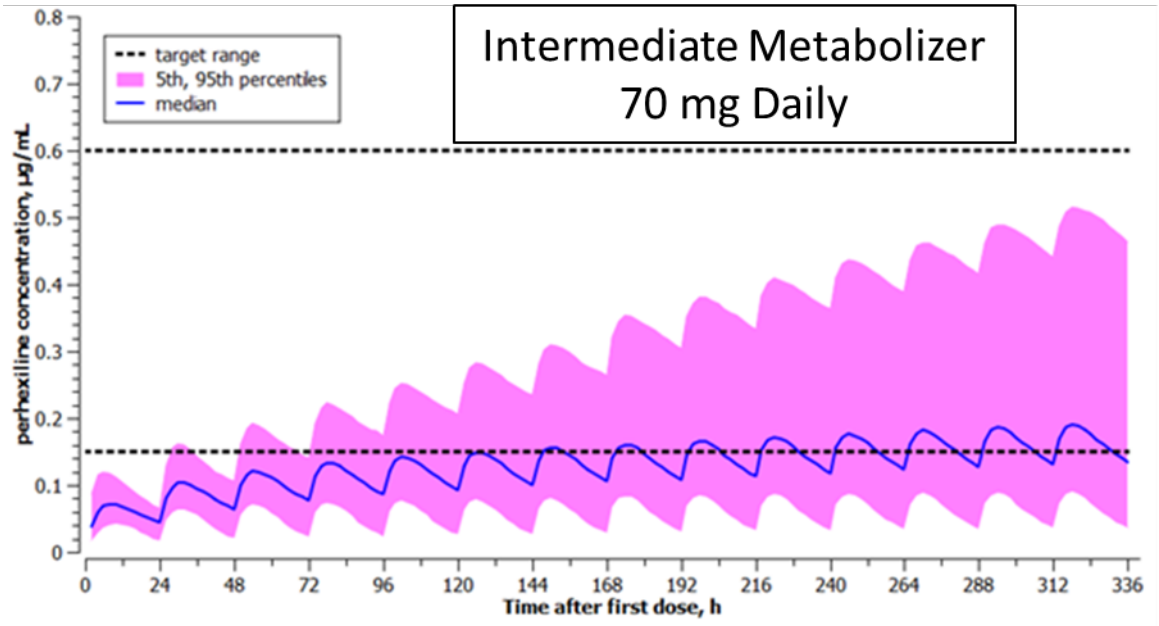
In order to ensure that risk of QT prolongation is minimized in this study, patients with a screening or baseline QTcF >500msec if QRS is ≤100msec or a JTcF >410msec if QRS >100msec will be excluded; these limits were chosen in light of the QT prolongation observed in the TQT study. In addition, dose adjustment for QTcF/JTcF prolongation will be done after either:

a. Patients with a QRS interval ≤ 100 msec WITH;
- A prolonged QTcF > 540 msec OR,
- An increase in QTcF > 75 msec over baseline AND QTcF > 500 msec

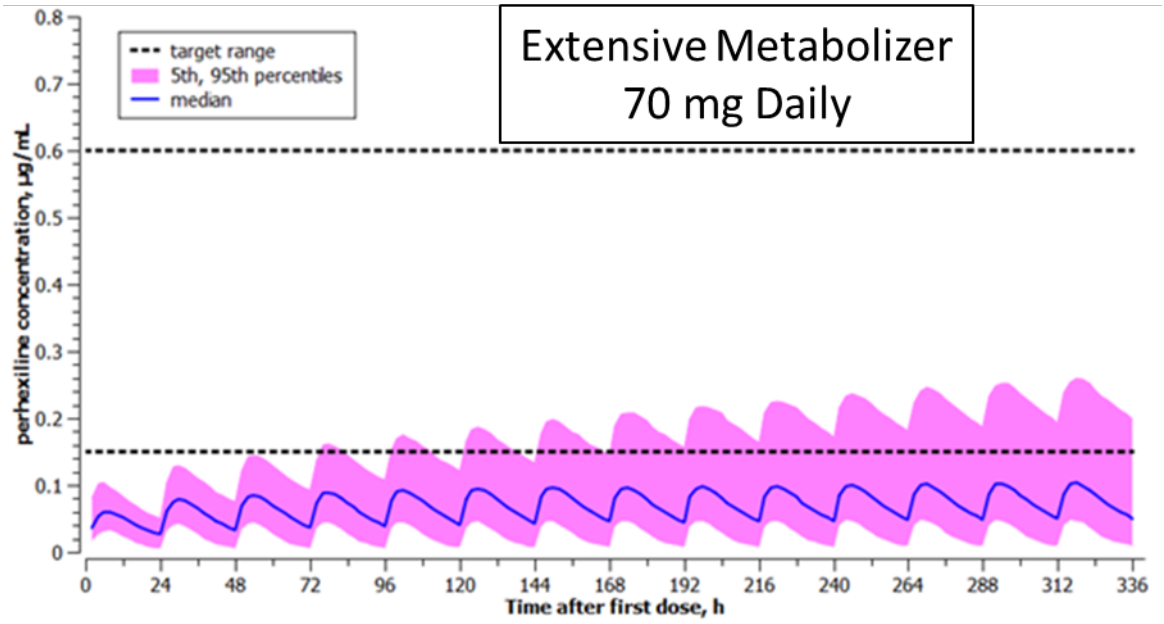
b. Patients with a baseline OR any on-study QRS interval > 100 msec WITH:
- An increase in the JTcF > 75 msec over baseline AND the JTcF > 410 msec OR
- An on-study JTcF interval > 450 msec

Figure 2.1 2-Week simulations of PEX concentrations at 70 mg per day for different CYP2D6 metabolizers

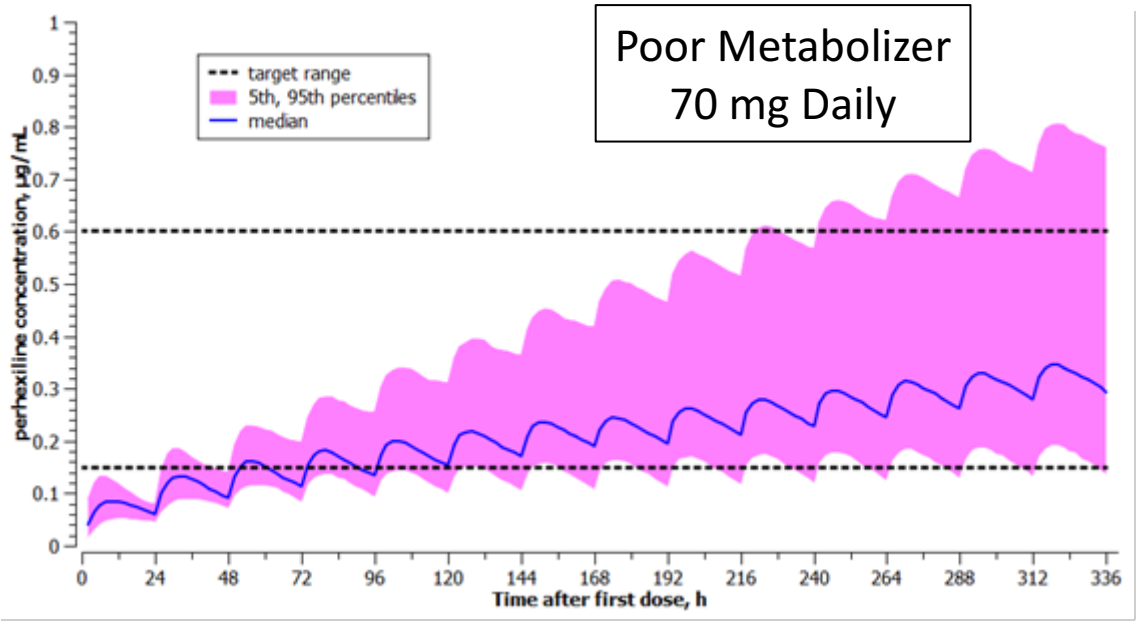
A) Intermediate metabolizer



B) Extensive metabolizer



C) Poor metabolizer



2.8.4 Monitoring of Systemic Levels and Dose Adjustment of Perhexiline

Because of the potential safety risk from study-drug accumulation, a dose-adjustment algorithm will be used (see section 4.4.3) based on the systemic plasma levels of PEX determined from regular blood sampling throughout the dosing regimens in Periods 1 and 2. The objective of the dose adjustment decisions will be to achieve steady-state systemic plasma levels of PEX within the recommended target therapeutic range of either 100-300 ng/mL in Period 1 or 300-500 ng/ml in Period 2.

Considering the intra-day Cmin-Cmax range of plasma concentrations projected by PK simulations (section 2.8) it is proposed that the blood sampling timepoints will be scheduled approximately 12h following study drug dosing on the previous day in order to coincide with the approximate intra-day mean systemic plasma level of PEX.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the effect of PEX on the change from baseline of VO2MAX in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days.

3.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to evaluate:

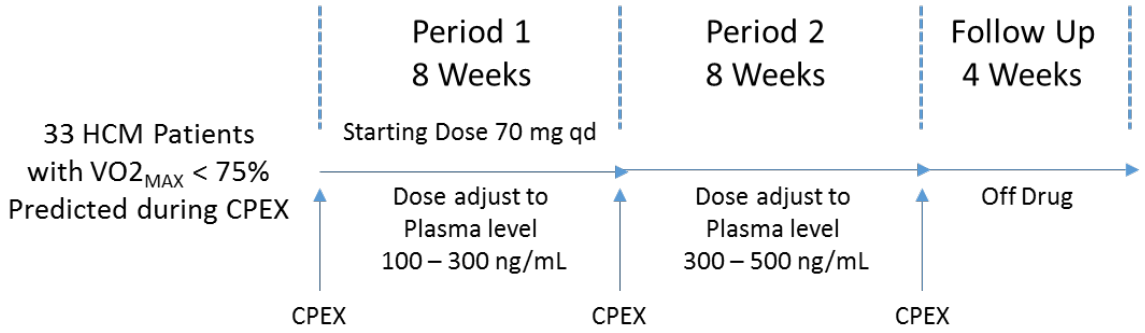
- The ascending dose-response effect on the change from baseline of VO2MAX in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days
- The electrocardiographic (ECG) response, tolerability and safety of orally administered PEX in patients with HCM and moderate-to-severe heart failure with preserved LV function following repeat dosing with PEX for 112 days

4 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN

This is a Phase 2, open label study that will enroll approximately 33 patients with HCM at approximately 7-10 study sites in the US; recruitment will be competititve across sites. Eligible patients will be unable to exercise more than 75% of their maximum predicted VO2MAX capacity during CPEX at screening (Figure 4.1).

