



**CLINICAL STUDY PROTOCOL**

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**Study Title:** A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy

**Sponsor:** Gilead Sciences, Inc.  
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Foster City, California 94404  
United States

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**Indication:** Hypertrophic Cardiomyopathy

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**PROTOCOL SYNOPSIS**  
**Gilead Sciences, Inc.**  
**333 Lakeside Drive**  
**Foster City, California 94404**  
**United States**

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**Study Title:** A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy

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**IND Number:** 112806  
**EudraCT Number:** 2013-004429-97  
**Clinical Trials.gov Identifier:** To be determined

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**Study Centers Planned:** Approximately 40-50 centers in North America, Europe and Israel

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**Objectives:** The primary objective of this study is to:

- Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO<sub>2</sub> achieved during cardiopulmonary exercise testing (CPET), in subjects with symptomatic hypertrophic cardiomyopathy (HCM).

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of GS-6615 in subjects with symptomatic HCM.
- Evaluate the effect of GS-6615 on quality of life as measured by the Minnesota Living With Heart Failure Questionnaire (MLHFQ).
- Evaluate the effect of GS-6615 on treadmill exercise time during CPET.
- Evaluate the effect of GS-6615 on arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation).

The exploratory objectives of this study are to:

PPD [REDACTED]

[REDACTED]

[REDACTED]

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<b>Study Design:</b>	<p>This is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the effect of GS-6615 on exercise capacity in subjects with symptomatic HCM.</p> <p>Eligible subjects will be enrolled and randomized 1:1 to receive either GS-6615 or matching placebo for a treatment duration of 24 weeks. Randomization will be stratified by sex and by age (<math>\geq 50</math> years and <math>&lt; 50</math> years).</p>
Number of Subjects Planned:	<p>Approximately 180 subjects randomized (90 subjects per arm).</p> <p>A blinded sample size re-estimation is planned when approximately 50% of subjects have completed the Week 12 visit in order to re-evaluate the assumptions for the sample size calculations. If the observed (blinded) standard deviation in Peak <math>VO_2</math> is higher than the assumed standard deviation, then the number of randomized subjects may be increased to up to approximately 220 subjects (110 subjects per arm).</p>
Target Population:	Subjects with symptomatic HCM
Duration of Treatment:	<p>24 weeks</p> <p>At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in a long-term open-label extension period until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country. Subjects will continue to be followed for periodic assessments throughout the open-label period.</p>
Diagnosis and Main Eligibility Criteria:	<p>Subjects with symptoms (NYHA Class <math>\geq</math> II dyspnea or CCS Class <math>\geq</math> II angina) due to HCM (defined as a maximal LV wall thickness of <math>\geq 15</math>mm in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed) will be randomized.</p> <p>Subjects with and without left ventricular outflow tract obstruction will be eligible.</p> <p>Medications commonly used in the treatment of HCM are permitted, unless specifically excluded, and may be continued throughout the study. Allowed concomitant medications include beta-blockers, calcium channel blockers, and Class III antiarrhythmics (eg, amiodarone and sotalol). It is recommended that the doses of such medications remain stable after screening through the end of the double-blind treatment period, unless clinically warranted at the discretion of the investigator.</p>

### **Inclusion Criteria**

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

- 1) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- 2) Males and females 18 to 70 years old, inclusive
- 3) Established diagnosis of Hypertrophic Cardiomyopathy defined by standard criteria as a maximal LV wall thickness  $\geq$  15 mm at initial diagnosis in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed
- 4) Exertional symptoms including at least one of the following:
  - a) New York Heart Association (NYHA) Class  $\geq$  II Dyspnea
  - b) Canadian Cardiovascular Society (CCS) Class  $\geq$  II Angina
- 5) Screening (baseline) Peak  $VO_2 < 75\%$  of predicted for age, sex, and body size based on the Wasserman Hansen equation ([Appendix 4](#)), as confirmed by the investigator
- 6) Ability to perform an upright treadmill cardiopulmonary exercise test (CPET)
- 7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol-specified method(s) of contraception as described in [Appendix 7](#)

### **Exclusion Criteria**

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study.

- 1) Known aortic valve stenosis (moderate or severe) as confirmed by echocardiogram
- 2) Known coronary artery disease (defined as  $\geq 50\%$  stenosis in  $\geq 1$  epicardial coronary artery)
- 3) Severe left ventricular systolic dysfunction (ejection fraction  $< 35\%$ ), known or detected during Randomization visit
- 4) Known moderate or severe Chronic Obstructive Pulmonary Disease (defined as  $FEV_1 < 80\%$  predicted)
- 5) Known moderate or severe restrictive lung disease (defined as total lung capacity  $< 70\%$  predicted)



- 6) Recent septal reduction procedure (ie, surgical myectomy or alcohol septal ablation) within six months prior to Screening or such a procedure scheduled to occur during the study
- 7) Atrial fibrillation on 12-lead ECG at Screening or detected during Randomization visit. Subjects with paroxysmal atrial fibrillation in whom sinus rhythm is restored may be re-screened at a later date.
- 8) Known or suspected infiltrative myocardial disease or glycogen storage disorder
- 9) Severe renal impairment at Screening (defined as an estimated GFR < 30 mL/min/1.73m<sup>2</sup> as calculated by the Modification of Diet in Renal Disease [MDRD] equation by the central laboratory)
- 10) Abnormal liver function tests at Screening, defined as ALT or AST > 2xULN, or total bilirubin > 1.5xULN
- 11) Known or suspected history of seizures or epilepsy
- 12) Use of Class I antiarrhythmic drugs, including disopyramide, within 7 days prior to Screening
- 13) Use of ranolazine within 7 days prior to Screening
- 14) Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A (see [Appendix 8](#)) within 5- half-lives prior to Screening
- 15) Known hypersensitivity to study drug (GS-6615 or placebo), its metabolites, or formulation excipient
- 16) Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. A negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization visit are required for female subjects of childbearing potential (refer to [Appendix 7](#) for definition of female of childbearing potential).
- 17) In the judgment of the investigator, any clinically significant ongoing medical condition that might jeopardize the subject's safety or interfere with the study, including participation in another investigational drug or investigational device study within the 30 days prior to Screening with potential residual effects that might confound the results of this study
- 18) Any condition that in the opinion of the investigator would preclude compliance with the study protocol

Study Procedures/  
Frequency:

Subjects will be seen in the clinic for a Screening visit (within 7 to 28 days prior to Randomization), a Randomization visit, and during the treatment period at Week 4, 12, 18, and 24 visits. Subjects will be contacted between study visits for assessment of adverse events and concomitant medications. At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible to continue in the study and receive GS-6615 in an open-label extension period. During the open-label extension period subjects will continue to undergo periodic required assessment. A 30-day safety follow-up visit will occur 30 days after the last dose of study drug.

Upon providing written informed consent, subjects will be evaluated for eligibility at Screening, including medical history and concomitant medication review, physical examination (PE), 12-lead resting electrocardiography (ECG), and screening labs. Subjects who are eligible to continue will be required to wear a noninvasive cardiac rhythm monitoring patch (ZIO<sup>®</sup> XT Patch) for 7 days starting at the end of the Screening visit.

At Screening, Week 12 and Week 24 study visits, subjects will undergo an upright treadmill CPET using the Modified Naughton Protocol ([Appendix 3](#)). At the Screening visit, subjects will be required to have a Peak  $VO_2 < 75\%$  of predicted based on the Wasserman Hansen equation ([Appendix 4](#)). Subjects whose Screening (baseline) Peak  $VO_2$  is  $\geq 75\%$  of predicted will not be eligible to continue.

Prior to the Randomization visit the investigator will review the Screening visit assessments (ECG, screening laboratory results) for each subject against study inclusion/exclusion criteria to confirm eligibility. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible. The Randomization visit will occur within 7-28 days after the Screening visit. At the end of the Randomization visit, eligible subjects will be randomly assigned to GS-6615 or matching placebo.

At Randomization and Week 4, 12, 18, and 24 visits, subjects will undergo PE including vital sign collection and 12-lead ECG. Samples for laboratory tests will be collected at every post randomization study visit to assess safety. Additionally, at Randomization, Week 12 and 24 visits subjects will undergo ECHO and NT-proBNP and hsTnT testing and will complete the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

At the Week 12 visit, subjects will also be provided with another noninvasive cardiac rhythm monitoring patch (ZIO<sup>®</sup> XT Patch) that will record heart rhythm between Week 12 and Week 13.

At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible to continue in the study and receive GS-6615 in an open-label extension period. Open-label extension visits will occur at Weeks 28, 40, and 52, and every 24 weeks thereafter.

All subjects (ie, both subjects who continue and subjects who do not continue into the open-label extension period) will complete a safety follow-up visit approximately 30 days after the last dose of study drug. At the 30-day Follow-up visit subjects will undergo PE including vital sign collection, 12-lead ECG, and clinical lab assessments.

PK sample collection will occur at Randomization, every post-randomization study visit through Week 52, and the 30-day Follow-up visit.

Adverse events and concomitant medications will be collected throughout the study.

The safety of the study will be monitored by an independent Data Monitoring Committee (DMC).

A core exercise physiology laboratory will collect cardiopulmonary data and provide centralized blinded adjudication of the primary endpoint (Peak VO<sub>2</sub>). A core ECG laboratory will collect ECG data and provide centralized blinded adjudication of ECG parameters. A core imaging laboratory will collect all echocardiographic data and provide centralized blinded adjudication of echocardiographic endpoints (diastolic function, systolic function, dynamic obstruction, and LV wall thickness).

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**Test Product, Dose,  
and Mode of  
Administration:**

**Day 1 through Week 24:** Oral single loading dose of 30 mg GS-6615 (3 x 10 mg tablets) on Day 1, followed by maintenance dose of 6 mg GS-6615 (2 x 3 mg GS-6615 tablets) once daily through the Week 24 study visit

**Open-label extension period:** Oral single double-blind loading dose of GS-6615 or matching placebo (3 tablets) on day of Week 24 visit (to maintain blinding to double-blind study treatment assignment), followed by maintenance dose of open-label GS-6615 (2 x 3 mg GS-6615 tablets) once daily through the end of the open-label extension period.

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**Reference Therapy,  
Dose, and Mode of  
Administration:**

**Day 1 through Week 24:** Oral single loading dose of placebo to match GS-6615 (3 x placebo tablets) on Day 1, followed by maintenance dose of matching placebo (2 x placebo tablets) once daily until the Week 24 study visit

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**Criteria for  
Evaluation:**

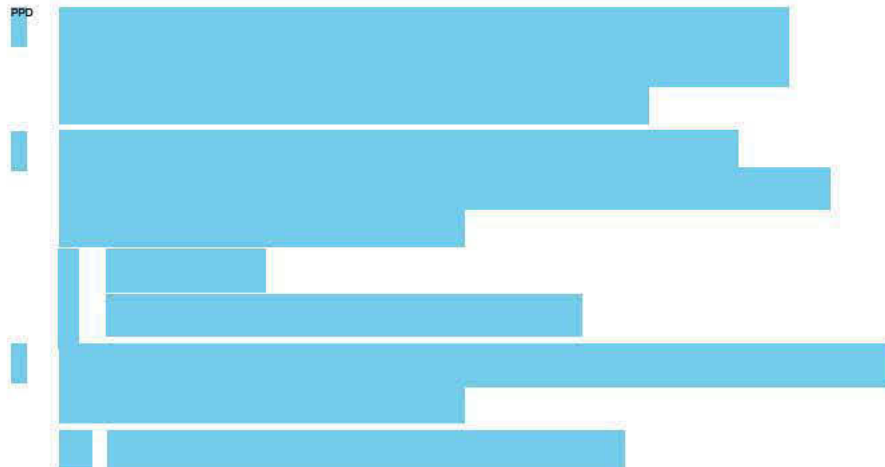
**Safety:** Safety will be assessed by the incidence of treatment-emergent AEs, (including physical exam findings new from baseline), clinically significant abnormalities in vital signs, laboratory parameters, and ECG variables.

**Efficacy:** The primary endpoint of this study is the change in Peak VO<sub>2</sub> between Screening (baseline) and Week 12.

The secondary endpoints of this study include:

- Change in Peak VO<sub>2</sub> between baseline and Week 24.
- Change in the Minnesota Living With Heart Failure Questionnaire between baseline and Week 12.
- Change in treadmill exercise time during CPET between baseline and Week 12.
- Change in the Minnesota Living With Heart Failure Questionnaire between baseline and Week 24.
- Change in treadmill exercise time during CPET between baseline and Week 24.
- Changes in arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation) between the 7-day baseline period (prior to randomization) and Week 12 to 13 on blinded study drug (ZIO<sup>®</sup> XT Patch).

The exploratory endpoints of this study include:



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**Statistical Methods:****Randomization:**

Following successful completion of the Screening and Randomization assessments, eligible subjects will be randomized in a 1:1 ratio to 30 mg single loading dose followed by 6 mg maintenance dose of GS-6615 or matching placebo. Randomization will be stratified by sex and by age ( $\geq 50$  years and  $< 50$  years).

**Timing of Analyses:**

A futility analysis may be performed after at least 50% of subjects have been randomized. Details of the futility stopping rules will be specified in the DMC charter.

After all subjects have completed the Week 24 visit (or the 30-day follow-up visit if not continuing in the open-label extension), the database will be cleaned and locked for the primary analysis of efficacy and safety through Week 24.

At the end of the study (ie, after all subjects have completed the open-label extension period including the 30-day follow-up visit), the database will be cleaned and locked for the secondary analysis of safety and PK data collected during the open-label extension period.

**Efficacy Analysis Specifications:**

Baseline is defined as the Randomization visit value, if available, otherwise the Screening visit value serves as baseline.

The primary endpoint is the change in Peak  $VO_2$  between the Screening and the Week 12 visits. The treatment effect of GS-6615 compared to placebo will be evaluated using analysis of covariance (ANCOVA) including terms for treatment, sex, age (as a continuous variable), and Peak  $VO_2$  at baseline. The treatment effect on secondary and exploratory endpoints, including changes in Peak  $VO_2$  at Week 24, MLHFQ, exercise time, arrhythmia burden, echocardiographic indices of diastolic and systolic function, biomarkers of myocardial wall stress and microvascular ischemia, and ECG parameters will also be evaluated using ANCOVA for continuous variables (including terms for treatment, sex, age, and baseline value) and Cochran-Mantel-Haenszel (CMH) or logistic regression for categorical and binary data, respectively. The stratified Wilcoxon rank sum test will be used as a sensitivity analysis for continuous variables. Mixed models repeated measurement (MMRM) analyses will also be performed for the Week 12 and Week 24 Peak  $VO_2$ , MLHFQ, and treadmill exercise time endpoints.