Figure 4.1 Study design for Periods 1 and 2



Following screening, this study will include two sequential, 8-week study-drug dosing periods for each patient. The patients will be started on 70 mg PEX daily with subsequent dose titration to a plasma level of 100-300 ng/ml over 8 weeks (Period 1). During the second 8-week period (period 2), the dose will be titrated further to a plasma level of 300-500 ng/ml. CPEX will be completed at baseline (before the start of study-drug dosing on Day 1, Week 1, Period 1), and again at the end of Periods 1 and 2. After completion of study-drug dosing (end of Period 2) there will be a follow-up safety observation period before patients reach end-of-study. Approximately 30 patients are projected to reach and complete the end-of-study procedures and evaluations.

4.2 INCLUSION CRITERIA

4.2.1 General Inclusion Criteria

a. Adult, at least 18 years of age

b. Able and willing to give written informed consent

4.2.2 Cardiomyopathy-Related Inclusion Criteria

a. Hypertrophic cardiomyopathy with moderate-to-severe heart failure meeting all of the 2011 American College of Cardiology Foundation/American Heart Association Criteria for the Diagnosis of Hypertrophic Cardiomyopathy [Gersh *et al.* 2011, Appendix B].

b. Left ventricular hypertrophy (LVH) with maximum LV wall thickness ≥ 15 mm measured within the past 12 months without an alternative explanation.

c. Left ventricular ejection fraction ≥ 50%

d. Able to perform exercise testing but unable to exceed 75% of the predicted age-adjusted maximum level (as determined by VO2MAX measured during Screening CPEX). VO2MAX will be determined again at Baseline and must not exceed ±20% of the Screening VO2MAX.

e. Normal sinus rhythm at Screening and Baseline (atrial fibrillation pattern acceptable for patients with chronic atrial fibrillation and controlled ventricular response)

f. If taking any medications for the treatment of HCM (including beta-blockers, calcium channel blockers, diuretics), the medication has been taken a stable dose for at least 60 days prior to screening and will be continued at the same dose throughout the study

4.3 EXCLUSION CRITERIA

4.3.1 General Exclusion Criteria:

a. Pregnant women, women who intend to become pregnant, or woman who are not practicing contraception, either pharmacologically or with a barrier method

b. Lactating women

c. CYP2D6 Poor Metabolizer (PM) status, based on genotype known prior to Screening, or as determined by genotype assessed at Screening.

   CYP2D6 Poor Metabolizer status will be reported by the central laboratory in the screening report according to CPIC guidelines [Crews *et al.*, 2014].

d. Any patient who regularly takes a medication known to be a strong inhibitor of CYP2D6 (bupropion, fluoxetine, paroxetine, quinidine, or ritonavir)

e. Any concomitant disease, condition, or treatment that could interfere with the conduct of the study, or that would, in the opinion of the investigator or sponsor, pose an unacceptable risk to patients and/or interfere with the interpretation of study data.

f. History of a known toxic or inflammatory peripheral neuropathy, such as mononeuritis multiplex, acute or chronic inflammatory demyelinating polyneuropathy, axonal sensorimotor neuropathies, drug-related neuropathy or neuritis, or diabetic neuropathy (history of a compression neuropathy, such as carpal tunnel syndrome, is acceptable)

g. Poorly controlled diabetes mellitus (*e.g.*, HbA1c > 9.0%)

h. Clinically severe chronic obstructive pulmonary disease (*i.e.*, Chronic Obstructive Pulmonary Disease requiring home oxygen or history of intra-venous or oral steroid use)

i. History of a known chronic liver disease including cirrhosis of any cause, or chronic hepatitis B or hepatitis C

j. History of porphyria

k. History of recurrent hypoglycemia

l. Active infection requiring antibiotics

m. Life expectancy of less than 2 years

n. Evidence of an active or suspected cancer or systemic treatment within the previous 5 years for a malignancy, except for skin squamous cell or basal cell carcinomas that did not require systemic therapy and are considered to be cured

o. History of substance abuse, including alcohol or illicit drugs within the past 12 months

4.3.2 QT Interval-Related Exclusion Criteria

a. Personal history of congenital long QT syndrome, TdP, or drug-induced long QT
b. On the basis of the mean of triplicate ECGs at screening or baseline:
   i. QTcF > 500 msec if QRS ≤ 100 msec
   ii. JTcF > 410 msec if QRS > 100 msec
c. Serum potassium < 3.8 mEq/L (may be repeated up to two times during screening after attempts at medical management)
d. Currently taking a medication with known risk of QT prolongation and TdP as listed in the "Known Risk of TdP" Risk Category on www.crediblemeds.org [Woosley and Romero].
e. If possessing a pacemaker or Implantable Cardioverter Defibrillator (ICD), ventricular pacing > 10% of the time

4.3.3 Other Exclusion Criteria

a. Abnormal safety studies of clinical significance at Screening such as:
   i. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or lactate dehydrogenase (LDH) > 1.5x upper limit of normal
   ii Total Bilirubin > 2x upper limit of normal (unless subject is known to have Gilbert's syndrome)
b. Known hypersensitivity to perhexiline
c. Unable or unwilling to comply with the protocol
d. Enrolled in another therapeutic trial for HCM

4.3.4 Cardiomyopathy-related Exclusion Criteria

a. Asymptomatic patients or patients whose symptoms are controlled with medications
b. Resting Left Ventricular Outflow Tract (LVOT) gradient > 50 mmHg or exercise-induced LVOT gradient > 80 mmHg
c. Absence of an operational implantable cardioverter defibrillator if there is a history of non-sustained ventricular tachycardia (> 5 beats), or an immediate family history of sudden cardiac death or arrest
d. Known coronary artery disease (> 50% arterial luminal narrowing of a major epicardial vessel
e. History of cardiac transplantation
f. Cardiac surgery or septal reduction surgery planned in the next 6 months or having occurred within past 6 months
g. HCM believed to be caused by infiltrative disorders, glycogen storage disorders, and hypertensive heart disease (including genotypic or phenotypic evidence of Fabry's Disease)

4.4 STUDY-DRUG DOSING AND SYSTEMIC DRUG-LEVEL MONITORING

4.4.1 Study-Drug Dosing

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

of water or other non-alcoholic oral beverage, regardless of food intake. All patients will initially receive 70mg daily during weeks one and two in Period 1. Formal dose adjustments will not be done during this time, although the PEX dose may be decreased at any time for suspected elevated PEX levels or related AE.

4.4.2 Monitoring of Systemic Perhexiline and cis- and trans-Hydroxy Perhexiline

All determinations of systemic blood levels of PEX, CIS, and TRANS will be measured using the PEX-CIS assay.

On the morning of day 8 (± 1 day) (after completion of a minimum of 6 days of dosing) patients will provide a blood sample for the measurement of PEX, CIS and TRANS; the sampling timepoint will be scheduled at approximately 12h after dosing on the previous study day. The analytical results will be available within 3-5 calendar days of the blood sampling and results for PEX and CIS will be reported to the study sites. These will be used to determine the following:

- Patients deemed to be phenotypic PMs based on these results will 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 will provide a blood sample for the measurement of PEX, CIS and TRANS; the sampling timepoint will be scheduled at approximately 12h after dosing on the previous study day. The analytical results will be available within 3-5 calendar days of the blood sampling and results for PEX and CIS will be reported to the study sites. These will be 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 will be obtained and plasma levels of PEX, CIS and TRANS determined at the end (±3 days) of every second week (weeks 4, 6, and 8 in Period 1, and weeks 10, 12 and 14 in Period 2); the sampling timepoint will be scheduled at approximately 12h after dosing on the previous study day. The analytical results will be available within 3-5 calendar days of the blood sampling and results for PEX and CIS will be reported to the study sites. These will be used to guide dose adjustment according to Table 4.1 below and to evaluate the CIS:PEX ratio. At the conclusion (± 3 days) of Period 2 (end of Week 16), an additional blood sample will be obtained at approximately 12h after dosing on the previous study day and plasma levels of PEX, CIS and TRANS determined. A final blood sample will be obtained at the conclusion of the 4-week safety follow-up period (end of week 20) and plasma levels of PEX, CIS and TRANS determined.

4.4.3 Dose-Adjustment of Study Drug

Throughout the dosing period the following will apply:

1) PEX dose may be decreased at any time for suspected elevated PEX levels or related AE.
2) Possible PEX dose levels will be:
   a. Period 1: 35, 70, 105, 140, 175, and 210 mg (tablet strength of 35 mg).
   b. Period 2: 35, 70, 105, 140, 175, 210, 245, and 280 mg (tablet strength of 35 mg).
3) In general, only one dose adjustment should be made per two-week period starting at the end of week 2 in Period 1. If the PI thinks an additional dose adjustment should be made, the PI should contact the Medical Monitor.
4) Upon notification of a dose adjustment the site should contact patient as soon as possible to initiate dose adjustment.

5) To achieve the higher target range for PEX in Period 2, the dose will initially be adjusted based on the plasma PEX level measured at Week 6 in Period 1. This dose adjustment will be performed at the end of the Week 8 visit (start of Period 2) in accordance with the Period 2 column in Table 4.1. **Important:** Any change made at Week 6 will need to be accounted for when adjusting the dose at Week 8.