The primary endpoint (change in Peak VO<sub>2</sub> between Screening [baseline] and Week 12) will be compared between the GS-6615 treatment group and the placebo group at a significance level of 0.01. If the comparison is statistically significant ( $p \leq 0.01$ ), then the first secondary endpoint (change in Peak VO<sub>2</sub> between baseline and Week 24) will be tested at a significance level of 0.01. If this comparison is statistically significant ( $p \leq 0.01$ ), then the second secondary endpoint (change in MLHFQ between baseline and Week 12) will be tested at a significance level of 0.05. If this comparison is statistically significant ( $p \leq 0.05$ ), then the third secondary endpoint (change in treadmill exercise time between baseline and Week 12) will be tested at a significance level of 0.05. All other secondary and exploratory endpoints will be tested at a 2-sided nominal significance level of 0.05, with no adjustment for multiple testing.

#### **Safety Analyses Specifications:**

Baseline is defined as the Randomization visit value, if available, otherwise the Screening visit value serves as baseline.

AEs will be coded using the MedDRA dictionary. The incidence of each treatment-emergent AE will be summarized by system organ class, preferred term and treatment assignment. Multiple AEs mapped to the same preferred term will be counted once per subject.

Concomitant medications will be coded using the WHO Drug Dictionary with generic term and therapeutic use (ATC code) and summarized by ATC code, WHO generic name, and treatment. Reasons for early termination will be summarized by treatment group assignment.

Safety laboratory findings, vital signs, and 12-lead ECG data will be summarized descriptively and listed by treatment assignment and visit. Data and change from baseline at scheduled time points will be summarized.

All laboratory data will be listed. An additional listing of treatment-emergent laboratory abnormalities will be provided.

#### **Sample Size Determination:**

The sample size of 90 subjects per arm provides greater than 90% power assuming an effect size of 3mL/kg/min in the primary endpoint (Peak VO<sub>2</sub>), a standard deviation of 4mL/kg/min, and a two-sided alpha of 0.01. This assumes that the analysis will be performed on subjects who have peak VO<sub>2</sub> measured at Week 12 and allows for a dropout rate of approximately 15% (13 subjects).



A blinded sample size re-estimation is planned when approximately 50% of subjects have completed the Week 12 visit in order to re-evaluate the assumptions for the sample size calculations. The observed pooled (blinded) standard deviation in Peak VO<sub>2</sub> will be compared with the assumed standard deviation. If the observed standard deviation is higher than the assumed standard deviation, then the number of randomized subjects may be increased to up to approximately 220 subjects (110 subjects per arm).

As this analysis will be performed on blinded data, no adjustments to the overall type-I error rate will be performed.

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This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

## GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

%	percent
°C	degrees Celsius
°F	degrees Fahrenheit
AADs	anti-arrhythmic drugs
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	action potential
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	antitachycardia pacing
AUC	area under the concentration-time curve
BLQ	below limit of quantitation
bpm	beats per minute
BTPS	body temperature and pressure, saturated
BUN	blood urea nitrogen
Ca <sup>2+</sup>	calcium
CBC	complete blood count
CCS	Canadian Cardiovascular Society
cECG	continuous ECG
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
cm	centimeters
C <sub>max</sub>	the maximum observed serum/plasma/peripheral blood mononuclear (PMBC) concentration of drug
CO <sub>2</sub>	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test(ing)
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRT-D	cardiac resynchronization therapy device
CSR	clinical study report
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DFT	defibrillation threshold testing
DMC	data monitoring committee

## GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECHO	echocardiography
eCRF	electronic case report form
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ER	emergency room
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FEV <sub>1</sub>	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
H <sub>0</sub>	null hypothesis
H <sub>1</sub>	alternative hypothesis
hCG	human chorionic gonadotropin
HCM	hypertrophic cardiomyopathy
HDPE	high density polyethylene
HEENT	head, ears, eyes, nose, and throat
HF	heart failure
HIV	human immunodeficiency virus
HLGH	high-level group term
HLT	high-level term
hr	hour
hsTnT	high-sensitivity Troponin T
ICD	implantable cardioverter-defibrillator
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
I <sub>Na</sub>	sodium current
IND	Investigational New Drug
IRB	institutional review board
IUD	intrauterine device
IXRS	Interactive Voice/Web Response System
kg	kilogram(s)
LA	left atrial

## GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

late $I_{Na}$	late sodium current
LLT	lower-level term
LQTS	long QT syndrome
LQT3	long QT3
LV	left ventricular
LVOT	left ventricular outflow tract
MAD	multiple ascending dose
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
mm	millimeter
mmHG	millimeter of mercury
MMRM	mixed models repeated measurement
msec	millisecond
$Na^+$	sodium
nsVT	non-sustained ventricular tachycardia
NT-proBNP	N-terminal-pro-brain natriuretic peptide
NYHA	New York Heart Association
$O_2$	oxygen
PD	pharmacodynamic(s)
Peak $VO_2$	peak oxygen consumption
PE	physical examination
PG	pharmacogenomic(s)
PK	pharmacokinetic(s)
PR interval	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PT	preferred term
PVC	premature ventricular complex
Q1	first quartile
Q3	third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization.
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula

## GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

RER	respiratory exchange ratio, the ratio carbon dioxide production to oxygen consumption ( $VCO_2/VO_2$ )
RR	respiratory rate
RR interval	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
RV	right ventricular
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SBP	systolic blood pressure
SCD	sudden cardiac death
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
STPD	standard temperature and pressure, dry
SUSAR	suspected unexpected serious adverse reaction
UA	urinalysis
ULN	upper limit of normal
USA	United States of America
$VCO_2$	carbon dioxide output
VE	pulmonary ventilation
VF	ventricular fibrillation
$VO_2$	oxygen uptake
VT	ventricular tachycardia
WHO	World Health Organization

## 1. INTRODUCTION

### 1.1. Background

HCM is an inherited cardiac disorder that occurs in approximately 1 in 500 people in the general population {26627}. The disease is usually caused by autosomal-dominant mutations in genes encoding contractile components of the cardiac sarcomere {26638}.

Clinically, HCM is recognized as unexplained left ventricular (LV) hypertrophy (typically  $\geq 15$ mm thickness of the left ventricular wall) in the absence of other cardiac or systemic conditions capable of producing the magnitude of hypertrophy observed {26625}. Typical symptoms include shortness of breath, angina, palpitations, fatigue and syncope. In a small percentage of patients, sudden cardiac death (SCD) may be the first presentation {26749}.

HCM may present at any time (from infancy to old age), however, it is most commonly diagnosed in the third and fourth decades of life {26750}. The majority of patients are asymptomatic at the time of diagnosis, and an even greater number of individuals who may satisfy the morphologic criteria for diagnosis are never brought to medical attention {26640}. It is estimated that only 25% of patients with HCM (approximately 150,000 individuals in the United States) develop symptoms that include shortness of breath and chest pain with exertion, palpitations, fatigue and syncope {26784}, {26874}. In the subset of patients who are symptomatic, the disease can progress along several discrete, but not mutually exclusive pathways {26626}:

- Diastolic dysfunction resulting in heart failure with preserved ejection fraction.
- Microvascular ischemia resulting in angina.
- Dynamic obstruction to blood flow in the LV outflow tract resulting in exercise limitation and syncope.
- Atrial fibrillation resulting in exacerbation of heart failure and increased risk of stroke.
- Malignant ventricular arrhythmias leading to sudden cardiac death or implantable cardioverter-defibrillator (ICD) shock.

There are currently no approved drugs for the treatment of HCM. The development of evidence-based novel treatments for HCM was identified in 2010 as an urgent need by the Working Group of the National Heart Lung and Blood Institute on “Research Priorities in Hypertrophic Cardiomyopathy” {26634}.

Empirical medical therapy is considered first-line, and is based on using agents that decrease cardiac contractility {26624}. Beta-blockers are typically prescribed for the treatment of dyspnea in patients with or without LV outflow tract obstruction, but their use is limited by lack of efficacy, tolerability and bradycardia. Non-dihydropyridine calcium channel blockers are recommended as second-line agents, but may worsen outflow tract obstruction due to peripheral



vasodilatation. Disopyramide (an inhibitor of the peak inward sodium current) is sometimes used to treat dynamic LV obstruction, but is associated with significant anticholinergic side effects. The evidence base for pharmacologic therapies used in this disease is minimal, and these drugs have never been shown to impact the natural history of the disease nor alter its phenotypic expression in a beneficial manner. Lastly, amiodarone may be effective in controlling atrial fibrillation and reducing ventricular arrhythmic burden, but is not recommended in younger patients due to chronic toxicities, and does not confer protection against sudden cardiac death {28193}. Invasive therapy for HCM is an option only for the subset of patients with LV outflow tract obstruction, employing techniques aimed at reducing the thickness of the septum {26623}. Open heart surgery in the form of septal myectomy may be effective, but is limited to refractory cases referred to regional centers. Alcohol septal ablation is a minimally-invasive alternative to surgery and involves the deliberate creation of a large septal myocardial infarction to thin the obstructing muscle. While the most common complication of this approach is complete heart block (requiring a permanent pacemaker), there may be additional risks associated with the creation of a large myocardial scar {26631}. In patients at high risk for sudden cardiac death, placement of an ICD is standard of care {26637}.

In summary, the treatment of patients with functional limitation due to symptomatic HCM remains an important unmet medical need more than half a century since the initial description of the disease {26639}. There are no approved medications for this indication and all current therapies have significant drawbacks. Improvement of functional capacity and relief of symptoms in HCM is therefore a worthwhile target for novel therapeutic intervention.

## **1.2. GS-6615**

### **1.2.1. General Information**

GS-6615 is a new chemical entity and a potent and selective inhibitor of the cardiac late inward sodium current ( $I_{Na}$ ) that is being developed by Gilead Sciences, Inc. (Gilead) for the treatment of symptomatic HCM.

Late  $I_{Na}$  has been shown to play a critical role in the pathogenesis of ischemic heart disease, arrhythmia, and heart failure {16861}, {19886}. The sodium channel is activated during the upstroke (Phase 0) of the action potential (AP), leading to passage of a large inward sodium current (peak  $I_{Na}$ ). Under normal physiological conditions, the majority of sodium channels are inactivated quickly and only a small number of sodium channels fail to inactivate completely, resulting in very small persistent sodium current during the plateau phase. This persistent sodium current is called late  $I_{Na}$ . Late  $I_{Na}$  is pathologically enhanced as a consequence of congenital and acquired disorders affecting the inactivation of sodium channels. Enhancement of late  $I_{Na}$  leads to excessive cellular  $Na^+$  and  $Ca^{2+}$  uptake (through the  $Na^+/Ca^{+2}$  exchanger). The resultant disruption of myocyte  $Na^+$  and  $Ca^{2+}$  homeostasis causes mechanical and electrical dysfunction of the myocardium, including diastolic dysfunction, further exacerbation of ischemia, and arrhythmogenesis.

For further information on GS-6615, please refer to the current investigator's brochure for GS-6615.

### **1.2.2. Preclinical Pharmacology and Toxicology**

Further information is available in the current investigator's brochure for GS-6615.

### **1.2.3. Clinical Trials of GS-6615**

As of January 2014, a total of 76 subjects have been exposed to GS-6615 across three Phase 1 studies (see below). GS-6615 has demonstrated an acceptable tolerability and safety profile, with no clinically significant changes in vital signs or laboratory parameters. There have been no serious adverse events related to GS-6615 from any of the recently completed/ongoing studies.

Further information is available in the current investigator's brochure for GS-6615.

Clinical trials of GS-6615 include:

- GS-US-279-0101: A Phase 1 single ascending dose (SAD) study of GS-6615, Study GS-US-279-0101, was conducted in 48 healthy subjects. This first-in-human study was a randomized, double-blind, placebo-controlled single ascending oral dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of GS-6615 in healthy subjects. The study evaluated 6 single oral doses of GS-6615 (3 mg, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg) in a sequential manner.
- GS-US-279-0102: A Phase 1 multiple ascending dose (MAD) study of GS-6615, Study GS-US-279-0102, was conducted in 36 healthy subjects. This was a randomized, single-blind, placebo-controlled multiple ascending oral dose study to evaluate the safety, tolerability, and PK of GS-6615 in healthy subjects. The study evaluated 3 cohorts in a sequential manner: Cohort 1, 6 mg once daily for 7 days followed by 3 mg once daily for 14 days; Cohort 2, 12 mg once daily for 7 days followed by 6 mg once daily for 14 days; and Cohort 3, 20 mg once daily for 7 days followed by 9 mg once daily for 14 days.
- GS-US-279-0110: Study GS-US 279-0110 is an ongoing Phase 1 open-label single and multiple dose study designed to evaluate the effect of GS-6615 on the QTc interval in subjects with Long QT3 (LQT3). Up to 25 subjects with LQT3 identified from the LQTS registry with proven mutations in the cardiac sodium channel ( $\Delta$ KPQ, R1623Q, N1325S, E1784K or S1787N) and a baseline QTc > 460 msec will be enrolled. This study is being performed in five sequential cohorts; four single dose cohorts followed by one multiple dose cohort. Eligible subjects will receive a single dose of GS-6615 under fasting conditions (Cohort 1: 10 mg; Cohort 2: 20 mg; Cohort 3: 30 mg; Cohort 4: 60 mg) or multiple doses of GS-6615 (Cohort 5: Day 1 - 20 mg, Day 2 - 40 mg, Days 3-7 - 6 mg once daily). All single dose cohorts (ie, Cohorts 1-4) are complete, with a total of 13 subjects (10 unique) enrolled. All AE's reported as of January 2014 were assessed as mild and not related to study drug. No clinically significant trends were seen in vital signs or laboratory results.

### 1.3. Rationale for This Study

Recent studies have identified increased late  $I_{Na}$  as an important mechanism in the pathogenesis of human HCM. In a study of left ventricular tissue removed during septal myectomy from patients with severe HCM {25938}, late  $I_{Na}$  was found to be elevated greater than twofold in HCM cardiomyocytes compared to controls. This was accompanied by corresponding electrical and mechanical abnormalities including prolongation of the action potential duration, elevation of diastolic intracellular calcium concentration, increased susceptibility to triggered arrhythmias, systolic hypercontractility, and increased diastolic tension. All of these abnormalities were improved or abolished by exposure to the late  $I_{Na}$  inhibitor ranolazine. In a study of arrhythmia-prone induced pluripotent stem cell-derived cardiomyocytes obtained from a large family with HCM, ranolazine demonstrated restoration of normal beat frequency {26633}. Thus, late  $I_{Na}$  inhibition represents a promising pharmacological approach to HCM, targeting several of its key pathophysiology features, including diastolic dysfunction, microvascular ischemia, propensity to supraventricular and ventricular arrhythmias and, due to a modest negative inotropic effect, dynamic left ventricular outflow tract (LVOT) obstruction. Moreover, extensive experience with the use of late sodium channel blockers in coronary artery disease supports pharmacodynamic compatibility with the existing pharmacologic agents used in HCM such as beta-blockers and non-dihydropyridine calcium channel blockers.

Given its enhanced potency and selectivity for late  $I_{Na}$ , GS-6615 is expected to demonstrate efficacy on the electromechanical abnormalities in HCM. Recent results from Study GS-US-279-0110, an open-label study of GS-6615 in LQT3 subjects, have confirmed the in vivo activity of GS-6615 on late  $I_{Na}$ .

The current study will determine whether late  $I_{Na}$  inhibition by GS-6615 improves exercise capacity in subjects with symptomatic HCM.

#### 1.3.1. Rationale for Dose Selection

In Study GS-US-279-0102, MAD study of GS-6615 in healthy subjects, the PK profile of GS-6615 after 21 days of dosing was evaluated using a once daily loading dose for 7 days, followed by a lower maintenance dose for 14 days. The observed mean  $C_{max}$  values on Day 21 were 157, 380, and 590 ng/mL for the maintenance doses of 3 mg, 6 mg and 9 mg, respectively (Table 1-1.).

Because QTc prolongation in patients with LQT3 is a direct consequence of mutations in the cardiac sodium channel, and since GS-6615 is a potent and selective inhibitor of the cardiac late sodium current, Study GS-US-279-0110, a Phase 1 mechanism of action study, was conducted in subjects with LQT3 to evaluate the effect of GS-6615 on QTc interval shortening. Shortening of the QTc interval was observed at all dose levels evaluated (10, 20, 30, and 60 mg single dose), the largest effect on QTc interval shortening was observed at the 30 mg dose with a mean  $C_{max}$  of 300 ng/mL. Since the magnitude of pathologically enhanced late  $I_{Na}$  is comparable in cardiac myocytes from patients with LQT3 and with symptomatic HCM, the observed mean  $C_{max}$  for the 30 mg cohort in Study GS-US-279-0110 (300 ng/mL) is estimated as the target therapeutic  $C_{max}$  for the current study.

In general, the PK profile of GS-6615 after multiple dosing was well predicted from the SAD Study GS-US-279-0101 PK parameters using two-compartmental analysis. Given the long terminal half-life of GS-6615 observed in the SAD Study GS-US-279-0101 (median 213 hours), and in order to achieve pharmacologically effective concentrations in an efficient manner, the following dosing regimen has been proposed for this study: a single loading dose of 30 mg followed by daily maintenance doses of 6 mg. In view of the relative rarity of symptomatic HCM, which limits the number of subjects available for enrollment, only a single dose (6 mg) will be tested. However, down-titration of the study drug maintenance dose to 3 mg will be permitted in the event of intolerance to the 6 mg dose. PK simulation for this proposed dosing regimen was conducted based on the observed PK data from SAD Study GS-US-279-0101 and was shown to yield comparable steady-state  $C_{max}$  values to those observed in the MAD Study GS-US-279-0102 (Table 1-1 and Figure 1-1).

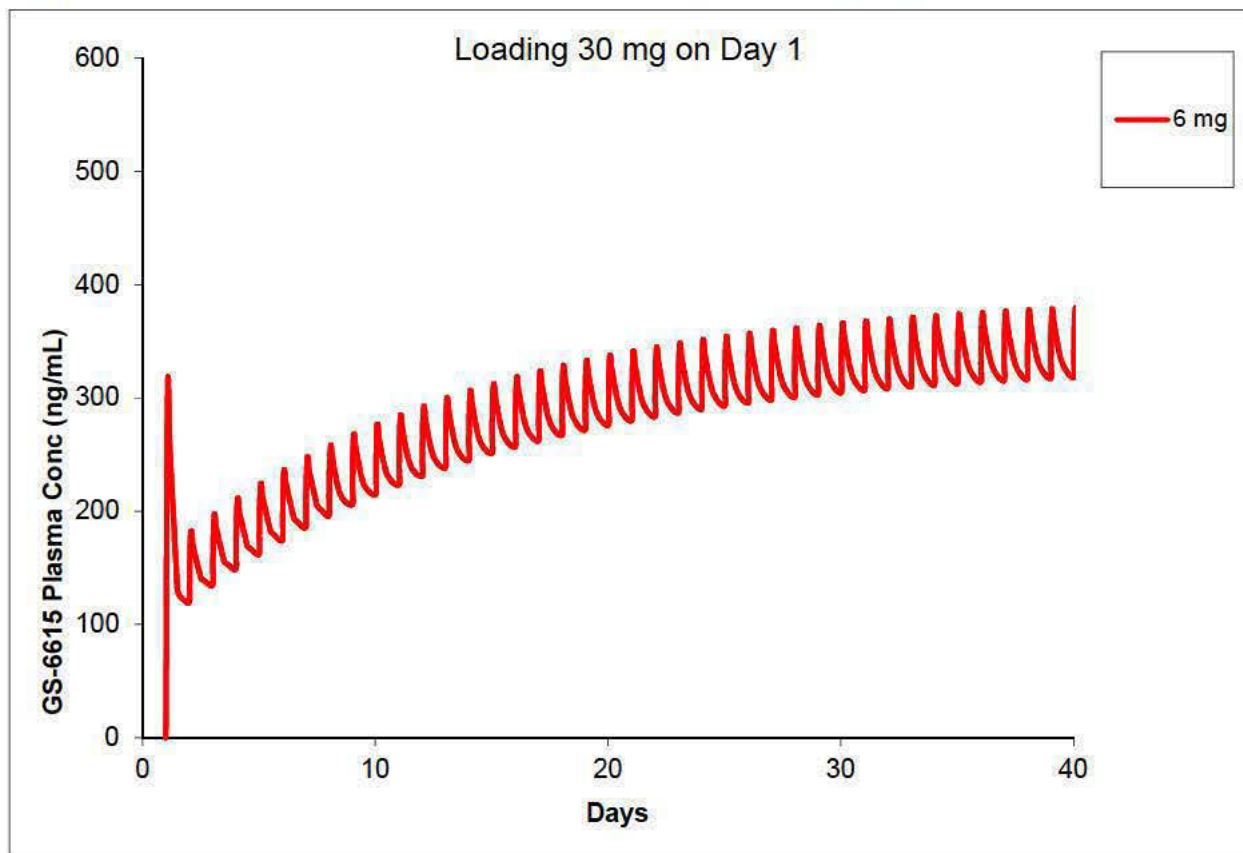
**Table 1-1. Comparison of PK Profiles (actual and simulated) Using Two Different Loading Doses of GS-6615**

Dosing regimen	Actual $C_{max}$ on Day 21, ng/mL*	Simulated steady-state $C_{max}$ , ng/mL**
6 mg for 7 d followed by 3 mg for 14 d	157	-
12 mg for 7 d followed by 6 mg for 14 d	380	-
20 mg for 7 d followed by 9 mg for 14 d	590	-
30 mg single dose followed by 3 mg QD	-	196
30 mg single dose followed by 6 mg QD	-	391

\* Value shown is the mean  $C_{max}$  observed in the MAD Study GS-US-279-0102.

\*\* Value shown is simulated value using the median PK parameters observed in the SAD Study GS-US-279-0101.

**Figure 1-1. Simulated PK Profile for Proposed Dosing Regimen**



In summary, based on the effects on QTc interval shortening observed in subjects with LQT3 and the observed and simulated PK profiles, the GS-6615 dosing regimen in this study will be a 30 mg single loading dose followed by a 6 mg maintenance dose. At these exposures, GS-6615 has been well-tolerated with no clinically important safety or tolerability issues identified.

#### **1.4. Compliance**

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

## 2. OBJECTIVES

The primary objective of this study is to:

- Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO<sub>2</sub> achieved during cardiopulmonary exercise testing (CPET), in subjects with symptomatic hypertrophic cardiomyopathy (HCM).

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of GS-6615 in subjects with symptomatic HCM.
- Evaluate the effect of GS-6615 on quality of life as measured by the Minnesota Living With Heart Failure Questionnaire (MLHFQ).
- Evaluate the effect of GS-6615 on treadmill exercise time during CPET.
- Evaluate the effect of GS-6615 on arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation).

The exploratory objectives of this study are to:

- [REDACTED]
- [REDACTED]
- [REDACTED]



### 3. STUDY DESIGN

#### 3.1. Endpoints

Please refer to Section 8.1 for details.

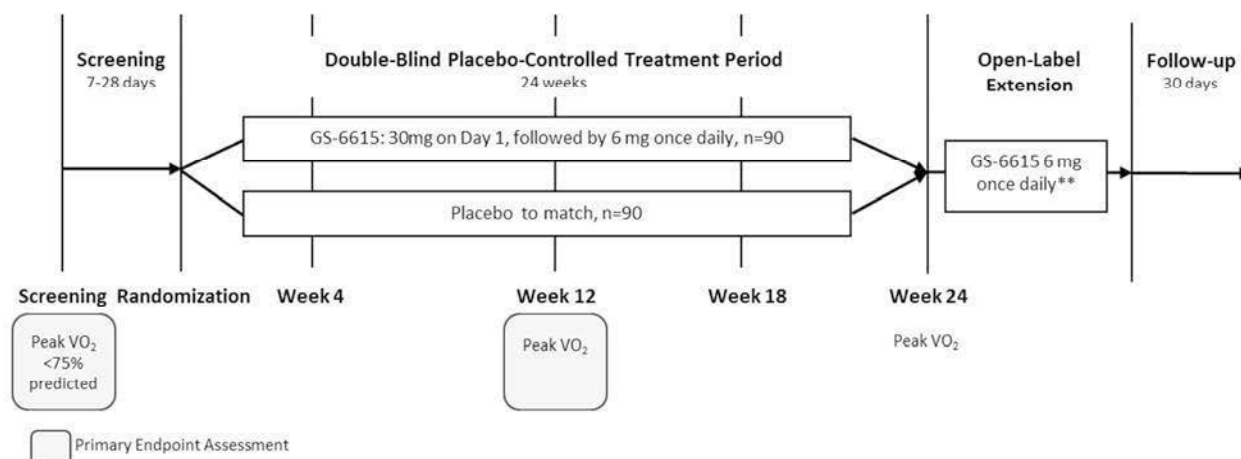
#### 3.2. Study Design

This protocol describes a randomized, double-blind, placebo-controlled study to evaluate the effect of GS-6615 on exercise capacity in subjects with symptomatic HCM.

Subjects will be seen in the clinic for a Screening visit, Randomization visit, and at Week 4, 12, 18 and 24 visits. Subjects will be contacted between study visits for assessment of adverse events (AEs) and concomitant medications. At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in an open-label extension period until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country. Subjects will complete a safety follow-up visit 30-days after last dose of study drug.

At Screening, Week 12, and Week 24 study visits, subjects will undergo an upright treadmill CPET using the Modified Naughton Protocol (Appendix 3). At the Screening visit, subjects will be required to have a Screening (baseline) Peak VO<sub>2</sub> of < 75% of predicted based on the Wasserman Hansen equation (Appendix 4).

Figure 3-1. Study Schema



\*\* Subjects who complete Week 24 at a down-titrated dose of 1 tablet of blinded study drug once daily are eligible to continue into the open-label extension period. It is encouraged that these subjects attempt the target dose of GS-6615 6 mg once daily (2 x 3 mg GS-6615 tablets), if appropriate in the opinion of the investigator.

### **3.3. Study Treatments**

Eligible subjects will be randomized in a 1:1 ratio to 30 mg single loading dose followed by 6 mg daily maintenance dose of GS-6615 or matching placebo. Randomization will be stratified by sex and by age ( $\geq 50$  years and  $< 50$  years).

Refer to Section 5 for further details on dose, regimen, packaging, and labeling of the study drug.

### **3.4. Duration of Treatment**

Subjects who meet the eligibility criteria will be randomized and receive study drug for 24 weeks.

At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in a long-term open-label extension period until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country. Subjects will continue to be followed for periodic assessments throughout the open-label period.

### **3.5. Discontinuation Criteria**

The study may be discontinued at the request of Gilead, a regulatory agency, or an IRB/IEC. Refer to Section 6.9 for criteria for subject discontinuation from study drug.

### **3.6. Source Data**

Refer to Section 9.1.5, Study Files and Retention, for description of source data to be retained on site. No source data will be recorded directly into the study database (ie, not previously written or recorded) in the conduct of this trial.

### **3.7. Biomarker Testing**

#### **3.7.1. Biomarker Samples to Address the Study Objectives**

Blood samples will be collected and used to evaluate the association of systemic biomarkers with study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of HCM and related diseases. The specific analyses will include NT-proBNP and high-sensitivity Troponin T (hsTnT), but will not be limited to the biomarkers listed. Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined is based upon the current state of scientific knowledge and may change during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

Blood samples will be collected from all subjects at Randomization, Week 12, and Week 24 visits for analysis of NT-proBNP and high-sensitivity Troponin T (hsTnT). These are validated biomarkers of myocardial wall stress and microvascular ischemia respectively that have been shown to predict long-term prognosis in patients with HCM {26635}, {26636}.

**3.7.2. Biomarker Samples for Optional Future Research**

PPD [Redacted]

[Redacted]

**3.7.3. Biomarker Samples for Optional Pharmacogenomic Research**

PPD [Redacted]

## 4. SUBJECT POPULATION

### 4.1. Number of Subjects and Subject Selection

Approximately 180 subjects with symptoms (NYHA Class  $\geq$  II dyspnea or CCS Class  $\geq$  II angina) due to HCM (defined by standard criteria as a maximal LV wall thickness of  $\geq$  15 mm in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed) will be randomized.

A blinded sample size re-estimation is planned when approximately 50% of subjects have completed the Week 12 visit in order to re-evaluate the assumptions for the sample size calculations. If the observed standard deviation in Peak  $VO_2$  is higher than the assumed standard deviation, then the number of randomized subjects may be increased to up to approximately 220 subjects.

Subjects with and without LVOT obstruction will be eligible.

Medications commonly used in the treatment of HCM are permitted, unless specifically excluded, and may be continued throughout the study. Allowed concomitant medications include beta-blockers, calcium channel blockers, and Class III antiarrhythmics (eg, amiodarone and sotalol). It is recommended that the doses of such medications remain stable after screening through the end of the double-blind treatment period, unless clinically warranted at the discretion of the investigator.