6) Dose adjustments will proceed based on the following criteria (see Table 4.1):

Table 4.1 Possible dose-adjustments in Periods 1 and 2

Systemic Perhexiline Levels (PEX) (ng/mL)**	**Period 1 (Weeks 2 – 8)** Target Range 100-300 ng/mL Start Dose of 70 mg/day, 2 tablets/day (tablets to be taken orally in the evening) Maximum Dose 210 mg (6 tablets)	**Period 2 (Weeks 9 – 16)** Target Range 300-500 ng/mL Start dose will be the dose-adjustment decision based on the Period 1, Week 6 level of PEX† (tablets to be taken orally in the evening) Maximum Dose 280 mg (8 tablets)
< 50	+2 tablets per day#	+2 tablets per day#
50 to 100	+1 tablet per day#	+2 tablets per day#
101 to 200	No change	+1 tablet per day#
201 – 300	No change	+1 tablet per day#
301 – 400	-1 tablet per day*	No change
401 – 500	-2 tablets per day*	No change
501 – 600	-3 tablets per day*	-1 tablet per day*
601 – 700	**Discontinue for 1 day**, and -3 tablets per day*	**Discontinue for 1 day**, and -2 tablets per day*
701 - 900	**Discontinue for 3 days**, and -4 tablets per day*	**Discontinue for 1 day**, and -3 tablets per day*
901 - 1200	**Discontinue for 7 days**, and -5 tablets per day*	**Discontinue for 3 days**, and -4 tablets per day*
> 1200	**Discontinue for 7 days**, and -5 tablets per day*	**Discontinue for 7 days**, and -5 tablets per day*

\# Unless the patient has already reached the highest daily dose permitted of six (6) tablets or 210 mg in Period 1 and eight (8) tablets or 280 mg in Period 2

* The lowest daily dose is one (1) tablet per day or 35 mg.

** Blood sampling for plasma PEX, CIS and TRANS measurement should be obtained approximately 12 hours following dosing on the previous day.

† Any change made at Week 6 will need to be accounted for when adjusting the dose at Week 8.

4.4.4 Dose-Adjustment for QTcF/JTcF Prolongation

Any dose adjustment instructions due to QTcF/JTcF prolongation will be at the direction of the ECG Core laboratory. Decisions to hold dosing until ECG Core Laboratory analysis is complete may be made at the site.

Dose adjustment for QTcF/JTcF prolongation (regardless of systemic PEX levels, unless the PEX levels and dose adjustment algorithm result in a dose reduction or discontinuation of a greater magnitude) will be done as described below for:

a. Patients with a QRS interval ≤ 100 msec WITH;
   - A prolonged QTcF > 540 msec OR,
   - An increase in QTcF > 75 msec over baseline AND QTcF > 500 msec
b. Whenever either the baseline or a subsequent ECG has a prolonged QRS > 100 msec, changes in the JTcF will be used for all further dose-adjustment decisions throughout the remainder of the study for those patients. In a patient with a baseline or an on-study ECG showing a QRS interval >100 msec, the dose will be adjusted as described below IF;
   - The change from baseline in JTcF is > 75 msec over baseline AND the JTcF interval is > 410 msec OR,
   - An on-study JTcF interval is > 450 msec

The dose of study drug for such patients will be stopped for 2 days and the daily dose subsequently reduced by 35 mg (for patients receiving ≤ 105 mg) or 70 mg (for patients receiving ≥ 140 mg) and restarted only if the QTcF/JTcF measurement has fallen back into the acceptable range for continued dosing. If the QTcF/JTcF measurement has NOT fallen back into the acceptable range after stopping drug for 2 days, the process of holding study drug and rechecking the ECG every 2 to 3 days will continue until the QTcF or JTcF limits are not exceeded and at which time study drug may be restarted at the reduced dose. The dose of study drug will not be increased any further during the remainder of the study (neither Period 1 or Period 2) if a dose reduction for QTcF or JTcF prolongation is required.

4.5 MANAGEMENT OF POSSIBLE PEX OVERDOSAGE

For the purpose of this study an overdose is defined when there is a systemic level of PEX >1,200 ng/ml at any timepoint. Suspected overdose associated with lower PEX systemic levels should also be reported as an AE or SAE if warranted by the clinical history and/or laboratory findings. Alternative explanations, such as a change in medications that may alter the patient's CYP2D6 metabolism, should be considered.

Reported symptoms following overdosage are nausea and vomiting. Other symptoms that have not been reported but would be anticipated are ataxia and headache. Hepatic damage and cardiac arrhythmias may possibly occur [Pexsig Product Information 2000].

Treatment should be symptomatic and supportive. PEX overdose should result in careful monitoring of drug levels, continuous cardiac monitoring and serial blood glucose recordings in diabetic patients. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Adequate urinary output should also be maintained.

Dialysis is not indicated because of the high degree of protein and tissue binding.

4.6 PATIENT WITHDRAWAL AND DISCONTINUATION

Patients have the right to withdraw from the study at any time without needing to give any reason. Should a patient withdraw, all efforts should be made to complete and report observations prior to withdrawal as thoroughly as possible. Patients who choose to discontinue from the study will not be replaced.

The Investigator may withdraw patients in the event of intercurrent illness, AEs, protocol violations, administrative or other reasons. The Investigator is strongly encouraged to contact the Medical Monitor prior to discontinuation of study drug or withdrawal of patient from the study.

Discontinuation of PEX or discontinuation from the study is **mandatory** for:

- Patients whose baseline VO2MAX is more than ±20% of their screening VO2MAX, *i.e.*;
  $(BASELINE\ VO2MAX - SCREEN\ VO2MAX)/\ SCREEN\ VO2MAX\ > \pm 20\%$
- Patients who are unable or unwilling to return to the study site to repeat a CPEX test that did not meet the prospectively defined acceptance criteria as determined by the centralized CPEX assessor
- Patients identified as PMs of PEX at the week 1 (day 8) study visit. Despite the screening genotyping, which is 95-97% effective at identifying PMs, there may a limited number of phenotypic PMs. Phenotypic PM subjects will be identified by determination of the PEX metabolic ratio (MR). This MR is the ratio of CIS to the parent compound, PEX. If the CIS:PEX is <0.4, the patient will be deemed a phenotypic PM regardless of genotype. These patients are at risk for clinically significant elevated plasma PEX levels. Such elevated plasma levels could decrease tolerability or increase the risk of short, self-limited toxicity; if unchecked longer term toxicities could result. Hence, as with the genotypic PMs, these phenotypic PM subjects will be withdrawn from the study. (Patients with a CIS:PEX ratio <0.4 after the week 1 visit will not automatically be withdrawn from the study. These patients should be further evaluated and the patient status will be discussed with the Medical Monitor.)
- Patients with persistent elevations in ALT or AST; see Appendix C for the definition of "persistent"
- Female study participants discovered to be pregnant during the treatment period

Discontinuation of PEX should be considered in the following situations [Phan *et al.*, 2009a] following discussion with the Medical Monitor:

- Appearance of new onset or exacerbation of peripheral neuropathy. However, discontinuation for peripheral neuropathy should only be done after consultation with the Medical Monitor.
- Persistent or marked hypoglycemia that is unresponsive to therapeutic modification (such as reduction of dose of insulin or oral hypoglycemic agent)
- Excessive weight loss
- Hospitalization for newly diagnosed ventricular tachycardia, or ventricular fibrillation

4.7 CONCOMITANT MEDICATION

Some medications or drug classes are known to have potential for adverse interactions with PEX. They may be used in the protocol, but they should be considered with caution. A list of these agents is included in the Appendix A: Concomitant Medication.

4.8 STUDY MONITORING TEAM

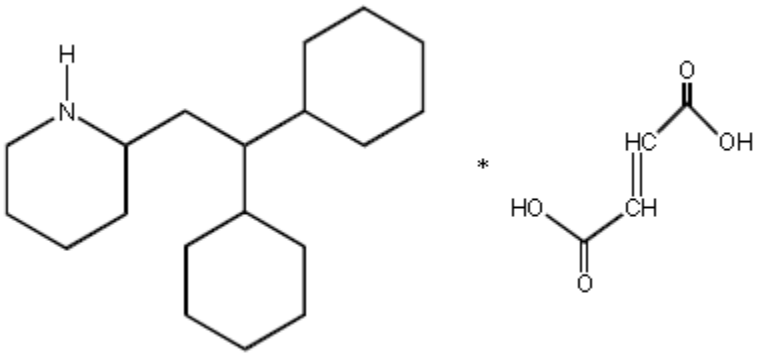
A Study Monitoring Team will be established to review and discuss the available study data as patients are enrolled. The team will evaluate all available data listings approximately every two months (until the study is completed) following 25% enrollment in the study. The review will include observed 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. The Study Monitoring Team will include at a minimum an independent cardiologist, the Medical Monitor (CRO), the study biostatistician (CRO), and a Sponsor representative.

5 STUDY DRUG SUPPLIES

5.1 PERHEXILINE

The pharmaceutical formulation contains PEX as its maleate salt (PHM); 2-(2,2-Dicyclohexylethyl) piperidine maleate and its chemical structure is shown in Figure 5.1. The molecular formula of PHM is $C_{19}H_{35}N,C_4H_4O_4$

Figure 5.1 Chemical Structure of PHM (CAS-6724-53-4)



5.2 STUDY DRUG FORMULATION

PEX investigational tablets will be supplied in a dose strength of 35 mg. The study-drug tablets will be packaged and supplied in induction-sealed HDPE bottles with child-resistant closures.

The investigational drug products are immediate release tablets containing 35 mg of PEX for every 50 mg of PHM. Excipients include mannitol, microcrystalline cellulose, starch, croscarmelose sodium, talc and magnesium stearate. The tablets are coated with an aqueous, yellow film coat.