### 4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

- 1) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- 2) Males and females 18 to 70 years old, inclusive
- 3) Established diagnosis of Hypertrophic Cardiomyopathy defined by standard criteria as a maximal LV wall thickness  $\geq$  15mm at initial diagnosis in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed
- 4) Exertional symptoms including at least one of the following:
  - a) New York Heart Association (NYHA) Class  $\geq$  II Dyspnea
  - b) Canadian Cardiovascular Society (CCS) Class  $\geq$  II Angina
- 5) Screening (baseline) Peak  $VO_2$   $<$  75% of predicted for age, sex, and body size based on the Wasserman Hansen equation ([Appendix 4](#)), as confirmed by the investigator
- 6) Ability to perform an upright treadmill cardiopulmonary exercise test (CPET)
- 7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol-specified method(s) of contraception as described in [Appendix 7](#)

### 4.3. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study. During Screening, the subject may have any of the laboratory tests repeated once for confirmation only when medically warranted (eg, suspected laboratory error, inappropriate handling of blood/plasma/serum samples, etc.).

- 1) Known aortic valve stenosis (moderate or severe) confirmed by echocardiogram
- 2) Known coronary artery disease (defined as  $\geq 50\%$  stenosis in  $\geq 1$  epicardial coronary artery)
- 3) Severe left ventricular systolic dysfunction (ejection fraction  $< 35\%$ ), known or detected during Randomization visit
- 4) Known moderate or severe Chronic Obstructive Pulmonary Disease (defined as  $FEV_1 < 80\%$  predicted)
- 5) Known moderate or severe restrictive lung disease (defined as total lung capacity  $< 70\%$  predicted)
- 6) Recent septal reduction procedure (ie, surgical myectomy or alcohol septal ablation) within six months prior to Screening or such a procedure scheduled to occur during the study
- 7) Atrial fibrillation on 12-lead ECG at Screening or detected during Randomization visit. Subjects with paroxysmal atrial fibrillation in whom sinus rhythm is restored may be re-screened at a later date.
- 8) Known or suspected infiltrative myocardial disease or glycogen storage disorder
- 9) Severe renal impairment at Screening (defined as an estimated GFR  $< 30$  mL/min/1.73m<sup>2</sup> as calculated by the Modification of Diet in Renal Disease [MDRD] equation by the central laboratory)
- 10) Abnormal liver function tests at Screening, defined as ALT or AST  $> 2$ xULN, or total bilirubin  $> 1.5$ xULN
- 11) Known or suspected history of seizures or epilepsy
- 12) Use of Class I antiarrhythmic drugs, including disopyramide, within 7 days prior to Screening
- 13) Use of ranolazine within 7 days prior to Screening
- 14) Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A (see [Appendix 8](#)) within 5- half-lives prior to Screening

- 15) Known hypersensitivity to study drug (GS-6615 or placebo), its metabolites, or formulation excipient
- 16) Females who are pregnant or breastfeeding. Lactating females must agree to discontinue nursing before the study drug is administered. A negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization visit are required for female subjects of childbearing potential (refer to [Appendix 7](#) for definition of female of childbearing potential).
- 17) In the judgment of the investigator, any clinically significant ongoing medical condition that might jeopardize the subject's safety or interfere with the study, including participation in another investigational drug or investigational device study within the 30 days prior to Screening with potential residual effects that might confound the results of this study
- 18) Any condition that in the opinion of the investigator would preclude compliance with the study protocol

## **5. INVESTIGATIONAL MEDICINAL PRODUCTS**

### **5.1. Randomization, Blinding and Treatment Codes**

This is a randomized, double-blind, placebo-controlled study. At the end of the double-blind treatment period, subjects will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in an open-label extension period.

Following successful completion of the Screening and Randomization assessments, eligible subjects will be randomized in a 1:1 ratio to 30 mg single loading dose of GS-6615 followed by 6 mg daily maintenance dose of GS-6615 or matching placebo. Randomization will be stratified by sex and by age ( $\geq 50$  years and  $< 50$  years).

Once eligibility has been confirmed, the investigator or designee will randomize the subject using the Interactive Voice/Web Response System (IXRS). The IXRS will assign study drug bottle numbers at Randomization and at all double-blind and open-label treatment period visits. Study drug will be dispensed to the subject in a blinded fashion during the double-blind treatment period. Initiation of treatment with the study drug will take place on Day 1 at the end of the Randomization visit.

Blinding of oral investigational product will be accomplished by the sponsor providing GS-6615 and matching placebo tablets that are visually indistinguishable. Packaging for study drug (active and placebo) will be identical with the exception of a unique identification number on the bottle.

#### **5.1.1. Procedures for Breaking Treatment Codes**

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. In case of technology failure, the investigator may obtain treatment assignment by contacting the IXR provider directly. Gilead recommends but does not require that the investigator contact the Medical Monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to inform emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Medical Monitor within 48 hours upon any instances of treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

## **5.2. Description and Handling of GS-6615**

### **5.2.1. Formulation**

GS-6615 will be supplied as 3 mg or 10 mg strength round, white, biconvex, plain-faced, film-coated tablets. In addition to the active ingredient, GS-6615 tablets contain the following commonly used excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Matching placebo tablets will be supplied that are identical in physical appearance to the 3 mg or 10 mg GS-6615 tablets and contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

### **5.2.2. Packaging and Labeling**

GS-6615 tablets and matching placebo are packaged in white, high density polyethylene (HDPE) bottles with polyester fiber coil. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to centers in the United States and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

### **5.2.3. Storage and Handling**

GS-6615 or matching placebo tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the study drug should be stored in the containers in which they were supplied.

## **5.3. Dosage and Administration of GS-6615 or Placebo**

Subjects will be randomized in a 1:1 ratio to receive either oral GS-6615 once daily or placebo to match GS-6615 (matching placebo) during the double-blind placebo-controlled treatment period, followed by an open-label extension period in which all subjects who continue in the study will receive GS-6615. The study drug doses are shown in [Table 5-1](#).



**Table 5-1. Study Drug Doses**

	Double-blind treatment period			Open-label extension period
	Day 1 (dosing on site)	Day 2 to Week 24	Day of Week 24 visit (dosing on site)	
GS-6615 treatment arm	30 mg GS-6615 (3 x 10 mg GS-6615 tablets)	6 mg GS-6615 (2 x 3 mg GS-6615 tablets) once daily	<b>Start of Week 24 visit:</b> 6 mg GS-6615 (2 x 3 mg GS-6615 tablets) <b>End of Week 24 visit/start of OLE:</b> Matching placebo (3 placebo tablets)	6 mg GS-6615 (2 x 3 mg GS-6615 tablets) once daily
Placebo treatment arm	Matching placebo (3 placebo tablets)	Matching placebo (2 placebo tablets) once daily	<b>Start of Week 24 visit:</b> Matching placebo (2 placebo tablets) <b>End of Week 24 visit/start of OLE:</b> 30 mg GS-6615 (3 x 10 mg GS-6615 tablets)	

Initiation of treatment with the study drug will take place on the day of randomization (Day 1). After confirmation of eligibility, subjects will be randomized via IXRS and study drug will be dispensed. Subjects will then take the Day 1 loading dose of study drug on site.

At the end of the double-blind, placebo-controlled treatment period (ie, Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country.

On the day of the Week 24 visit, all subjects will take their normal daily dose of double-blind study drug on site during the study visit. Subjects continuing in the open-label extension period will be assigned and take a double-blinded loading dose of study drug on site at the end of the Week 24 visit. The double-blinded loading dose on the day of the Week 24 visit will ensure that all subjects entering the open-label extension period receive the appropriate loading dose and will maintain blinding to double-blind study treatment assignment.

All subjects will receive a maintenance dose of 6 mg GS-6615 once daily (2 x 3 mg GS-6615 tablets) during the open-label extension period starting the day after the Week 24 visit. Subjects who complete Week 24 at a down-titrated dose of 1 tablet of blinded study drug once daily are eligible to continue into the open-label extension period. It is encouraged that these subjects attempt the target dose of GS-6615 6 mg once daily (2 x 3 mg GS-6615 tablets), if appropriate in the opinion of the investigator. Refer to Section 5.3.1 for further information about dose modification.

GS-6615 and matching placebo tablets will be provided by Gilead and will be taken orally with water, once a day, with or without meals. The study drug should be swallowed whole.

Subjects will take their daily maintenance dose of study drug with water every day at approximately 24 hour intervals. On the day of double-blind treatment period study visits, subjects should hold the daily dose of study drug so that it may be taken on site during the study visit.

If the subject misses a dose, he/she should be instructed to take the study drug as soon as he/she remembers, unless more than 6 hours has elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time. Subjects should not take more than one dose of study drug at a time.

### **5.3.1. Dose Modification for Adverse Events**

The investigator is encouraged to manage adverse events (depending on their severity) with standard medical therapy prior to consideration of dose modification.

Down-titration or interruption of study drug is discouraged but permitted if necessary in the event of intolerance to study drug. Subsequent up-titration of study drug back to the target dose should be attempted whenever appropriate.

If it is believed that an adverse event may be drug-related, and depending on its severity, and with approval by the Medical Monitor, the study drug may be:

- reduced from 2 tablets once daily to 1 tablet once daily
- interrupted temporarily with a plan to re-initiate treatment
- discontinued permanently

Subjects who are unable to tolerate a dose of 1 tablet once daily will discontinue study drug dosing. If a subject discontinues study drug dosing, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures through Week 24, the end of the double-blind treatment period.

Subjects who complete Week 24 at a down-titrated dose of 1 tablet of blinded study drug once daily are eligible to continue into the open-label extension period. It is encouraged that these subjects attempt the target dose of GS-6615 6 mg once daily (2 x 3 mg GS-6615 tablets), if appropriate in the opinion of the investigator.

### **5.4. Prior and Concomitant Medications**

All concomitant medications will be recorded at each study visit from 30 days prior to Screening through the end of the study (ie, 30-day follow-up visit). Any medications given for an SAE that occurs within 60 days of the last dose of study drug will also be recorded.

Existing oral medications should continue at a stable dose throughout the study. Medications commonly used in the treatment of HCM are permitted, unless specifically excluded, and may be continued throughout the study. Allowed concomitant medications include beta-blockers, calcium channel blockers, and Class III antiarrhythmics (eg, amiodarone and sotalol). It is recommended that the doses of such medications remain stable after screening through the end of the double-blind treatment period, unless clinically warranted at the discretion of the investigator.

The following medications are excluded throughout the entire study:

- Class I antiarrhythmic drugs, including disopyramide, within 7 days prior to Screening
- Ranolazine within 7 days prior to Screening
- Strong inhibitors or inducers of CYP3A (see [Appendix 8](#)) within 5-half-lives prior to Screening

#### **5.4.1. Other Protocol Restrictions**

Subjects will refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice while participating in the study.

#### **5.5. Study Drug Accountability**

The investigator is responsible for ensuring adequate accountability of all used and unused study drug bottles. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug
- Record the date, subject number, subject initials, and the study drug bottle number dispensed
- Record the date, quantity of used and unused study drug returned (tablets and bottles), along with the initials of the person recording the information.

#### **5.5.1. Investigational Medicinal Product Return or Disposal**

Refer to Section [9.1.7](#) for detailed instructions.

## **6. STUDY PROCEDURES**

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in [Appendix 2](#) and described in the text that follows. Additional information is provided in the study procedures manuals.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

### **6.1. Subject Enrollment and Treatment Assignment**

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment and throughout the study.

Once informed consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, subjects will be enrolled (randomized) and assigned a unique subject identification number via IXRS.

Subjects will receive the study treatment as described in [Section 5](#).

### **6.2. Pretreatment Assessments**

#### **6.2.1. Screening Visit**

Subjects will be screened within 7-28 days prior to the Randomization visit to determine eligibility for participation in the study. Subjects who are screen failures for any reason may only be re-screened with approval from the Medical Monitor.

The following will be performed and documented at Screening:

- Obtain written informed consent prior to initiation of study procedures
- Review and record inclusion and exclusion criteria
- Obtain medical history including cardiovascular and surgical history, sarcomeric mutation if known, history of allergies, and history of prior (within previous 30 days) and current medication use. For female subjects, confirm documentation of childbearing potential as defined in [Appendix 7](#).
- Complete physical examination including vital signs, body weight, and height, as described in [Sections 6.16](#) and [6.17](#)
- Standard 12-lead resting ECG as described in [Section 6.12](#)

- Cardiopulmonary Exercise Testing (CPET) using the Modified Naughton Protocol as described in Section 6.11 and according to the study-specific CPET Manual.
  - At the Screening visit, subjects are required to have a Screening (baseline) Peak VO<sub>2</sub> of < 75% of predicted based on the Wasserman Hansen equation (Appendix 4). Subjects whose baseline Peak VO<sub>2</sub> is ≥ 75% of predicted will not be eligible to continue.
- Collect blood and urine samples for Clinical Laboratory Assessments as described in Section 6.18
- Collect blood sample for serum pregnancy testing for females of childbearing potential only
- ZIO<sup>®</sup> XT Patch wear starts at the end of the Screening visit for 7 days. Subjects will be provided with instructions for wear and removal of patch. The ZIO<sup>®</sup> XT Patch will be collected at the Randomization visit.
- Serious adverse events and all adverse events related to protocol-mandated procedures observed during the screening period are to be captured as adverse events
- All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured as medical history
- Record all concomitant medication use (including new medications, ongoing medications, and medications taken within 30 days prior to screening) occurring after signing of the consent form

Subjects meeting all of the inclusion criteria and none of the exclusion criteria at the Screening Visit will return to the clinic within 7-28 days for the Randomization visit.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events for additional details.

### **6.3. Randomization (Day 1)**

The Randomization visit will occur within 7-28 days after the Screening visit on Day 1. At the end of the Randomization visit, eligible subjects will be randomly assigned to receive GS-6615 or matching placebo.

The following will be performed and documented at the Randomization visit:

- Review inclusion and exclusion criteria to confirm continued eligibility
- Predose PK sample collection as described in Section 6.19 before the subject has taken the first dose of study drug

- Blood sample collection for NT-proBNP and hsTnT testing
- PPD
- Urine pregnancy test for females of childbearing potential only
- Abbreviated physical examination including vital signs as described in Sections 6.16 and 6.17
- MLHFQ administration as described in Section 6.15
- Standard 12-lead resting ECG as described in Section 6.12
- ECHO as described in Section 6.14, including measurement left ventricular ejection fraction to confirm continued eligibility
- Collect ZIO<sup>®</sup> XT Patch
- Review of concomitant medications
- Review of adverse events
- After confirmation of eligibility, randomize subject via IXRS and dispense study drug. Provide subject with dosing instructions. Subject will take the Day 1 loading dose of study drug on site.
- Obtain second blood sample for PK as described in Section 6.19. The second PK sample should be collected 2-3 hours after the subject has taken the first dose of study drug. If 2-3 hours postdose collection is not possible, the PK sample should be collected as late as possible before the subject leaves the clinic.
- Instruct the subject to hold the study drug dose on the day of the Week 4 visit so subject can take the study drug while on site.

#### **6.4. Treatment Assessments Post Randomization to Week 24 (Double-Blind Placebo-Controlled Period)**

##### **6.4.1. Week 1 Contact**

Subjects will be contacted on Day 7  $\pm$ 3 days to review adverse events and concomitant medications and to remind the subject to hold study drug dose on the day of the next visit so subject can take the study drug while on site.

#### **6.4.2. Week 4 Visit**

The Week 4 visit will occur on Day 28 (to Day 42). On the day of the visit, subjects should take study drug on site. The following will be performed and documented at the Week 4 visit:

- Predose PK sample as described in Section 6.19. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- Witness daily study drug dosing after predose PK sample collection
- Abbreviated physical examination including vital signs as described in Sections 6.16 and 6.17
- Standard 12-lead resting ECG as described in Section 6.12
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance
- Dispense study drug
- Second PK sample as described in Section 6.19. The second PK sample should be collected approximately 3 hours after the subject has taken the daily dose of study drug. If 3 hours postdose is not possible, the PK sample should be collected as late as possible before the subject leaves the clinic.
- Instruct the subject to hold the study drug dose on the day of the next visit so the subject can take the study drug while on site.

#### **6.4.3. Week 9 Contact**

Subjects will be contacted on Day 63  $\pm$ 3 days to review adverse events and concomitant medications and to remind the subject to hold study drug dose on the day of the next visit so subject can take the study drug while on site.

#### **6.4.4. Week 12 Visit**

The Week 12 visit will occur on Day 84 ( $\pm$ 7 days). On the day of the visit, subjects should take study drug on site. If needed, the Week 12 visit may be conducted over 2 consecutive days.

**Recommended order of assessments at Week 12 visit:** (1) predose PK sample collection, (2) witnessed study drug dosing, (3) MLHFQ, (4) ECG, (5) CPET, (6) ECHO, and (7) all other blood sample collection including postdose PK sample. All other required visit assessments may occur at any point during the study visit. It is important that the MLHFQ administration occurs prior to CPET.

The following will be performed and documented at the Week 12 visit:

- Abbreviated physical examination including vital signs as described in Sections 6.16 and 6.17
- Predose PK sample as described in Section 6.19. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Witness daily study drug dosing after predose PK sample collection
- MLHFQ administration as described in Section 6.15
- Standard 12-lead resting ECG as described in Section 6.12
- Cardiopulmonary Exercise Testing (CPET) using the Modified Naughton Protocol as described in Section 6.11 and according to the study-specific CPET Manual
- ECHO as described in Section 6.14
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- Blood sample collection for NT-proBNP and hsTnT testing
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance
- Dispense study drug
- Second PK sample collection as described in Section 6.19. The second PK sample should be collected approximately 3 hours after the subject has taken the daily dose of study drug. If 3 hours postdose is not possible, the PK sample should be collected as late as possible before the subject leaves the clinic.



- ZIO<sup>®</sup> XT Patch wear starts at the end of the Week 12 visit for 7 days. Subjects will be provided with instructions for wear and removal of patch. The ZIO<sup>®</sup> XT Patch will be collected at the Week 18 visit.
- Instruct the subject to hold the study drug dose on the day of the next visit so the subject can take the study drug while on site.

#### **6.4.5. Week 15 Contact**

Subjects will be contacted on Day 105 ( $\pm 3$  days) to review ZIO<sup>®</sup> XT Patch use/removal, adverse events and concomitant medications, and to remind the subject to hold study drug dose on the day of the next visit so subject can take the study drug while on site.

#### **6.4.6. Week 18 Visit**

The Week 18 visit will occur on Day 126 ( $\pm 7$  days). On the day of the visit, subjects should take study drug on site.

The following will be performed and documented at the Week 18 visit:

- Predose PK sample collection as described in Section 6.19. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- Witness daily study drug dosing after predose PK sample collection
- Abbreviated physical examination including vital signs as described in Sections 6.16 and 6.17
- Standard 12-lead resting ECG as described in Section 6.12
- Review of concomitant medications
- Review of adverse events
- Collect ZIO<sup>®</sup> XT Patch
- Collect and review used and unused study drug for accountability and calculate compliance
- Dispense study drug

- Second PK sample collection as described in Section 6.19. The second PK sample should be collected approximately 3 hours after the subject has taken the daily dose of study drug. If 3 hours postdose is not possible, the PK sample should be collected as late as possible before the subject leaves the clinic.
- Instruct the subject to hold the study drug dose on the day of the next visit so the subject can take the study drug while on site.

#### **6.4.7. Week 21 Contact**

Subjects will be contacted on Day 147 ( $\pm 3$  days) to review adverse events and concomitant medications and to remind the subject to hold study drug dose on the day of the next visit so subject can take the study drug while on site.

#### **6.4.8. Week 24 Visit**

The Week 24 visit will occur on Day 168 ( $\pm 7$  days). On the day of the visit, subjects should take study drug on site. If needed, the Week 24 visit may be conducted over 2 consecutive days.

**Recommended order of assessments at Week 24 visit:** (1) predose PK sample collection, (2) witnessed study drug dosing, (3) MLHFQ, (4) ECG, (5) CPET, (6) ECHO, and (7) all other blood sample collection including postdose PK sample. All other required visit assessments may occur at any point during the study visit. It is important that the MLHFQ administration occurs prior to CPET.

The following will be performed and documented at the Week 24 visit:

- Abbreviated physical examination including vital signs, as described in Sections 6.16 and 6.17
- Predose PK sample collection as described in Section 6.19. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Witness daily study drug dosing after predose PK sample collection
- MLHFQ administration as described in Section 6.15
- Standard 12-lead resting ECG as described in Section 6.12
- Cardiopulmonary Exercise Testing (CPET) using the Modified Naughton Protocol as described in Section 6.11 and according to the study-specific CPET Manual.
- ECHO as described in Section 6.14
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18

- Urine pregnancy test for females of childbearing potential only
- Blood sample collection for NT-proBNP and hsTnT testing
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance
- Second PK sample collection as described in Section 6.19. The second PK sample should be collected approximately 3 hours after the subject has taken the daily dose of study drug. If 3 hours postdose is not possible, the PK sample should be collected as late as possible before the subject leaves the clinic. If the subject is participating the open-label extension, the second PK sample must be collected before the subject takes the blinded loading dose.

At the end of the double-blind, placebo-controlled treatment period, Week 24, all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in an open-label extension period until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country. Subjects who continue into the extension period will be seen in clinic at Week 28, Week 40, Week 52, and then every 24 weeks.

If the subject will continue in the GS-6615 open-label extension period, the following will be performed and documented at the Week 24 visit:

- Dispense study drug. Provide subject with dosing instructions for GS-6615 extension period. All subjects will take a blinded loading dose of study drug on site.

#### **6.5. Treatment Assessments Post Week 24 (Open-label Extension)**

At the end of the double-blind, placebo-controlled treatment period (Week 24), all subjects who complete the treatment period (including study drug dosing) will be eligible, at the discretion of the investigator, to continue in the study and receive GS-6615 in an open-label extension period until this drug is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM in the subject's home country.

See Section 6.4.8 for open-label extension entry procedures to be performed at the end of Week 24 visit.

### **6.5.1. Open-label Extension Period (OLE) Visits**

GS-6615 open-label extension period visits will occur at the following time points: Week 28 (Day 196 +14 days), Week 40 (Day 280 ±7 days), Week 52 (Day 364 ±7 days) and every 24 weeks (±14 days) thereafter (ie, Week 76, Week 100, and so on).

At each OLE visit the following will be performed and documented:

- Abbreviated physical examination including vital signs, as described in Sections 6.16 and 6.17
- Standard 12-lead resting ECG as described in Section 6.12
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- PK sample collection at each visit through Week 52 (approximately 6 months after entry into open-label extension period) as described in Section 6.19
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance
- Dispense study drug

### **6.5.2. OLE Week 25 Contact**

Subjects will be contacted at Week 25 (Day 175 ±3 days) to review adverse events and concomitant medications.

## **6.6. Post-treatment Assessments**

### **6.6.1. 30-day Follow-up Visit**

Subjects will complete a safety follow-up visit 30 days (+7 days) after the last dose of study drug. Subjects who permanently discontinue study drug prior to Week 24 (ie, during the double-blind treatment period) and continue to attend normal study visits (at minimum one visit) after study drug discontinuation are not required to complete the follow-up visit. Please refer to Section 6.8, Assessments for Premature Discontinuation from Study, for assessments for subjects who discontinue study participation in addition to discontinuing study drug prior to Week 24.

The following will be performed and documented at the safety follow-up visit:

- Abbreviated physical examination including vital signs, as described in Sections 6.16 and 6.17
- Standard 12-lead resting ECG as described in Section 6.12
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- PK sample collection as described in Section 6.19
- Review of concomitant medications
- Review of adverse events
- Additional unscheduled assessments may be performed at the discretion of the investigator (eg, for evaluation of AEs and laboratory abnormalities).

#### **6.7. Unscheduled Visits**

Additional unscheduled assessments may be performed at the discretion of the investigator (eg, for evaluation of AEs and laboratory abnormalities).

#### **6.8. Assessments for Premature Discontinuation from Study**

Please refer to Section 5.3.1, Dose Modification for Adverse Events, for down-titration and study drug interruption instructions.

**If a subject permanently discontinues study drug dosing prior to Week 24, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures until end of the double-blind treatment period (ie, Week 24).** If this is not possible or acceptable to the subject or investigator, the subject will be withdrawn from the study.

If a subject permanently discontinues study drug dosing at or after Week 24, the 30-day Follow-up visit will be completed. Please refer to Section 6.6.1 for 30-day Follow-up visit details.

##### **6.8.1. Early Termination Visit**

If prior to Week 24, in addition to study drug discontinuation, a subject prematurely discontinues study participation, the subject will be asked to return to the study center for the Early Termination (ET) Visit. When possible, the ET Visit should be performed within 48 hours of decision to prematurely withdraw.

The following will be performed and documented at the ET visit:

- Confirm reason for permanent withdrawal and that subject is not willing to continue to perform study-related follow-up and procedures until study end of the double-blind treatment period (ie, Week 24). If appropriate, discuss options for study drug dose modification per Section 5.3.1.
- Abbreviated physical examination including vital signs, as described in Sections 6.16 and 6.17
- Standard 12-lead resting ECG as described in Section 6.14
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.18
- Urine pregnancy test for females of childbearing potential only
- PK sample collection as described in Section 6.19
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance, if applicable

#### **6.9. Criteria for Discontinuation of Study Treatment**

Please refer to Section 5.3.1, Dose Modification for Adverse Events, for down-titration and study drug interruption instructions.

Study drug may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require treatment with a medication prohibited during the study. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator with approval by the Medical Monitor.
- Subject requires treatment with prohibited medications during the study. Following use of such prohibited medications, the subject may resume study dosing with approval by the Medical Monitor.
- Adverse Events that, in the judgment of the investigator, may jeopardize subject safety by continued participation in the study. Refer to Section 5.3.1, Dose Modification for Adverse Events.
- Subject request to discontinue study drug for any reason
- Subject withdraws consent

- Subject noncompliance
- Subject's treatment assignment is disclosed to the investigator
- Pregnancy during the study; refer to [Appendix 7](#)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

#### **6.10. End of Study**

End of study is defined as the last subject's last visit (ie, 30-day Follow-up visit).

#### **6.11. Cardiopulmonary Exercise Testing (CPET)**

Subjects will undergo an upright treadmill CPET using the Modified Naughton Protocol ([Appendix 3](#)) three times during the study, at Screening, Week 12, and Week 24 study visits. If possible, all exercise tests should be performed in the morning and the same study team members should perform all subjects' tests.

At Screening, the investigator will review CPET data for Peak VO<sub>2</sub> result to confirm subject eligibility.

A core exercise physiology laboratory will collect cardiopulmonary data and provide centralized blinded adjudication of the primary endpoint (Peak VO<sub>2</sub>).

Details of the core exercise physiology laboratory procedures including site qualification, instructions for transmittal of data, and analysis of all ECG and ventilatory gas exchange data collected during the study will be specified in the CPET study manual.

##### **6.11.1. CPET Equipment Preparation**

All calibration of testing equipment must be performed within one hour before beginning each of the scheduled exercise tests according to manufacturer specifications and the minimum calibration procedures specified in the CPET study manual.

The Modified Naughton Protocol ([Appendix 3](#)) should be pre-programmed into each exercise system, so that the changes in speed and grade are automatic.

The ECG, using standard 12 leads, must be set to print each minute throughout the exercise test. The metabolic system should be set to record the rolling 30-second averages for the following respiratory gas exchange variables every 10 seconds during the exercise test. The respiratory gas exchange variables include: Ventilation (VE, L/min, BTPS); Oxygen uptake (mL/kg/min and L/min, STPD); Carbon dioxide production (L/min, STPD); Respiratory exchange ratio (RER); and Respiratory rate (RR).

##### **6.11.2. CPET Instructions for Subjects**

The instructions below should be reviewed with the subject prior to the CPET at Screening, Week 12 and Week 24 visits.

#### 6.11.2.1. Pre-test Instructions for Subject

Provide subjects with the following instructions in preparation for CPET testing. If on the day of CPET the subject has not followed the recommended restrictions listed below, the CPET may proceed at the discretion of the investigator. If CPET does not proceed, the CPET should be rescheduled to occur within study visit window.

- 1) Withhold all medications the morning of the test (including study drug which will be taken on site).
- 2) Withhold beverages containing alcohol or caffeine 6 hours before the scheduled test time.
- 3) Do not ingest anything orally except water for 2 hours before the scheduled test time.
- 4) Withhold products containing nicotine 3 hours before the scheduled test time.
- 5) Refrain from performing strenuous exercise 12 hours before the scheduled test time.
- 6) Wear clothes and shoes that are appropriate for treadmill exercise.

#### 6.11.2.2. Test Procedure Instructions for Subject

Review the following CPET procedures with the subject prior to each CPET:

- 1) Review the procedure for getting on and off the treadmill.
- 2) Review the procedure for walking without holding the handrails. If a subject must use the handrails, encourage him/her to use 2 fingers on the handrail for balance only, or when necessary, hold them very lightly.
- 3) Review the procedure for reporting perceived exertion (Borg scale, each minute) and chest pain sensations, if chest pain occurs.
- 4) Review expected exercise performance (ie, subject should be encouraged to achieve maximal effort).
- 5) Familiarize the subject with the ventilatory gas exchange apparatus.
- 6) Review procedure for communicating with test operators while wearing a mask, including indicating the desire to stop.