5.3 DRUG STORAGE

All study drug required for completion of this study will be provided by the Sponsor or its designee. Upon receipt of clinical trial materials, the study-site recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. The Investigator or designee will inventory supplies and return appropriate copies of the shipment receipt form to the Sponsor and/or the drug supply vendor. The Investigator will maintain study drug in a pharmacy or locked and secure storage facility with a temperature control monitoring system, accessible only to those individuals authorized by the Investigator to dispense the study drug. The study drug should be stored at controlled room temperature from 15°C to 25°C with an allowed range up to 30°C for short time periods.

5.4 STUDY-DRUG DISPENSING AND DOSING INSTRUCTIONS

It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. All material not dispensed to patients must be accounted for and retained at the study site until the conclusion of the trial when the sponsor authorizes the destruction or return of material. The names and signatures of site personnel authorized by the Investigator to dispense study drug must be documented on the site personnel log, or other appropriate form.

Patients will be given instructions on the number of tablets to take in each dose and on the timing of dosing. All study-drug dosing must be completed in the evening (preferably 8-11p.m.) on every day of dosing (with the exception of the first dose of study drug, which will

be administered under the supervision of the study-site staff). Patients will record daily dosing (number of tablets taken) on each day in a patient diary designed for that purpose. In addition, the patients will record the time of dosing on the day prior to study-site visits to facilitate the calculation of the time of blood sampling (approximately 12h after dosing) for the determination of systemic study-drug levels. It is the Investigator's responsibility to ensure, at each study visit, that patients understand these dosing requirements.

Patients will be instructed to store their dispensed study-drug supplies at ambient room temperature and to take precautions to ensure that those supplies do not experience extremes of temperature (*e.g.*, not to store in a refrigerator, not to leave the study drug in their car or near a window where it may be exposed to direct sunlight and or heat for a prolonged period of time).

5.5 WITHDRAWAL OF PERHEXILINE AT STUDY TERMINATION

At completion of study-drug dosing or premature withdrawal, diabetic subjects who require hypoglycemic agents should be cautioned that the need for an increase in dosage of the hypoglycemic medications may be required when PEX is discontinued.

5.6 TREATMENT COMPLIANCE

Patients will record their study-drug dosing details in a diary which will be reviewed by study-site staff in addition to a study-drug tablet count at each study visit.

5.7 DRUG ACCOUNTABILITY

An accurate accounting of study medication received and dispensed must be recorded by the study pharmacist or designated study personnel on the Drug Accountability Forms. Investigational drug shipment requests, site records of drug receipt, dispensing records, and all inventory forms will be examined and reconciled for each subject enrolled in the study. Both used and unused drug must be accounted for on a drug disposition and accountability form. Instructions for return or destruction of unused drug will be reviewed at the end of the study. Copies of all drug accountability forms must be retained in the pharmacy and/or Investigator file on site and be available for inspection by the monitor or regulatory agency. Upon receipt of clinical trial materials, the Investigator or designee will inventory supplies and return appropriate copies of the shipment receipt form to the Sponsor or the drug supply vendor. The Investigator or designee will maintain adequate drug accountability records, including shipment and receipt forms, drug disposition with dates, quantity, dispensation, and use by subjects, and return forms.

The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other clinical sites, investigators or subjects, or allow the study drug to be used other than as directed by this protocol without prior authorization from the Sponsor or its designee.

Periodically during the study, the Sponsor or designee will conduct a drug supply inventory and verify disposition on the drug accountability log.

6 STUDY SCHEDULE AND ACTIVITIES

6.1 SCHEDULING WINDOWS FOR STUDY PROCEDURES AND EVALUATIONS

The scheduling windows for the various timepoints for study procedures and evaluations are summarized in Table 6.1, below. Study procedures and evaluations should be scheduled to commence in the morning of each study site visit.

Table 6.1 Time windows for study procedures and evaluations

Timepoint	Permitted Time Window
Screening	In the 28 days before the Baseline visit
Baseline Visit (Day 1)	This is time zero for the study and all other visit dates will be estimated in reference to this visit
Day 8 (±1 Day), End Week 1 / Start Week 2, Period 1	Day 7, 8, or 9; following at least the first 6 days of study-drug dosing
Day 15 (±1 Day), End Week 2 / Start Week 3, Period 1	Day 14, 15 or 16; following at least the first 13 days of study-drug dosing
All other timepoints	±3 Days. Subject should be taking study-drug until the day prior to the End of Treatment visit.

6.2 SCHEDULE OF ASSESSMENTS

The flowchart of procedures, measurements and other assessments is shown in table 6.2.

Table 6.2 Schedule of Time and Events for Protocol Activities

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 History, 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 must be performed within 28 days prior to dosing.

B. Entry criteria to be evaluated: Baseline CPEX compared to Screening CPEX, and ECG exclusion criteria

C. ECGs should be done in triplicate prior to blood draws when possible and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes.

D. ECGs will be done first, the CPEX test will be second, and the 6MWT will be the last procedure completed during any visit by the patient to the study site in order to facilitate the patient's ability to adequately complete a CPEX and a 6MWT in a single day

E. The baseline ECG must not meet any of the exclusion criteria detailed in section 4.3.2; this must be confirmed by the central ECG reader before study-drug can be dispensed to the patient

F. i. All CPEX test results will be reviewed by the centralized CPEX assessor for compliance with prospectively defined CPEX test acceptance criteria

ii. The Screening CPEX will be performed to show that patient is 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 must be confirmed by the centralized CPEX assessor before the Baseline CPEX is done

ii. The Baseline VO_{2MAX} must not vary from the screening VO_{2MAX} by more than ±20% (with the screening test being the reference); this will 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 deems the EOT CPEX test to be invalid**,** the subject 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 will be sent to the central lab for analysis (with the exception of the urine pregnancy test at Baseline which will be performed locally).

K. Females of child bearing potential. (Eligible patients will 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 is defined by the CPIC guidelines.

P. All determinations of systemic blood levels of PEX, CIS, and TRANS will be measured using the PEX-CIS assay. Blood sampling for determination of PEX, CIS and TRANS will be scheduled approximately 12h after dosing on the previous study day. Results for PEX and CIS will be reported to the study sites for confirmation of a patient's phenotypic status for PEX metabolism and for dose-adjustment decisions.

Q. Patients will 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 will be dispensed once the ECG Corelab confirms that the Baseline ECG meets the entry criteria. The first study-drug dose will be administered under the supervision of the study-site staff once the study-site staff confirm that the Baseline VO_{2MAX} is within ±20% of the Screening CPEX.

Note:

- If for any reason the ECG Corelab is not able to immediately confirm the ECG outcome, the patient will return home without receiving any dispensed study-drug. In such cases, once the ECG Corelab confirmation becomes available the patient will return to the site to collect the study-drug supply. The patient will then commence study-drug dosing (defined as Day 1).
- All Baseline ECG confirmations will be received by study sites from the ECG Corelab within a maximum of 48h.
- Before dosing has commenced; if the centralized CPEX assessor confirms the Baseline VO_{2MAX} is not within ±20% of the Screening CPEX then the patient will not enter the study
- Before dosing has commenced; if the centralized CPEX assessor confirms an invalid Baseline VO_{2MAX} the patient will be invited to repeat the Baseline CPEX test within the 28-day period allowed between Screening and the start of study-drug dosing
- After dosing has commenced; if the centralized CPEX assessor deems the Baseline CPEX test to have been invalid or not within ±20% of the Screening CPEX then the patient will remain in the study and the patient's Screening CPEX result will be taken as the valid Baseline result
- All Baseline CPEX confirmations will be received by study sites from the centralized CPEX assessor within a maximum of 48h.

S. AEs should be documented and recorded at each visit. All AEs (serious and non-serious, and related and non-related) will be documented and recorded through the Follow-Up visit. Patients must 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 is 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 should 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 will be recorded.

6.3 SCREENING

In the 28 days before the start of study-drug dosing, patients will attend the investigational site where they will be screened for eligibility to enter the study. Once a patient has given written informed consent to participate in the study the following procedures and measurements will be completed and recorded for each patient:

- Inclusion and exclusion criteria will be reviewed
- Demographic data, including age, will be recorded
- Medical history will be recorded
- A physical examination including vital signs and body weight, will be measured; heart rate and blood pressure will be measured in the seated position after 5 minutes of rest
- A 12-lead ECG will be recorded in triplicate; ECGs should be taken prior to CPEX testing or blood draws and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes
- CPEX Testing to establish VO_{2MAX} will be done; the screening CPEX test results must confirm that the patient is able to perform exercise testing but unable to exceed 75% of the predicted age-adjusted maximum level
    - A valid Screening CPEX must be confirmed by the centralized CPEX assessor before the Baseline CPEX is done
- Blood samples will be taken for routine laboratory testing at a central laboratory including;
    - Serum pregnancy test for female patients of child bearing potential; eligible patients will be advised to use an adequate contraceptive method
    - Serum Chemistry; sodium, potassium, bicarbonate, chloride, calcium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, lactate dehydrogenase, total cholesterol
    - Complete blood count; hemoglobin, hematocrit, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution, white blood cells with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils), platelets
    - CYP2D6 Metabolizer status
    - Coagulation tests: prothrombin time, partial thromboplastin time, and international normalized ratio.
    - Biomarker; Hemoglobin A1c
- AEs that occur after the signing of the informed consent form
- Prior and concomitant medication will be recorded; prior medications received up to and including 30 days prior to the start of study medication will be recorded

6.4 PERIOD 1: BASELINE VISIT AND COMMENCEMENT OF STUDY-DRUG DOSING

Once a patient has met the entry criteria for the study and completed all of the screening procedures they will then visit the study site for the baseline visit and commencement of study-drug dosing in Period 1. At this visit the following will be completed:

- A 12-lead ECG will be recorded in triplicate
    - ECGs should be taken prior to CPEX testing or blood draws and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes

  - The baseline ECG must not meet any of the exclusion criteria detailed in section 4.3.2; this must be confirmed by the central ECG reader before study-drug can be dispensed to the patient
- CPEX testing will follow ECG recording
  - The Baseline VO2MAX must not exceed ±20% of the Screening VO2MAX with the screening test being the reference (i.e., $(BASELINE\ VO2MAX - SCREEN\ VO2MAX)/\ SCREEN\ VO2MAX \leq \pm 20\%$); this will be calculated by study-site staff in order to allow a decision on patient inclusion in the study during the Baseline site-visit
  - All Baseline CPEX test validation reports will be received by study sites from the centralized CPEX assessor within a maximum of 48h; the timing of the availability of the centralized CPEX assessor report will define the following status for the patients:
    - CPEX Report BEFORE study-drug dosing has started shows VO2MAX is not within ±20% of the Screening CPEX; the patient will not enter the study
    - CPEX Report BEFORE study-drug dosing has started shows an invalid test; the patient will be invited to repeat the Baseline CPEX test within the 28-day period allowed between Screening and the start of study-drug dosing
    - CPEX Report AFTER study-drug dosing has started shows an invalid test or shows VO2MAX is not within ±20% of the Screening CPEX; the patient will remain in the study and the patient's Screening CPEX result will be taken as the valid Baseline result
- Vital signs and body weight, will be measured; heart rate and blood pressure will be measured in the seated position after 5 minutes of rest
- Urine sampling for an on-site urine pregnancy test for female patients of child bearing potential
- Study-drug storage, dosing and accountability instructions will be reviewed with the patient
- Study-drug sufficient for daily dosing until the next scheduled patient visit to the study site will be dispensed to the patient
  - Study-drug will be dispensed once the ECG Corelab confirms that the Baseline ECG meets the entry criteria
  - If for any reason the ECG Corelab is not able to immediately confirm the ECG outcome, the patient will return home without receiving any dispensed study-drug. In such cases, once the ECG Corelab confirmation becomes available the patient will return to the site to collect the study-drug supply. The patient will then commence study-drug dosing (defined as Day 1).
  - All Baseline ECG confirmations will be received by study sites from the ECG Corelab within a maximum of 48h.
- If, during the Baseline visit, the ECG Corelab confirms that the Baseline ECG meets the entry criteria, the first dose of study-drug will then be administered to the patient under the supervision of the study-site staff. If for any reason the ECG Corelab is not able to immediately confirm the ECG outcome, the patient will return home without receiving any dispensed study-drug. In such cases, once the ECG Corelab confirmation becomes available the patient will return to the site to collect the study-drug supply. The patient will then commence study-drug dosing.
  - The day study-drug dosing commences will be Day 1 of Week 1 in Period 1

- AEs since the patient's previous site visit will be recorded. (As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of an SAE.)
- Concomitant medication used since the patient's previous visit will be recorded
- A 6MWT will be done as the last procedure of the Baseline visit

6.5 PERIOD 1; DAY 8 (± 1 DAY), AFTER COMPLETION OF WEEK 1 (AFTER COMPLETION OF AT LEAST SIX DAYS OF DOSING)

After a minimum of 6 days of study-drug dosing the following will be completed:

- A blood sample will be obtained for analysis of PEX, CIS and TRANS approximately 12h after dosing on the previous study day
    - CIS:PEX ratio will be evaluated for phenotypic PM status (Section 4.4.2)
- Study-drug storage, dosing and accountability instructions will be reviewed with the patient
- Study-drug sufficient for daily dosing until the next scheduled patient visit to the study site will be dispensed to the patient
- AEs since the patient's previous site visit will be recorded. (As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of an SAE.)
- ADEs will be assessed for and recorded
- Concomitant medication used since the patient's previous visit will be recorded

6.6 PERIODS 1 AND 2; AFTER COMPLETION OF WEEK 2 (DAY 15 ±1 DAY) AND WEEKS 4, 6, 8, 10, 12 & 14 (DAYS 29, 43, 57, 71, 85 & 99 ±3 DAYS)

At these timepoints the following will be completed:

- Vital signs will be measured; heart rate and blood pressure will be measured in the seated position after 5 minutes of rest
- A 12-lead ECG will be recorded in triplicate; ECGs should be taken prior to CPEX testing (Week 8 only) or blood draws and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes
- A blood sample will be obtained for analysis of PEX, CIS and TRANS approximately 12h after dosing on the previous study day (blood sampling after 2 weeks must be done within ±1 day of study Day 15, and after the completion of at least 13 days of dosing; at all other study visits the blood sample will be obtained within ±3 days of the calculated calendar date for the visit).
    - Evaluate CIS:PEX ratio (see Section 4.4.2)
    - Evaluate for dose adjustment (see Section 4.4.3)
- Study-drug storage, dosing and accountability instructions will be reviewed with the patient
- Study-drug sufficient for daily dosing until the next scheduled patient visit to the study site will be dispensed to the patient
- AEs since the patient's previous site visit will be recorded. (As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of an SAE.)
- ADEs will be assessed for and recorded
- Concomitant medication used since the patient's previous visit will be recorded

6.7 PERIOD 1; ADDITIONAL PROCEDURES AT COMPLETION OF WEEK 8 (DAY 57) VISIT

In addition to the procedures described above in section 6.6, the following procedures will be completed during the Period 1, Week 8 (Day 57) study visit:

- CPEX testing will be done following completion of the ECG recordings
- Body weight will be measured
- Blood samples will be obtained for routine serum chemistry safety tests and for biomarker levels of hemoglobin A1c
- The 6MWT will be done as the last procedure of the Week 8 visit

6.8 PERIOD 2: END OF TREATMENT AND AFTER COMPLETION OF WEEK 16 (DAY 113 ±3 DAYS)

Dosing should continue through the day prior to this visit. At this visit the following will be completed:

- A 12-lead ECG will be recorded in triplicate; ECGs should be taken prior to CPEX testing or blood draws and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes
- CPEX testing will be done following completion of the ECG recordings
    - If the centralized CPEX assessor deems the EOT CPEX test to be invalid**,** the subject may be required to return for a repeat test
- Vital signs and body weight, will be measured; heart rate and blood pressure will be measured in the seated position after 5 minutes of rest
- A blood sample will be obtained for analysis of PEX, CIS and TRANS approximately 12h after dosing on the previous study day
- Blood samples will be obtained for a complete blood cell count, routine serum chemistry safety tests and for biomarker levels of hemoglobin A1c
- Study-drug accountability will be reviewed with the patient. All remaining study-drug will be collected.
- AEs since the patient's previous site visit will be recorded. (As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of an SAE.)
- ADEs will be assessed for and recorded
- Concomitant medication used since the patient's previous visit will be recorded
- A 6MWT will be done as the last procedure of the week 16 visit

6.9 FOLLOW-UP VISIT (FOUR WEEKS FOLLOWING THE CONCLUSION OF DOSING)

At this visit the following will be completed:

- Vital signs and body weight, will be measured; heart rate and blood pressure will be measured in the seated position after 5 minutes of rest
- A 12-lead ECG will be recorded in triplicate; ECGs should be taken prior to blood draws and obtained after the patient has been resting comfortably in a supine position for approximately 10 minutes
- A blood sample will be obtained for analysis of PEX, CIS and TRANS
- Blood samples will be obtained for a complete blood cell count, routine serum chemistry safety tests, a pregnancy test and for biomarker levels of hemoglobin A1c
- AEs since the patient's previous site visit will be recorded. (As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of an SAE.)

- ADEs will be assessed for and recorded
- Concomitant medication used since the patient's previous visit will be recorded

6.10 PATIENT CONTACT FOR DOSE-ADJUSTMENT INSTRUCTIONS

When the laboratory result for the levels of PEX and CIS are available the Investigators will decide if a dose adjustment is required according to the dose adjustment guidelines presented in section 4.4. Patients who require dose adjustment will be contacted immediately by study-site personnel who will ensure that the dose-adjustment required is fully understood by the patient who will initiate the required dose adjustment at their next scheduled study drug dosing.

6.11 SUBJECTS WHO WITHDRAW FROM THE STUDY

If a patient chooses to withdraw from the study during the study-drug dosing phase in Period 1 and 2, the study-site will attempt to get the following information before the patient is lost to follow-up:

- Vital signs
- Blood sample for PEX, CIS and TRANS
- Blood sampling for a full blood cell count, routine safety serum chemistry tests, serum pregnancy test and serum levels of hemoglobin A1c
- 12-Lead ECG
- CPEX Testing
- 6MWT
- Treatment Compliance
- Concomitant Medications
- AEs
- Study-drug accountability

7 SAFETY MONITORING

The Study Monitoring Team will review all available data in listings approximately every 2 months (until the study is completed) following 25% enrollment in the study with an emphasis on observed outcomes related to patient safety and tolerance (*i.e.*, AEs, ADEs, vital signs measurements, ECGs, laboratory assessments, and concomitant medications). These listing 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.

7.1 ADVERSE EVENTS

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

7.2 LIFE-THREATENING ADVERSE EVENT OR LIFE-THREATENING SUSPECTED ADVERSE REACTION

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

7.3 SERIOUS ADVERSE EVENT OR SERIOUS SUSPECTED ADVERSE REACTION

A Serious Adverse Event (SAE) or serious suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor the event:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (*e.g.*, medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

All pregnancies, regardless of outcome, should be reported to the Sponsor, including pregnancies that occur in the female partner of a male study subject. All pregnancies should be followed to outcome.

Although overdose (PEX >1,200 ng/ml) is not always serious by regulatory definition, this event should be reported as an SAE in this study. Suspected overdose associated with lower PEX systemic levels should also be reported as an AE or SAE if warranted by the clinical history and/or laboratory findings. Alternative explanations, such as a change in medications that may alter the patient's CYP2D6 metabolism, should be considered.

Cancer, also, is not always serious by regulatory definition; this event (excluding basal-cell or squamous-cell carcinomas of the skin) should be reported to the Sponsor at the earliest possible moment.