#### 6.11.3. CPET Conduct

Prior to the start of each CPET at the Screening, Week 12, and Week 24 visits, the site should ensure that equipment calibration is complete, the Modified Naughton protocol has been programmed, and the ECG and metabolic system have been set-up as described above and specified in the CPET study manual.



#### 6.11.3.1. Conduct of CPET

The following instructions apply to the conduct of the exercise tests at the Screening, Week 12, and Week 24 visits. Please refer to the CPET study manual for full detail on required data collection during exercise testing.

- 1) Weigh the subject.
- 2) Provide detailed test instructions to the subject (Section 6.11.2).
- 3) Attach ECG electrodes to the subject in the standard 12-lead configuration and record baseline resting 12-lead ECGs in both the supine and standing positions.
- 4) Measure the subject's baseline resting blood pressure and heart rate in the supine and standing position.
- 5) Prior to beginning the Modified Naughton exercise protocol, allow the subject to stand on the treadmill and acclimate to the gas exchange equipment. Record the resting CPET data for a minimum of two minutes. Once the subject's RER is between 0.70 and 0.85, begin the test. Make certain that the test starting point is clearly labelled in order to distinguish resting and exercise data.
- 6) Begin the Modified Naughton Protocol exercise test. Perform continuous, 3-lead minimum ECG monitoring, and print a 12-lead ECG each minute throughout the exercise test.
- 7) At the end of each minute, have the subject assign a Borg Scale (Appendix 5) rating between 6 and 20.
- 8) Record gas exchange data continuously. The CPET printout must show 30-second rolling averages collected every ten seconds for the entire test.
- 9) Measure the subject's blood pressure and heart rate within the last 30 seconds of each 2-minute exercise stage.
- 10) Maximal effort should be encouraged. The exercise test should be stopped based on standard indications for stopping (see Section 6.11.3.2).

#### 6.11.3.2. Termination of CPET exercise test

Terminate the exercise test when the subject completes all stages of the exercise test, or if any of the following occur.

- Abnormal clinical symptoms including:
  - Moderately severe angina or angina equivalent (3 on a scale of 1 to 4) of a nature that would normally cause the subject to stop activities
  - Moderately severe dyspnea (3 on a scale of 1 to 4) of a nature that would normally cause the subject to stop activities.

- Lightheadedness
- Vertigo
- Lower extremity fatigue
- Emergence of abnormal ECG or hemodynamic responses including:
  - Exertional hypotension, defined as a sustained decrease in systolic blood pressure > 10 mmHg below baseline or > 10 mmHg decrease after an initial rise with exercise
  - Severely increased systolic blood pressure ( $\geq 250$  mmHg)
  - Severely increased in diastolic blood pressure ( $\geq 115$  mmHg)
  - ECG abnormalities (clinically significant ventricular dysrhythmias such as recurrent or sustained VT, repeated couplets, or couplets increasing in both frequency and complexity)
  - New or exercise-induced left bundle branch block
  - Marked ST segment displacement defined as  $\geq 2.0$  mm of horizontal or downsloping ST depression below the resting ST segments, or  $\geq 1.0$  mm of ST elevation above the resting ST segments in leads without Q waves

#### 6.11.3.3. Recovery period

After terminating exercise, place the subject in the supine position and continuously record the ECG for at least 8 minutes and until the subjects' ECG and vital signs are clinically stable.

### 6.12. Electrocardiogram (ECG)

A standard 12-lead resting electrocardiogram (ECG) will be performed at every study visit, in addition to exercise ECGs collected during CPET.

A core ECG laboratory will collect ECG data and provide centralized blinded adjudication of ECG parameters for ECGs collected through Week 24, the end of the double-blind treatment period.

ECGs collected post Week 24 during the open-label extension will be reviewed by the investigator and ECG parameters will be collected in the eCRF.

Instructions for the collection of ECGs and transmittal of ECGs to the core laboratory will be provided in the ECG study manual.

The investigator will review the ECGs for any clinically significant abnormalities to ensure subject safety. Abnormal ECG findings that are considered clinically significant by the investigator and meet the definition of an AE should be reported and recorded in the AE eCRF page.

### **6.13. ZIO<sup>®</sup> XT Patch**

The ZIO<sup>®</sup> XT Patch will be worn starting at the Screening visit for 7 days and starting at the Week 12 visit for 7 days.

The ZIO<sup>®</sup> XT Patch is a single use continuously recording ECG monitor. Used ZIO<sup>®</sup> XT Patches will be returned to iRhythm for analysis. Instructions for ZIO<sup>®</sup> XT Patch use and return for processing will be provided in a study-specific ZIO<sup>®</sup> XT Patch manual.

Investigators should reference the study manual for warnings and precautions for ZIO<sup>®</sup> XT Patch use prior to applying the ZIO<sup>®</sup> XT Patch to the subject.

The site staff will apply the ZIO<sup>®</sup> XT Patch on site following the instructions provided in the study manual, review instructions for wear with the subject, and instruct the subject on timing and removal of the patch. At the conclusion of the 7 day wear period, the subject will remove the ZIO<sup>®</sup> XT Patch at home and will return it to the site at the next scheduled study visit.

### **6.14. Echocardiogram (ECHO)**

Subjects will undergo three separate echocardiograms at Randomization, Week 12, and Week 24 visits. Images will be digitized and stored to optical disk for subsequent analysis.

A core imaging laboratory will collect all echocardiographic data and provide centralized blinded adjudication of secondary endpoints (diastolic function, systolic function, dynamic obstruction, and LV wall thickness). Instructions for the collection and transmittal of ECHOs to the core laboratory will be provided in the ECHO study manual.

The investigator will review the ECHOs for any clinically significant abnormalities to ensure subject safety. Abnormal ECHO findings that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

### **6.15. Minnesota Living with Heart Failure Questionnaire (MLHFQ)**

The MLHFQ ([Appendix 6](#)) will be administered at Randomization, Week 12, and Week 24 study visits.

The MLHFQ is designed to measure the effects of symptoms, functional limitations, and psychological distress on an individual's quality of life. The MLHFQ is 21-items measured on a 6-point Likert scale (0 to 5) and is scored by summing the responses to all 21 questions and takes approximately 5-10 minutes to complete.

Subjects should complete the questionnaire prior to other assessments and interactions that may bias their responses. It is important that the MLHFQ is administered prior to CPET and review of adverse events and concomitant medications.

Ample, uninterrupted time should be provided for the subject to complete the questionnaire. The subject should answer the questions without being influenced by others such as their spouse or family members.

It is recommended that the site use the first question to give the subject more detailed instructions by reading the introductory paragraph at the top of the questionnaire and then reading the first question with the subject and explaining how to complete the questionnaire. For example:

- Read with the subject: “Did your heart failure prevent you living as you wanted during the last month (4 weeks) by causing swelling in your ankles or legs?” Then tell the subject:
  - If you did not have any ankle or leg swelling during the past month (4 weeks) you should circle the zero (0) after this question.
  - If you did have swelling that was caused by a sprained ankle or some other cause that you are sure was not related to heart failure, you should circle the zero (0) after this question.
  - If you had swelling that might be related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do or feeling the way you would like to feel. In other words, how much did the swelling affect your life? Circle either the 0, 1, 2, 3, 4 or 5 to indicate how much the swelling affected your life during the past month – zero (0) means not at all, one (1) means very little and five (5) very much.

Ask the subject to read and respond to all 21 questions. The entire questionnaire may be read directly to the subject if one is careful not to influence responses by verbal or physical cues.

Review the questionnaire before the end of the study visit to make sure there are no unanswered questions or questions with more than one answer. If a question does not apply to the subject they should circle the zero (0). Make sure there is only one answer clearly marked for each question.

Score the questionnaire by summing the responses to all 21 questions.

## **6.16. Physical Examination**

A complete physical examination (PE), including vital signs as described in Section 6.17, will be performed at Screening. The complete PE should include the following body systems: head, ears, eyes, nose, and throat (HEENT), lymph nodes, CV, respiratory, gastrointestinal, skin, neurologic, and musculoskeletal. Height and weight should also be recorded.

An abbreviated PE, including vital signs as described in Section 6.17, will be performed at Randomization and all post randomization visits. The following body systems should be reviewed and assessed as part of the abbreviated PE: CV, respiratory, gastrointestinal, and skin.

New or worsening abnormal PE findings that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

## **6.17. Vital Signs**

Vital signs including blood pressure (BP), heart rate (HR), and respiration rate will be measured in a sitting position throughout the study at every study visit. Refer to Section 6.11 and the study-specific CPET Manual for instructions for vital signs collected during CPET.

Abnormal vital signs measurements considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the event meets the definition of an AE.

## **6.18. Clinical Laboratory Assessments**

Blood and urine samples will be collected throughout the study as outlined in Section 6 and in Appendix 2.

During Screening, the subject may have any of the laboratory tests repeated once for confirmation only when medically warranted (eg, suspected laboratory error, inappropriate handling of blood/plasma/serum samples, etc.).

All clinical laboratory samples will be analyzed by a central laboratory. Complete instructions regarding the processing, packaging, and shipping of samples will be provided in a separate clinical laboratory manual. Copies of results of the laboratory tests will be filed with the subject's study records. The investigator will review the laboratory reports and comment on all clinically significant abnormal laboratory values.

If the results of any laboratory assessments are found to be abnormal, additional evaluation may be performed as clinically indicated. Abnormal laboratory values that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the event meets the definition of an AE.

### **6.18.1. Blood Samples**

Blood samples will be collected for the following laboratory analyses throughout the study as outlined in Section 6 and in Appendix 2:

- Hematology: Complete Blood Count (CBC) with differential and platelet count
- Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), bicarbonate, aspartate aminotransferase (AST), bilirubin (total), bilirubin (direct and indirect), blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyl transferase (GGT), glucose, magnesium, potassium, sodium.

The following will be assessed at Screening only:

- estimated GFR (eGFR) calculated by the MDRD equation by the central laboratory
- FSH, estradiol, and progesterone, for females only, upon request if needed for documentation of menopausal status as required by study protocol (see Appendix 7).

### **6.18.2. Urinalysis**

Urine samples will be collected for urinalysis at Screening and all post Randomization visits. Routine urinalysis (UA) of macroscopic panel will include pH, specific gravity, glucose, color, ketones, and occult blood.

### **6.18.3. Pregnancy Test**

A serum pregnancy test will be performed for all female subjects of childbearing potential (as defined in [Appendix 7](#)) at Screening. A urine pregnancy test for females of childbearing potential must be conducted at Randomization and all post Randomization visits. If at Screening menopausal status is not documented per the requirements detailed in [Appendix 7](#), pregnancy tests will be performed at each study visit until menopausal status is documented.

All female subjects of childbearing potential are required to have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization to be eligible for participation in this study.

Positive urine pregnancy tests will be confirmed by a serum pregnancy test. Results of the serum pregnancy test must be reviewed by the investigator prior to any additional study-related assessments. The results of the serum pregnancy test must be negative for continued participation in the study.

### **6.19. Plasma Pharmacokinetic (PK) Samples**

PK samples will be collected for assessment of plasma GS-6615 concentrations and metabolites for PK characterization and future population PK studies of GS-6615 in the HCM population.

Two PK samples will be drawn at the Randomization visit. The first sample should be collected before the subject has taken the first dose of study drug. The second sample should be collected approximately 2-3 hours after the subject has taken the first dose of study drug. If 2-3 hours postdose is not possible, the PK sample should be collected as late as possible before the subject leaves the site.

Two PK samples will be drawn at all visits after Randomization through Week 24. The first sample should be obtained before the subject has taken the daily study drug dose on site. The subject will then take the study drug while at the site and the second PK sample should be collected approximately 3 hours postdose. If 3 hours postdose is not possible, the second PK sample should be collected as late as possible before the subject leaves the site. For subjects who have discontinued study treatment but who are continuing in the study, a single PK sample will be collected at each follow-up visit.

A single PK sample will be collected at the Early Termination visit. The date and approximate time of the last dose of study drug should be recorded, if applicable.

A single PK sample will be collected at each open-label extension period visit and at the 30-day Follow-up visit. The date and approximate time of the last dose of study drug should be recorded, if applicable.

Detailed instructions for the processing, packaging, and shipping of PK samples will be provided in a separate manual.

#### **6.20. NT-proBNP and High-sensitivity Troponin T (hsTnT) Samples**

Blood samples for analysis of NT-proBNP and hsTnT prognostic biomarkers will be collected at Randomization, Week 12, and Week 24 visits. Refer to Section [3.7.1](#) for further detail on biomarker sample collection.

## **7. ADVERSE EVENTS**

### **7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events**

#### **7.1.1. Adverse Events**

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post- treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.5.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

#### **7.1.2. Serious Adverse Events**

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization



- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

### **7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events**

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

## **7.2. Assessment of Adverse Events and Serious Adverse Events**

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

### **7.2.1. Assessment of Causality for Study Drugs and Procedures**

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No: Evidence** exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures (eg, venipuncture).

### **7.2.2. Assessment of Severity**

The severity grading of AEs will be assessed as described below:

**Mild:** Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study drug; symptoms which do not interfere with subject's daily activities.

**Moderate:** Discomfort enough to cause interference with usual activities; the study drug may be interrupted. Symptoms which may interfere with subject's daily activities; being within reasonable limits; not excessive or extreme; medium or average extent; study drug may be interrupted.

**Severe:** Incapacitating with inability to do work or do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may be stopped, and treatment for the event may be required. Events which interrupt subject's usual daily activities and may require medical intervention or treatment; study drug may be stopped.

### **7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead**

#### **Requirements for collection prior to study drug initiation**

After informed consent, but prior to initiation of study drug, the following types of events should be reported on the eCRF: all SAEs and AEs related to protocol-mandated procedures.

#### **Adverse Events**

Following initiation of study drug, all AEs must be collected, regardless of cause or relationship, until 30 days after last dose of study drug, and be reported on the eCRF as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol defined follow up period. AEs ongoing at the time of death are to remain ongoing unless it is confirmed that the event resolved at or prior to the death.