NOTE: The following hospitalizations are not considered SAEs in the Sponsor's clinical studies:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (*e.g.*, routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (*e.g.*, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.4 SUSPECTED ADVERSE REACTION

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.5 UNEXPECTED ADVERSE EVENT OR UNEXPECTED SUSPECTED ADVERSE REACTION.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.6 ASSIGNMENT OF ADVERSE EVENT INTENSITY AND RELATIONSHIP TO PERHEXILINE

All AEs, including those that are serious, will be graded by the investigator as follows [NCI Guidelines, 2013]:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2); minimal, local, or non-invasive intervention (*e.g.*, packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living.
- Severe (Grade 3): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used [NCI Guidelines, 2013]:

- Unrelated: The AE is clearly not related to the intervention
- Possibly related: The AE may be related to the intervention
- Probably Related: The AE is likely related to the intervention.
- Definitely Related: The AE is clearly related to the intervention.

7.7 COLLECTION AND REPORTING OF ADVERSE EVENTS

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs:

- Onset,

- Duration,
- Intensity,
- Seriousness,
- Relationship to investigational product,
- Action taken,
- Treatment, if required.

If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply the Sponsor and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with any additional information requested, notably for reported deaths of subjects.

Completion of supplemental case report forms (CRFs) may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

7.7.1 Reporting Serious Adverse Events or Serious Suspected Adverse Reaction

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs should continue for 30 days after the last administration of PEX. If applicable, SAEs must be collected that relate to any later protocol-specified procedure. The investigator should notify the Sponsor of any SAE occurring after this time period that is believed to be related to the investigational product or protocol specified procedure.

If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

As part of the investigation and reporting of all SAEs, every attempt will be made to obtain a blood sample for analysis of PEX, CIS and TRANS as soon as possible after awareness of the event.

7.7.2 Handling of Expedited Safety Reports

In accordance with local regulations, the Sponsor will notify investigators and appropriate regulatory authorities of all unexpected SAEs having a "reasonable possibility" that the drug caused the event (*i.e.* there is evidence to suggest a causal relationship between the drug and the AE) /serious unexpected suspected adverse reactions (SUSARs).

Other important findings that the Sponsor may report as Expedited Safety Reports (ESR) include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (*e.g.*, animal) study, important safety recommendations from a study data monitoring committee, or the decision by the Sponsor to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from the Sponsor, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the Sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, the Sponsor will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.7.3 Non-serious Adverse Events

Following the subject's written consent to participate in the study, the investigator will begin collecting non-serious AE (NSAE) information. All identified NSAEs must be recorded and described on the AE case report form. If an ongoing NSAE worsens in its intensity, or if its relationship to the investigational product changes, a new NSAE entry for the event should be completed. NSAEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow up is also required for drug-related NSAEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with drug-related NSAEs at study completion should receive post-treatment follow up as appropriate.

7.8 LABORATORY TEST ABNORMALITIES

All laboratory test results captured as part of the study should be recorded following institutional procedures. When reporting a test result that constitutes an AE, the clinical term should be used; for example, the event should be reported as "anemia" not "low hemoglobin." Test results that constitute SAEs should be documented and reported as such.

7.9 ADVERSE DEVICE EFFECTS

If an AE or SAE is 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 or a Serious ADE (SADE) for the purpose of device reporting and statistical analysis.

7.9.1 Definitions

Adverse device effect (ADE): AE related to the use of an investigational medical device (PEX-CIS assay in the study).

Serious adverse device effect (SADE): ADE that has resulted in any of the consequences characteristic of a serious AE.

7.9.2 Reporting of ADEs

When assessing, recording, and reporting ADEs or SADEs, the same intensity grading system (Section 7.6) and reporting period (Sections 7.7.1 and 7.7.3) will be used for collecting and reporting of AEs.

ADEs will be reported on a separate ADE report form.

7.9.3 Unanticipated Adverse Device Effect (UADE)

An ADE or SADE is considered "unanticipated" if it was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The sponsor will immediately conduct an evaluation of any UADE.

7.10 PEX OVERDOSE

A PEX overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that results in a systemic level of PEX >1,200 ng/mL. All occurrences of overdose with a systemic PEX level > 1,200 ng/mL must be reported as an SAE. Suspected overdose associated with lower PEX systemic levels should also be reported as an AE or SAE if warranted by the clinical history and/or laboratory findings. Alternative explanations, such as

a change in medications that may alter the patient's CYP2D6 metabolism, should be considered.

7.11 PREGNANCY

Before study enrollment, women of child-bearing potential should be adequately advised on the potential risks versus benefits of PEX by the Investigator, including the potential risks to a human fetus.

7.11.1 Pregnancy Testing

Pregnancy testing will be performed as outlined in Section 6. If the pregnancy of a female study participant is discovered during the treatment period, the study medication should be discontinued.

7.11.2 Reporting of Pregnancy

If, while taking PEX, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after administration, the investigator will notify the Sponsor of this event and record the pregnancy on the Pregnancy Surveillance Form (not on an SAE form). Initial information on a pregnancy must be reported to the Sponsor, and information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to the Sponsor according to SAE reporting procedures.

Note: Any pregnancy that occurs in a female partner of a male study subject must also be reported to the Sponsor using the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow up must be performed for the subject unless contraindicated. Other appropriate pregnancy follow up procedures should be considered if indicated. Information regarding the course of the pregnancy, including perinatal and neonatal outcome, must be reported to the Sponsor on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

7.12 OTHER SAFETY CONSIDERATIONS

Any significant worsening noted in electrocardiograms, x-rays, and any other potential safety or physical assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

8 STATISTICAL CONSIDERATIONS

8.1 PRIMARY AND SECONDARY ENDPOINTS

8.1.1 Primary Endpoint

The primary endpoint of the study is the change from baseline of VO_{2MAX} at the end of Period 2 of the study.

8.1.2 Secondary Endpoints

The secondary endpoints of the study are:

- The change from baseline of VO_{2MAX} at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2.
- An evaluation of the change in VO_{2MAX} at the end of study-drug dosing Period 1 compared to baseline will be performed.
- 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

- The change from baseline at the end of study-drug dosing Period 2 in the Six-Minute Walk Test (6MWT) and change from baseline at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2
- Safety data (AEs, ECG abnormalities, routine laboratory safety test of blood, vital signs, and concomitant medication and patient withdrawals) during study-drug dosing Period 1 compared to study-drug dosing Period 2

8.1.3 Exploratory Endpoints

Exploratory endpoints are:

- Change from baseline of other ECG variables at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2
- Change from baseline of HbA1c at the end of study-drug dosing Period 1 compared to the change from baseline at the end of study-drug dosing Period 2

8.2 SAMPLE SIZE DETERMINATION

A two-sided, one-sample t-test of the change from baseline for the end of Period 2 is planned with the following assumptions:

- Mean change from baseline for Period 1 is 1.2mL O_2/kg/min
- Mean change from baseline for Period 2 is 2.0mL O_2/kg/min
- Standard deviation of change from baseline is 2.5mL O_2/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.

8.3 PATIENT POPULATION FOR ANALYSIS

The population for analysis for the primary, secondary and exploratory endpoints will be the Completer Population which will include all patients who complete all study procedures at Baseline, end of Period 1 and end of Period 2.

The population for safety analysis will be the Safety Population which will include all patients who start study-drug dosing following their baseline visit to the study site. The efficacy analysis will be repeated on the safety population

8.4 ANALYSES

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented as data listings and summary statistics.

8.4.2 Safety Analyses

8.4.2.1 Adverse Events

The original terms recorded on the subject's CRF by the Investigator for AEs will be standardized by assigning preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA). The Investigator, however, should ensure that the original terms recorded accurately reflect their intended description. All AEs will be described by individual subject listings and summarized in frequency tables broken down by body system, preferred term and dose group.

8.4.2.2 Vital Signs

Vital signs data will be presented in individual listings. In addition, tabular summaries will be used, as appropriate.

8.4.2.3 Clinical Laboratory Test Results

All clinical laboratory data will be presented as patient listings and summary statistics at each assessment time. Values outside the reference ranges will be flagged. As appropriate, summaries may also include change from Baseline and shift tables.

8.4.2.4 Concomitant Medications

The original terms recorded on the patient's eCRF for concomitant medications will be standardized by using the World Health Organization Drug (WHO Drug) coding dictionary. Concomitant medications will be listed by patient.

8.4.3 Efficacy Analyses

All CPEX tests will be assessed by the centralized CPEX assessor for compliance with prospectively defined CPEX test-protocol criteria.

A two-sided, one-sample t-test is planned for the comparison of $VO2_{MAX}$ at the end of Period 2 compared to baseline. The secondary and exploratory efficacy endpoints of the study will be examined by appropriate statistical methods as described in the statistical analysis plan.

8.4.4 Pharmacokinetic Analyses

Pharmacokinetic data (PEX, CIS and TRANS) will be listed by patient, and summarized for each sampling timepoint.

8.4.5 Pharmacogenetic Analyses

Pharmacogenetic data (CYP2D6 genotyping at screening) will be listed by patient, and incidences of polymorphisms will be summarized.

8.4.6 Pharmacodynamic Analyses

Hemoglobin A1c data will be presented as patient listings and summary statistics at each assessment time. Values outside the reference ranges will be flagged. As appropriate, summaries may also include change from Baseline and shift tables.

8.4.7 Ongoing Data Review and Analyses

8.4.7.1 Study Monitoring Team

All available data will be presented in listings approximately every 2 months (until the study is completed) following 25% enrollment in the study with an emphasis on observed outcomes related to patient safety and tolerance (*i.e.*, AEs, 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 or actions should be instituted to ensure the safety of the patients.

8.4.7.2 CPEX Analysis Following Completion of Period 1

A snapshot of the database will be taken for the CPEX data (listings and summary statistics) when all patients have completed Week 8. A two-sided, one-sample t-test will be performed for the comparison of $VO2_{MAX}$ at the end of Period 1 compared to baseline.