## Serious Adverse Events

All SAEs (including deaths), regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported on the eCRF and to Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 60 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow-up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead DSPH.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

## Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically (ie, the eCRF database is not functioning), record the SAE on the paper serious adverse event reporting form and submit within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH:

**Gilead DSPH: Fax:** +1-650-522-5477  
**Email:** Safety\_FC@gilead.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

#### **7.4. Gilead Reporting Requirements**

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

#### **7.5. Special Situations Reports**

##### **7.5.1. Definitions of Special Situations**

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only

when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

## **7.5.2. Instructions for Reporting Special Situations**

### **7.5.2.1. Instructions for Reporting Pregnancies**

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1-650-522-5477 or email [Safety\\_FC@gilead.com](mailto:Safety_FC@gilead.com).

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Informed consent must be obtained from the pregnant partner of a male study subject to allow follow-up. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1-650-522-5477 or email [Safety\\_FC@gilead.com](mailto:Safety_FC@gilead.com).

Refer to [Appendix 7](#) for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

#### 7.5.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section [7.3](#) and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

## 8. STATISTICAL CONSIDERATIONS

### 8.1. Analysis Objectives and Endpoints

#### 8.1.1. Analysis Objectives

The primary objective of this study is to:

- Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO<sub>2</sub> achieved during CPET, in subjects with symptomatic hypertrophic cardiomyopathy (HCM).

The secondary objectives of this study are to:

- Evaluate the safety and tolerability of GS-6615 in subjects with symptomatic HCM.
- Evaluate the effect of GS-6615 on quality of life as measured by the MLHFQ.
- Evaluate the effect of GS-6615 on treadmill exercise time during CPET.
- Evaluate the effect of GS-6615 on arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation).

The exploratory objectives of this study are to:

PPD [REDACTED]

[REDACTED]

[REDACTED]

#### 8.1.2. Primary Endpoint

The primary efficacy endpoint is the change in Peak VO<sub>2</sub> from baseline (Screening) to Week 12. Data will be sent to the core exercise physiology laboratory from the sites and the core exercise physiology laboratory will provide adjudicated results to Gilead. Adjudication will be blinded to treatment assignment.

#### 8.1.3. Secondary Endpoint

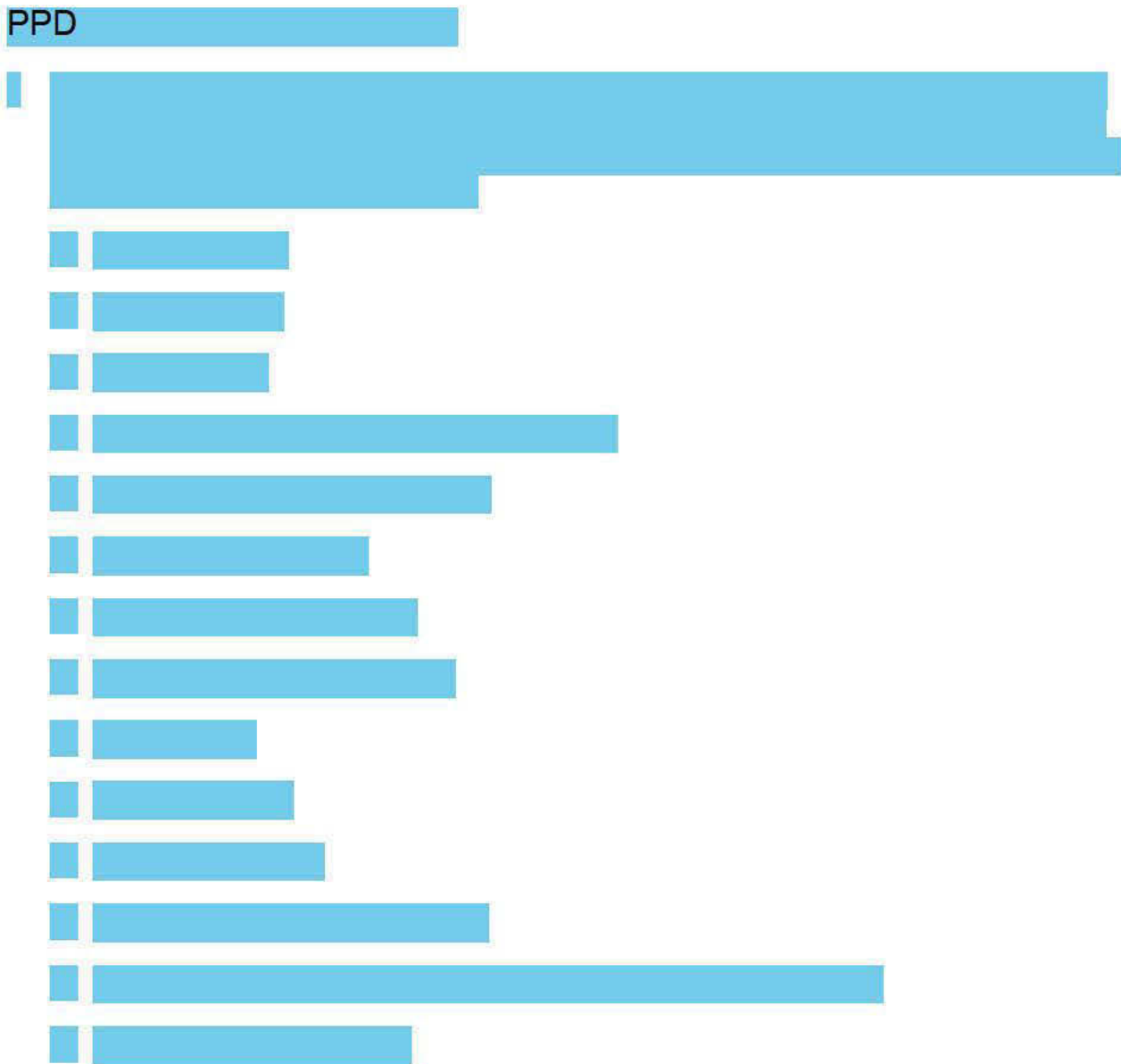
The secondary efficacy endpoints are:

- Change in Peak VO<sub>2</sub> between baseline and Week 24.
- Change in the MLHFQ between baseline and Week 12.
- Change in treadmill exercise time between baseline and Week 12.
- Change in the MLHFQ between baseline and Week 24.



- Change in treadmill exercise time between baseline and Week 24.
- Changes in arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation) between the 7-day baseline period (prior to randomization) and Week 12 to 13 on blinded study drug (ZIO<sup>®</sup> XT Patch). Percent of beats with premature ventricular complexes, number of nonsustained ventricular tachycardia episodes divided by patch time, and percent of patch time with atrial fibrillation for each subject will be calculated for the baseline period and the Week 12 to 13 period. The proportion of subjects with any premature ventricular complexes, nonsustained ventricular tachycardia, and episodes of atrial fibrillation will also be summarized.

#### 8.1.4. Exploratory Endpoints





PPD

### 8.1.5. Safety Endpoints

The safety endpoints include AEs, vital signs, clinical laboratory tests, and ECG data (PR, RR, QRS, QT and QTc interval).

## 8.2. Analysis Conventions

### 8.2.1. Analysis Sets

#### 8.2.1.1. Efficacy

The full analysis set (FAS) will be defined as all randomized subjects who received at least one dose of study drug and have an efficacy measurement both prior to study drug administration and after study drug administration, and do not have a major eligibility criteria violation. This will be the primary analysis set for evaluation of efficacy.

#### 8.2.1.2. Safety

The primary analysis set for safety analyses is defined as all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment received.

All data collected through the safety follow-up visit will be included in the safety summaries.

#### 8.2.1.3. Pharmacokinetics

The primary analysis set for the PK analyses is defined as all randomized subjects who received at least one dose of study drug and have any post-baseline plasma concentrations.

#### 8.2.1.4. Biomarkers

The primary analysis set for the biomarker (NT-proBNP, hsTnT) analyses is defined as all randomized subjects who received at least one dose of study drug and who have an NT-proBNP or hsTnT measurement both prior to study drug administration and after study drug administration.

### **8.2.1.5. Timing of Analyses**

A futility analysis may be performed after at least 50% of subjects have been randomized. Details of the futility stopping rules will be specified in the data monitoring committee (DMC) charter (see Section 8.10).

After all subjects have completed the Week 24 visit (or the 30-day follow-up visit if not continuing in the open-label extension), the database will be cleaned and locked for the primary analysis of efficacy and safety through Week 24.

At the end of the study (ie, after all subjects have completed the open-label extension period including the 30-day follow-up visit), the database will be cleaned and locked for the secondary analysis of the safety and PK data collected during the open-label extension period.

### **8.3. Data Handling Conventions**

Baseline is defined as the Randomization visit value, if available, otherwise the Screening visit value serves as baseline.

In general, missing values will not be imputed. However, if the randomization measurement is missing, the last predose value may be used as the baseline value.

PK concentration values below the limit of quantitation (BLQ) will be treated as zero for the determination of summary statistics. Individual values which are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least one subject has a concentration value BLQ for the time point, then the minimum value will be displayed as “BLQ.” If more than 50% of the subjects have a concentration data value BLQ for the time point, then the minimum and median values will be displayed as “BLQ.” If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], maximum) will be displayed as “BLQ.”

NT-proBNP and hsTnT results will be log-transformed prior to analysis.

### **8.4. Demographic Data and Baseline Characteristics**

Demographic and baseline characteristics will be summarized using standard descriptive methods (eg, sample size, mean, standard deviation, minimum, median, maximum, Q1, Q3) by treatment group.

Demographic and baseline characteristics and medical history will be listed by subject.

### **8.5. Efficacy Analysis**

The primary endpoint (change in Peak VO<sub>2</sub> between Screening and Week 12) will be compared between the GS-6615 treatment group and the placebo group at a significance level of 0.01. If the comparison is statistically significant ( $p \leq 0.01$ ), then the first secondary endpoint (change

in Peak VO<sub>2</sub> between Screening and Week 24) will be tested at a significance level of 0.01. If this comparison is statistically significant ( $p \leq 0.01$ ), then the second secondary endpoint (change in MLHFQ between Randomization and Week 12) will be tested at a significance level of 0.05. If this comparison is statistically significant ( $p \leq 0.05$ ), then the third secondary endpoint (change in treadmill exercise time between Randomization and Week 12) will be tested at a significance level of 0.05. All other secondary and exploratory endpoints will be tested at a 2-sided nominal significance level of 0.05, with no adjustment for multiple testing.

Descriptive statistics (mean, standard deviation, median, minimum, maximum, Q1, and Q3) will be presented for continuous variables. Categorical data will be summarized using frequencies and percentages. Summaries will be presented by treatment.

In general, continuous variables will be analyzed using an analysis of covariance (ANCOVA) model with terms for sex, age (as a continuous variable), baseline value and treatment. Sensitivity analyses may be performed for continuous variables using the stratified Wilcoxon rank sum test. Analyses of binary and categorical variables will be performed using Cochran-Mantel-Haenszel (CMH) tests or logistic regression, as appropriate. MMRM analyses will also be performed for selected endpoints as specified below.

#### **8.5.1. Primary Analysis**

The change in Peak VO<sub>2</sub> from baseline (Screening) to Week 12 for the GS-6615 treatment group will be compared to that of the placebo treatment group using ANCOVA including terms for baseline Peak VO<sub>2</sub>, sex, and age in the model.

The null hypothesis is that there is no difference between the mean change in Peak VO<sub>2</sub> between the GS-6615 treatment group and the placebo treatment group.

#### **8.5.2. Secondary Analyses**

Changes in Peak VO<sub>2</sub> at Week 24, MLHFQ, treadmill exercise time, and arrhythmia burden for the GS-6615 treatment group will be compared to those of the placebo treatment group using ANCOVA for continuous variables (including terms for baseline value, sex and age in the model), and CMH tests or logistic regression for categorical and binary variables, respectively. Sensitivity analyses will be performed for continuous variables using the stratified Wilcoxon rank sum test. MMRM analyses will also be performed for the Week 12 and Week 24 Peak VO<sub>2</sub>, MLHFQ, and treadmill exercise time endpoints.

Correlations between efficacy endpoints will be explored.

Pre-specified subgroup analyses will be performed, including subgroup analyses for subjects with baseline resting LVOT gradient  $> 30$  mmHg and  $\leq 30$  mmHg, as measured during the randomization echocardiogram.

### **8.5.3. Exploratory Analyses**

PPD



### **8.6. Safety Analysis**

For the primary analysis after the first database lock, safety data collected on or after the date that study drug was first administered up to the Week 24 visit (or the 30-day follow-up visit if not continuing in the open-label extension) will be summarized by treatment group (according to the study drug received).

For analysis of the open-label extension period after the second database lock, safety and PK data collected on or after the date that study drug was first administered up to the end of the study will be summarized.

Formal statistical comparisons between treatment groups will not be performed for the safety analyses.

Data for the pretreatment period will be included in data listings.

#### **8.6.1. Extent of Exposure**

Extent of exposure to study drug will be summarized by treatment group. Exposure is defined as the time from the first dose of study drug to the last dose of study drug. Reasons for early termination of study drug will be summarized by treatment group.

#### **8.6.2. Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date and time of first dose of study drug through 30 days after last dose of study drug.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC, HLT and PT) will be provided by treatment group. Multiple AEs mapping to the same preferred term will be counted once per subject.

#### **8.6.3. Laboratory Evaluations**

Selected laboratory data will be summarized by treatment group. Data and change from baseline at all scheduled time points will be summarized.



All laboratory data will be listed. In addition, a separate listing of treatment-emergent laboratory abnormalities, defined as post-baseline values outside the normal range, will be provided.

#### **8.6.4. Other Safety Evaluations**

Vital signs and 12-lead ECG data will be summarized by treatment group. Data and change from baseline at all scheduled time points will be summarized.

Concomitant medications will be coded using the WHO Drug Dictionary with generic term and therapeutic use (ATC code) and summarized by ATC code, WHO generic name, and treatment group.

#### **8.7. Pharmacokinetic Analysis**

Plasma concentrations of GS-6615 will be listed and summarized for each visit using descriptive statistics (sample size, mean, % coefficient of variation, standard deviation, median, minimum, maximum, Q1, and Q3).

Correlation between plasma concentration levels and the primary and secondary endpoints will be explored.

#### **8.8. Biomarker Analysis**

NT-proBNP and hsTnT values at each visit and change from baseline at Weeks 12 and 24 will be listed and summarized by treatment group using descriptive statistics (mean, standard deviation, median, minimum, maximum, Q1, and Q3). Geometric means and geometric mean ratios will be presented.

Changes in NT-proBNP and hsTnT for the GS-6615 treatment group will be compared to those of the placebo treatment group using MMRM with baseline value as a covariate. Values will be log-transformed prior to analysis. Sensitivity analyses will be performed using the stratified Wilcoxon rank sum test.

Correlations between NT-proBNP and hsTnT and other efficacy endpoints may be explored.