8.5 REPLACEMENT POLICY

Patients who withdraw from the study or are discontinued for any reason will not be replaced.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 GOOD CLINICAL PRACTICE

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical

principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study. The protocol, amendments, and ICF will also be submitted to regulatory authorities prior to commencing the trial as required.

All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (*e.g.*, loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

9.2 INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator will have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (*e.g.*, advertisements), and any other written information to be provided to subjects. The investigator will also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator will provide the IRB/IEC with reports, updates, and other information (*e.g.*, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

9.3 INFORMED CONSENT

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

Subjects unable to give their written consent may be enrolled in the study only with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, they must personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 COMPLIANCE WITH THE PROTOCOL

The study must be conducted as described in the final IRB/IEC-approved protocol. Documentation of approval, signed by the IRB/IEC chairperson or designee, will be sent to the Sponsor.

10.2 PROTOCOL MODIFICATIONS

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the coordinating investigator. Protocol modifications must be prepared, reviewed and approved by the Sponsor and by the relevant IRBs/IECs.

All protocol amendments and revisions to the informed consent will be submitted to the Sponsor and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the Sponsor and IRB/IEC; however, they do not require approval. The protocol, amendments, and ICF will also be submitted to regulatory authorities prior to commencing the trial as required.

If a protocol amendment mandates a revision to the informed consent, the revised consent must be used to obtain consent from subjects currently enrolled in the study if it affects them (*e.g.*, if it contains new information regarding safety), and the revised consent must be used to obtain consent from new subjects before enrollment.

10.3 PROTOCOL TERMINATION

Both the Sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

10.4 AUDITS, MONITORING AND INSPECTIONS

This study will be monitored by the Sponsor regularly to verify informed consent, source documentation, etc., are collected and stored according to the regulations and the data is entered into the electronic case report forms accurately.

10.5 RECORDS RETENTION AND DATA PROTECTION

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects as well as those entered as control subjects, if applicable. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (*e.g.*, the medical record) for the maximum period required by applicable regulations and guidelines or following institutional procedures. If the investigator withdraws from the study (*e.g.*, relocation or retirement), the records will be transferred to a mutually agreed upon designee, such as another investigator or an IRB. Written documentation of such transfer will be provided to the Sponsor.

The patient's personal data and Investigator's personal data which may be included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.6 PUBLICATION OF DATA

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accord with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor's personnel. Authorship will be determined by mutual agreement.

11 REFERENCES

1. Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, Kaur K, Taylor J, Henning A, Ashrafian H, Watkins H, Frenneaux M. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. Circulation. 2010;122:1562-9.
2. Ashrafian H, Horowitz JD, Frenneaux MP. Perhexiline. Cardiovasc Drug Rev. 2007;25:76-97.
3. Ashrafian H, McKenna WJ, Watkins H. Disease pathways and novel therapeutic targets in hypertrophic cardiomyopathy. Circ Res. 2011;109(1):86-96.
4. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122:191–225.
5. Barry WH, Horowitz JD, Smith TW. Comparison of negative inotropic potency, reversibility, and effects on calcium influx of six calcium channel antagonists in cultured myocardial cells. Brit J Pharmacol. 1985;85:51-59.
6. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, Elliott PM. Cardiopulmonary Exercise Testing and Prognosis in Hypertrophic Cardiomyopathy. Circ Heart Fail. 2015;8:1022-1031.
7. Crews, KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, Haidar CE, Shen DD, Callaghan JT, Sadhasivam S, Prows CA, Kharasch ED, Skaar TC. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharm Therap 2014;95:(4):376-382.
8. Drury NE, Howell NJ, Weber RJM, Calvert MJ, Lewis ME, Viant MR, Freemantle N, Frenneaux MP, Pagano D. Effect of perhexiline on myocardial protection during coronary artery surgery: a two-centre randomized double-blind placebo-controlled trial. Lancet. 2013;381:S36.
9. Drury NE, Licari G, Chong C-R,Howell NJ, Frenneaux MP, Horowitz JD, Pagano D, Sallustio BC. Relationship between plasma, atrial and ventricular perhexiline concentrations in humans: insights into factors affecting myocardial uptake. Brit J Clin Pharmacol. 2014;77:(5):789-795.
10. Eichenbaum G, Pugsley MK, Gallacher DJ, Towart R, McIntyre G, Shukla U, Davenport JM, Lu HR, Rohrbacher J, Hillsamer V. Role of mixed ion channel effects in the cardiovascular safety assessment of the novel anti-MRSA fluoroquinolone JNJ-Q2. Brit J Pharmacol. 2012;166:1694–1707.
11. Force T, Bonow RO, Houser SR, Solaro RJ, Hershberger RE, Adhikari B, Anderson ME, Boineau R, Byrne BJ, Cappola TP, Kalluri R, LeWinter MM, Maron MS, Molkentin JD, Ommen SR, Regnier M, Tang WH, Tian R, Konstam MA, Maron BJ, Seidman CE. Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute. Circulation. 2010;122(11):1130-3.
12. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, *et al.* 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm

Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:(25):212-260.

13. Grima M, VeHy J, Decker N, Marconiak G, Schwartz J. Inhibitory effects of some cyclohexylaralkylamines related to perhexiline on sodium binding, influx of [^{3}H]batrachotoxinin A 20-α-benzoate and [^{3}H] nitrendipine on guinea pig left atria contractions. Euro J Pharmacol. 1988;147:173-185.
14. Horowitz JD, Chirkov YY. Perhexiline and hypertrophic cardiomyopathy: a new horizon for metabolic modulation. Circulation. 2010;122(16):1547-9.
15. Hülsman R, Berger R, Storm B, Bojic A, Woloszczuk W, Bergler-Klein, Pacher R. Prediction of outcome by neurohumoral activation, the six minute walk test and the Minnesota Living with Heart Failure Questionnaire in an outpatient cohort with congestive heart failure. Eur Heart J. 2002;23:886-91.
16. Hussein, R, Charles BG, Morris, RG, Rasiah, RL. Population pharmacokinetics of perhexiline from very sparse, routine monitoring data. Therapeutic Drug Monitoring. 2001;23(6):636-643.
17. Krikler DM, Davies MJ, Rowland E, Goodwin JF, Evans RC, Shaw DB. Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways. Br Heart J. 1980;43(3):245-51.
18. McKenna WJ, Camm AJ. Sudden death in hypertrophic cardiomyopathy. Assessment of patients at high risk. Circulation. 1989;80(5):1489-92.
19. Mould D. Population Pharmacokinetic Analysis of Heart Metabolics Perhexiline, Protocol HM-PHX-004. Projections research Inc. 2016; Study Report for Heart Metabolics Ltd.
20. Morimoto S. Sarcomeric proteins and inherited cardiomyopathies. Cardiovasc Res. 2008 Mar 1;77(4):659-66.
21. National Cancer Institute Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs (Effective September 16, 2013).

    http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm
22. Pexsig Product Information. Aspen Pharma Pty Ltd. 2000.
23. Phan TT, Abozguia K, Shivu GN, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux, M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. Journal of the American College of Cardiology. 2009a;54(5):402-9.
24. Phan TT, Shivu GN, Choudhury A, Abozguia K, Davies C, Naidoo U, Ahmed I, Yousef Z, Horowitz J, Frenneaux M. Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. Eur J Heart Fail. 2009b;11:881-6.
25. Rampe D, Wang Z, Fermini B, Wible B, Dage RC, Nattel S. Voltage- and Time-Dependent Block by Perhexiline of K^+ Currents in Human Atrium and in Cells Expressing a Kv1.5-Type Cloned Channel. J Pharmacol Exp Ther. 1995;274:444-449.
26. Sager PT, Gintant G, Turner JR, *et al.* Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J 2014;167:292-300.
27. Shantsila E, Watson T, Lip GYH. Drug-induced QT-interval prolongation and proarrhythmic risk in the treatment of atrial arrhythmias. Eur Soc Cardiol. 2007;Suppl 4:iv37-44.
28. Walker BD, Valenzuela SM, Singleton CB, Tie H, Bursill JA, Wyse KR, Qiu MR, Breit SN, Campbell TJ. Inhibition of HERG channels stably expressed in a mammalian cell line by the antianginal agent perhexiline maleate. Brit J Pharmacol. 1999;127:243-251.

29. Woosley, RL and Romero, KA, *www.crediblemeds.org*, QT Drugs List, Accession Date October 1, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.

12 ABBREVIATIONS

Abbreviation	Definition
6MWT	Six minute walk test
ADE	Adverse device effect
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAD	Coronary Artery Disease
CIS	*cis*-Hydroxy-Perhexiline
CMR	Cardiovascular Magnetic Resonance
CPEX	Cardiopulmonary Exercise
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPK	Creatine Phosphokinase
CPT	Carnitine palmitoyltransferase
CRO	Contract Research Organization
CYP2D6	Cytochrome P450 2D6
CRF	Case Report Form(s)
ECG	Electrocardiogram or electrocardiographic
EM	Extensive Metabolizer
ESR	Expedited safety report
GCP	Good clinical practice
GLP	Good laboratory practice
HbA1c	Hemoglobin A1c or glycosylated hemoglobin
HCM	Hypertrophic Cardiomyopathy
ICD	Implantable cardiac defibrillator
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intermediate metabolizer
IND	Investigational New Drug
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LGE	Late Gadolinium Enhancement
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
MICE	Multiple Ion Channel Effect
MPI	Myocardial Perfusion Imaging
NHLBI	National Heart, Lung, and Blood Institute
NSAE	Non-serious adverse event

Abbreviation	Definition
PET	Positron Emission Tomography
PEX	Perhexiline
PHM	Perhexiline Maleate, when referring to the pharmaceutical formulation
PK	Pharmacokinetic
PM	Poor metabolizer
QTc	Corrected QT interval
QTcF	QT corrected according to Fridericia's formula
SADE	Serious adverse device effect
SAE	Serious adverse event
SCD	Sudden Cardiac Death
SPECT	Single Photon Emission Computed Tomography
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsade de Pointes
TEE	Trans-Esophageal Echocardiogram
TQT	Thorough QT
TRANS	*trans*-Hydroxy-Perhexiline
TTE	Trans-Thoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
UM	Ultra-rapid metabolizer
VO_{2MAX}	Maximal oxygen consumption
VT	Ventricular Tachycardia

APPENDIX A: CONCOMITANT MEDICATION

The following agents (and drug classes) may have interactions with the effects or metabolism of PEX and should be used with caution:

- Insulin and antidiabetic agents
- Adriamycin
- Anticoagulants, *e.g.* warfarin and phenindione
- Cytochrome P450 2D6 inhibitors or substrates, such as
    - B-Blockers (metoprolol, timolol, alprenolol, carvedilol, bufuralol, nebivolol, propranolol
    - Selective serotonin (5HT) uptake inhibitors, *e.g.* fluoxetine* and paroxetine*
    - Tricyclic and tetracyclic antidepressants, *e.g.* clomipramine hydrochloride and mirtazapine
    - Antiviral agents, *e.g.* ritonavir* and delavirdine
    - Antimalarials, *e.g.* proguanil and lumefantrine
    - Antinauseants, antiemetics, *e.g.* dolasetron and metoclopramide
    - Narcotic analgesics: *e.g.* codeine, morphine, oxycodone, pethidine and tramadol
    - Neuroleptics: *e.g.* risperidone
    - Cytotoxic drugs: *e.g.* tamoxifen, vinblastine, vincristine, vinorelbine, gefitinib and imatinib
    - Chlorpheniramine, dextromethorphan, ethosuximide, galantamine, tolterodine, celecoxib, cimetidine, terbinafine, bupropion* and moclobemide (RIMA).

* Bupropion, fluoxetine, paroxetine, and ritonavir known to be strong inhibitors of CYP2D6. Any patient who regularly takes one of these medications cannot be enrolled in this study per the protocol-defined inclusion and exclusion criteria. Any subject who is being considered for initiation of therapy with one of these medications during the study should be discussed with the medical monitor prior to initiating the medication.

APPENDIX B: ACC/AHA HCM DIAGNOSTIC CRITERIA

GENETIC TESTING STRATEGIES/FAMILY SCREENING — RECOMMENDATIONS

CLASS I

1. Evaluation of familial inheritance and genetic counselling is recommended as part of the assessment of patients with HCM
2. Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient
3. Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM
4. Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause

CLASS IIa

1. Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM

CLASS IIb

1. The usefulness of genetic testing in the assessment of risk of Sudden Cardiac Death (SCD) in HCM is uncertain

CLASS III: NO BENEFIT

1. Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation
2. Ongoing clinical screening is not indicated in genotype negative relatives in families with HCM

GENOTYPE-POSITIVE/PHENOTYPE-NEGATIVE PATIENTS — RECOMMENDATION

CLASS I

1. In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial ECG, Transthoracic Echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status

ELECTROCARDIOGRAPHY — RECOMMENDATIONS

CLASS I

1. A 12-lead ECG is recommended in the initial evaluation of patients with HCM
2. Twenty-four–hour ambulatory (Holter) electrocardiographic monitoring is recommended in the initial evaluation of patients with HCM to detect ventricular tachycardia (VT) and identify patients who may be candidates for ICD therapy
3. Twenty-four–hour ambulatory (Holter) electrocardiographic monitoring or event recording is recommended in patients with HCM who develop palpitations or light-headedness
4. A repeat ECG is recommended for patients with HCM when there is worsening of symptoms.

5. A 12-lead ECG is recommended every 12 to 18 months as a component of the screening algorithm for adolescent first degree relatives of patients with HCM who have no evidence of hypertrophy on echocardiography
6. A 12-lead ECG is recommended as a component of the screening algorithm for first-degree relatives of patients with HCM

CLASS IIa

1. Twenty-four–hour ambulatory (Holter) electrocardiographic monitoring, repeated every 1 to 2 years, is reasonable in patients with HCM who have no previous evidence of VT to identify patients who may be candidates for ICD therapy
2. Annual 12-lead ECGs are reasonable in patients with known HCM who are clinically stable to evaluate for asymptomatic changes in conduction or rhythm (*i.e.*, AF).

CLASS IIb

1. Twenty-four–hour ambulatory (Holter) electrocardiographic monitoring might be considered in adults with HCM to assess for asymptomatic paroxysmal atrial fibrillation/atrial flutter.

IMAGING

Echocardiography — Recommendations

CLASS I

1. A TTE is recommended in the initial evaluation of all patients with suspected HCM
2. A TTE is recommended as a component of the screening algorithm for family members of patients with HCM unless the family member is genotype negative in a family with known definitive mutations
3. Periodic (12 to 18 months) TTE screening is recommended for children of patients with HCM, starting by age 12 years or earlier if a growth spurt or signs of puberty are evident and/or when there are plans for engaging in intense competitive sports or there is a family history of SCD
4. Repeat TTE is recommended for the evaluation of patients with HCM with a change in clinical status or new cardiovascular event
5. A trans-esophageal echocardiogram (TEE) is recommended for the intraoperative guidance of surgical myectomy
6. TTE or TEE with intracoronary contrast injection of the candidate's septal perforator(s) is recommended for the intra-procedural guidance of alcohol septal ablation
7. TTE should be used to evaluate the effects of surgical myectomy or alcohol septal ablation for obstructive HCM

CLASS IIa

1. TTE studies performed every 1 to 2 years can be useful in the serial evaluation of symptomatically stable patients with HCM to assess the degree of myocardial hypertrophy, dynamic obstruction, and myocardial function
2. Exercise TTE can be useful in the detection and quantification of dynamic LVOT obstruction in the absence of resting outflow tract obstruction in patients with HCM
3. TEE can be useful if TTE is inconclusive for clinical decision making about medical therapy and in situations such as planning for myectomy, exclusion of subaortic membrane or mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus, or in assessment for the feasibility of alcohol septal ablation
4. TTE combined with the injection of an intravenous contrast agent is reasonable if the diagnosis of apical HCM or apical infarction or severity of hypertrophy is in doubt,

particularly when other imaging modalities such as Cardiovascular Magnetic Resonance (CMR) are not readily available, not diagnostic, or are contraindicated

5. Serial TTE studies are reasonable for clinically unaffected patients who have a first-degree relative with HCM when genetic status is unknown. Such follow-up may be considered every 12 to 18 months for children or adolescents from high-risk families and every 5 years for adult family members

CLASS III: NO BENEFIT

1. TTE studies should not be performed more frequently than every 12 months in patients with HCM when it is unlikely that any changes have occurred that would have an impact on clinical decision making
2. Routine TEE and/or contrast echocardiography is not recommended when TTE images are diagnostic of HCM and/or there is no suspicion of fixed obstruction or intrinsic mitral valve pathology

STRESS TESTING — RECOMMENDATIONS

CLASS IIa

1. Treadmill exercise testing is reasonable to determine functional capacity and response to therapy in patients with HCM
2. Treadmill testing with monitoring of an ECG and blood pressure is reasonable for SCD risk stratification in patients with HCM
3. In patients with HCM who do not have a resting peak instantaneous gradient of greater than or equal to 50 mm Hg, exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction

CARDIAC MAGNETIC RESONANCE — RECOMMENDATIONS

CLASS I

1. CMR Imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis
2. CMR Imaging is indicated in patients with known HCM when additional information that may have an impact on management or decision making regarding invasive management, such as magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles, is not adequately defined with echocardiography

CLASS IIa

1. CMR Imaging is reasonable in patients with HCM to define apical hypertrophy and/or aneurysm if echocardiography is inconclusive

CLASS IIb

1. In selected patients with known HCM, when SCD risk stratification is inconclusive after documentation of the conventional risk factors, CMR imaging with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision making
2. CMR Imaging may be considered in patients with LV hypertrophy and the suspicion of alternative diagnoses to HCM, including cardiac amyloidosis, Fabry disease, and genetic phenocopies such as *LAMP2* cardiomyopathy

DETECTION OF CONCOMITANT CORONARY DISEASE — RECOMMENDATIONS

CLASS I

1. Coronary arteriography (invasive or computed tomographic imaging) is indicated in patients with HCM with chest discomfort who have an intermediate to high likelihood of Coronary Artery Disease (CAD) when the identification of concomitant CAD will change management strategies

CLASS IIa

1. Assessment of coronary anatomy with computed tomographic angiography is reasonable for patients with HCM with chest discomfort and a low likelihood of CAD to assess for possible concomitant CAD
2. Assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography (SPECT) or positron emission tomography (PET) myocardial perfusion imaging (MPI; because of excellent negative predictive value) is reasonable in patients with HCM with chest discomfort and a low likelihood of CAD to rule out possible concomitant CAD

CLASS III: NO BENEFIT

1. Routine SPECT MPI or stress echocardiography is not indicated for detection of “silent” CAD-related ischemia in patients with HCM who are asymptomatic
2. Assessment for the presence of blunted flow reserve (microvascular ischemia) using quantitative myocardial blood flow measurements by PET is not indicated for the assessment of prognosis in patients with HCM

APPENDIX C: DISCONTINUATION FOR PERSISTENT CLINICAL LABORATORY ELEVATIONS

A patient will be discontinued from the study if persistent elevations in ALT or AST, occur according to the following criteria:

- If a patient develops an elevation in ALT or AST >5 × ULN, the test will be repeated within 7 days.
    - If, upon re-test, ALT or AST remains >5 × ULN, study drug should be stopped and the patient discontinued from the study.
    - If, upon re-test, ALT or AST is ≤5 × ULN, the patient may continue in the study and follow-up will be performed at regular study visits with unscheduled visits as needed at the discretion of the Investigator.
- The patient will be followed as clinically indicated/necessary until the abnormality reverts to normal or to patient's baseline level or until the abnormalities stabilize.

If at any time during the study a patient develops elevations in ALT or AST >5 x ULN, the study site will be alerted by the central laboratory.