#### **8.9. Sample Size**

Based on a 2-sided, 2-sample t-test ( $\alpha = 0.01$ ), and a standard deviation of 4 mL/kg/min, 90 subjects per treatment group will provide greater than 90% power assuming an effect size of 3mL/kg/min in the primary endpoint (Peak VO<sub>2</sub>). This assumes that the analysis will be performed on subjects who have Peak VO<sub>2</sub> measured at Week 12 and allows for a dropout rate of approximately 15% (13 subjects). This effect size is clinically significant and similar to that seen with alcohol septal ablation {26759}.

A blinded sample size re-estimation is planned when approximately 50% of subjects have completed the Week 12 visit in order to re-evaluate the assumptions for the sample size calculations. The observed pooled (blinded) standard deviation in Peak VO<sub>2</sub> will be compared with the assumed standard deviation. If the observed standard deviation is higher than the assumed standard deviation, then the number of subjects may be increased to up to approximately 110 subjects per treatment group (220 subjects randomized).

As this analysis will be performed on blinded data, no adjustments to the overall type-I error rate will be performed.

#### **8.10. Data Monitoring Committee**

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data at periodic intervals and provide recommendation to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

After at least 50% of subjects have been randomized, a futility analysis may be performed. Details of the futility stopping rules will be specified in the DMC charter.

#### **8.11. Endpoint Adjudication**

A core exercise physiology laboratory will collect cardiopulmonary data and provide centralized blinded adjudication of the primary endpoint (Peak VO<sub>2</sub>). A core ECG laboratory will collect ECG data and provide centralized blinded adjudication of ECG parameters. All core lab adjudications will be blinded to treatment assignment. A core imaging laboratory will collect all echocardiographic data and provide centralized blinded adjudication of echocardiographic endpoints (diastolic function, systolic function, dynamic obstruction, and LV wall thickness).

## **9. RESPONSIBILITIES**

### **9.1. Investigator Responsibilities**

#### **9.1.1. Good Clinical Practice**

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

#### **9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval**

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

#### **9.1.3. Informed Consent**

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB or IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

#### **9.1.4. Confidentiality**

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions or in accordance with local regulations. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

#### **9.1.5. Study Files and Retention of Records**

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, sex);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);



- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

#### **9.1.6. Case Report Forms**

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed promptly to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC

system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

#### **9.1.7. Investigational Medicinal Product Accountability and Return**

Gilead recommends that used and unused study drug supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

#### **9.1.8. Inspections**

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs or IECs, or to regulatory authority or health authority inspectors.

#### **9.1.9. Protocol Compliance**

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

## **9.2. Sponsor Responsibilities**

### **9.2.1. Protocol Modifications**

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

### **9.2.2. Study Report and Publications**

A clinical study report (CSR) will be prepared and provided to the regulatory agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

## **9.3. Joint Investigator/Sponsor Responsibilities**

### **9.3.1. Payment Reporting**

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

### **9.3.2. Access to Information for Monitoring**

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

### **9.3.3. Access to Information for Auditing or Inspections**

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

### **9.3.4. Study Discontinuation**

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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## 11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. Study Procedures Table
- Appendix 3. Modified Naughton Protocol
- Appendix 4. Wasserman Hansen Equations
- Appendix 5. Borg Perceived Exertion Scale
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- Appendix 8. Classification of Strong Inhibitors and Inducers of CYP3A



**Appendix 1. Investigator Signature Page**

**GILEAD SCIENCES, INC.  
333 LAKESIDE DRIVE,  
FOSTER CITY, CALIFORNIA 94404  
UNITED STATES**

**STUDY ACKNOWLEDGEMENT**

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy

GS-US-361-1157 Original 01 April 2014

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

RAMIN FARZANEH-FAR  
Ramin Farzaneh-Far, MD, FACC  
Medical Monitor

**PPD**  
Signature

7th April 2014  
Date

**INVESTIGATOR STATEMENT**

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

\_\_\_\_\_  
Principal Investigator Name (Printed)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Site Number

**Appendix 2. Study Procedures Table**

	Screening Period		Double-Blind Placebo-Controlled Treatment Period								OLE	Follow-up
	Screening Visit	Randomization Visit	Week 1 Contact	Week 4 Visit	Week 9 Contact	Week 12 Visit <sup>a</sup>	Week 15 Contact	Week 18 Visit	Week 21 Contact	Week 24 Visit <sup>a</sup>	OLE Visits Weeks 28, 40, & 52, then every 24 Weeks	30-day Follow-up Visit -or- Early Termination
	Day -28 to Day -7	Day 1	Day 7 ±3 days	Day 28 to Day 42	Day 63 ±3 days	Day 84 ±7 days	Day 105 ±3 days	Day 126 ±7 days	Day 147 ±3 days	Day 168 ±7 days		
Written Informed Consent	X											
Inclusion/Exclusion Criteria Review	X	X										
Medical History	X											
Physical Exam <sup>b</sup>	X	X		X		X		X		X	X	X
Vital Signs	X	X		X		X		X		X	X	X
Study drug dosing during visit <sup>c</sup>		X		X		X		X		X		
MLHFQ <sup>d</sup>		X				X				X		
12-Lead resting ECG	X	X		X		X		X		X	X	X
CPET/Peak VO <sub>2</sub> measurement	X					X				X		
Echocardiogram		X				X				X		
Clinical Laboratory Assessments <sup>e</sup>	X <sup>c</sup>			X		X		X		X	X	X

	Screening Period		Double-Blind Placebo-Controlled Treatment Period								OLE	Follow-up
	Screening Visit	Randomization Visit	Week 1 Contact	Week 4 Visit	Week 9 Contact	Week 12 Visit <sup>a</sup>	Week 15 Contact	Week 18 Visit	Week 21 Contact	Week 24 Visit <sup>a</sup>	OLE Visits Weeks 28, 40, & 52, then every 24 Weeks	30-day Follow-up Visit -or- Early Termination
	Day -28 to Day -7	Day 1	Day 7 ±3 days	Day 28 to Day 42	Day 63 ±3 days	Day 84 ±7 days	Day 105 ±3 days	Day 126 ±7 days	Day 147 ±3 days	Day 168 ±7 days		
Pregnancy Test <sup>f</sup>	X	X		X		X		X		X	X	X
PK sample collection		X <sup>g</sup>		X <sup>h</sup>		X <sup>h</sup>		X <sup>h</sup>		X <sup>h</sup>	X <sup>i</sup>	X <sup>i</sup>
NT-proBNP & hsTnT		X				X				X		
Optional PG sample collection <sup>j</sup>		X										
Start ZIO <sup>®</sup> XT Patch (7 day wear)	X					X						
Collect ZIO <sup>®</sup> XT Patch		X						X				
Dispense Study Drug		X		X		X		X		X <sup>k</sup>	X	
Study Drug Accountability & Compliance				X		X		X		X	X	X <sup>l</sup>
Contact Subject			X		X		X <sup>m</sup>		X	X <sup>n</sup>		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

- a Recommended order of assessments at Week 12 and Week 24 visits: (1) predose PK sample collection, (2) witnessed study drug dosing, (3) MLHFQ, (4) ECG, (5) CPET, (6) ECHO, and (7) all other blood sample collection including postdose PK sample. All other required visit assessments may occur at any point during the study visit.
- b Complete PE including body weight and height measurements at Screening, abbreviated PE at all other visits
- c At visits where study drug dosing occurs on site, the first PK sample should be collected before the subject has taken the daily dose of study drug.
- d It is very important that MLHFQ administration occurs prior to CPET.
- e Hematology, Serum Chemistry and Urinalysis will be assessed at all visits where clinical laboratory assessments are performed. eGFR (and upon request FSH, estradiol, and progesterone) will be assessed at Screening only.
- f Females of Child-Bearing Potential only. Serum pregnancy test at Screening and urine pregnancy test at all other visits.
- g Day 1 PK samples collected predose and 2-3 hours postdose, if 2-3 hours postdose is not possible postdose sample should be collected as late as possible before subject leaves the site
- h PK samples collected predose and 3 hours postdose, if 3 hours postdose is not possible postdose sample should be collected as late as possible before subject leaves the site
- i Single PK sample. Collected at OLE visits through Week 52.
- j Optional pharmacogenomic sample should be drawn at Randomization visit, but may be collected at any time during the study or at a separate post study visit, if necessary
- k Only dispense study drug if subject will continue into open-label extension period
- l ET visit only, when applicable
- m During Week 15 contact, review ZIO<sup>®</sup> XT Patch wear and removal
- n Contact subject at Week 25 (Day 175  $\pm$ 3 days) to review adverse events and concomitant medications. Additional subject contacts between OLE visits are at investigator discretion.

**Appendix 3. Modified Naughton Protocol**

<b>Stage</b>	<b>Speed (mph)</b>	<b>Elevation (%)</b>	<b>Duration (min)</b>	<b>(METs)</b>
1	1	0	2	1.0
2	1.5	0	2	2.0
3	2.0	3.5	2	3.5
4	2.0	7.0	2	4.5
5	2.0	10.5	2	5.5
6	3.0	7.5	2	6.5
7	3.0	10.0	2	7.5
8	3.0	12.5	2	8.5
9	3.0	15.0	2	9.5
10	3.4	14	2	10.5
11	3.4	17.5	2	12
12	3.4	20.0	2	13.5

**Appendix 4. Wasserman Hansen Equations**

**Predicted Maximum VO<sub>2</sub> in Normal Sedentary Adults, mL/min**

Sex	Ergometer	Overweight	Maximum VO <sub>2</sub> mL/min	Lower 95% Confidence Limit
Male	Treadmill	No*	$W \times (56.36 - 0.413 \times A)$	Predicted maximum VO <sub>2</sub> – 8.2 x W
		Yes*	$(0.79 \times H - 60.7) \times (56.36 - 0.413 \times A)$	
Female	Treadmill	No**	$W \times (44.37 - 0.413 \times A)$	
		Yes**	$(0.79 \times H - 68.2) \times (44.37 - 0.413 \times A)$	

Abbreviations: Weight (W) in kg, Height (H) in cm, and Age (A) in years.

\*Overweight for male treadmill exercise test is  $W > (0.79 \times H - 60.7)$

\*\*Overweight for female treadmill exercise test  $W > (0.79 \times H - 68.2)$

Reference: Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ. Normal values. In: Principles of Exercise Testing and Interpretation. 4th ed. Philadelphia: Lippincott, Williams and Wilkins; 2005.

**Appendix 5. Borg Perceived Exertion Scale**

<b>Score</b>	<b>Perceived Exertion</b>
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

**Appendix 6. Minnesota Living With Heart Failure Questionnaire**

**MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE**

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

<b>Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -</b>	<b>No</b>	<b>Very Little</b>			<b>Very Much</b>	
	0	1	2	3	4	5
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

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## **Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements**

### **1) Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential**

The risks of treatment with GS-6615 during pregnancy have not been evaluated. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study. Please refer to the latest version of the investigator's brochure for additional information.

### **2) Definition of Female of Childbearing Potential**

For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a pubertal female who has not yet started menstruating and perimenopausal women who have had a spontaneous menses in the last 12 months. A woman who has had a tubal sterilization is considered to be of childbearing potential for pregnancy testing purposes.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed)
- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (SD 1.73) years
- A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
  - If age  $\geq 54$  years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the postmenopausal range based on the laboratory reference range where the hormonal assay is performed
  - If age  $< 54$  years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the postmenopausal range, depressed estradiol (E2) level in the postmenopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed

### **3) Contraceptive Requirements**

Male subjects and female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening visit throughout the study period and for 90 days following the last dose of study drug. Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence

from heterosexual intercourse and regular pregnancy testing while taking study drug. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; (2) two barrier methods where one method is the male condom; or (3) use of an intrauterine device (IUD) or tubal sterilization; see [Appendix Table 1](#) below. Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNG 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used.

Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing (Randomization).

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization (Day 1) prior to receiving the first dose of study drug. Lactating females must discontinue nursing before study drug administration.

**Appendix Table 1. Protocol Specified Contraceptive Methods**

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	Barrier Methods (use both OR choose one and use with a hormone method)
<b>Intrauterine Devices (IUDs)</b> - Copper T 380A IUD - LNG 20 IUD	<b>Estrogen and Progesterone</b> - Oral contraceptives - Transdermal patch - Vaginal ring	- Diaphragm with spermicide OR - Cervical cap with spermicide - Male condom (with or without spermicide)
<b>Tubal Sterilization</b>	<b>Progesterone</b> - Injection - Implant	
Partner's vasectomy must be used with a hormone or barrier method.		

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

#### **4) Additional Requirements for Male Subjects**

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of study drug.

Use of condoms, with or without spermicide, has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

#### **5) Procedures to be Followed in the Event of Pregnancy**

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 90 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Male subjects whose female partner has become pregnant or suspects she is pregnant during the study and within 90 days of the last study drug dose of the male subject must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section [7.5.2.1](#).

**Appendix 8. Classification of Strong Inhibitors and Inducers of CYP3A**

<b>Strong CYP 3A Inhibitors<sup>a</sup></b>		
<b>Drug</b>	<b>Half-life</b>	<b>Time to 5 half-lives</b>
Clarithromycin	3 - 4 hours	15 – 20 hours
Indinavir	1.8 (± 0.4) hours	9 hours
Itraconazole	21 hours	105 hours
Ketoconazole	Plasma elimination is biphasic with a half-life of 2h during the first 10h, and a half-life of 8h after 10h	10 – 40 hours
Nefazodone	2 - 4 hours	10 – 20 hours
Nelfinavir	3.5 - 5 hours	17.5 – 25 hours
Ritonavir	3 - 5 hours	15 – 25 hours
Saquinavir	9 - 15 hours	45 – 75 hours
Telithromycin	10 hours	50 hours

a Please note the following: A strong inhibitor is one that caused a  $\geq 5$ -fold increase in the plasma AUC values or more than 80% decrease in clearance

<b>Strong CYP 3A Inducers</b>		
<b>Drug</b>	<b>Half-life</b>	<b>Time to 5 half-lives</b>
Carbamazepine	36 hours (single dose), 16-24 hours (repeated dosing)	180 hours (single dose), 80-120 hours (repeated dosing)
Efavirenz	40 - 55 hours	200 – 275 hours
Modafinil	15 hours	75 hours
Nevirapine	45 hours	225 hours
Oxcarbazepine	1 - 5 hours (healthy adults)	5 – 25 hours
Phenobarbital	53 - 118 hours	265 – 590 hours
Phenytoin	6 - 24 hours	30 – 120 hours
Rifabutin	28 - 62 hours	140 – 310 hours
Rifampin	1.5 - 5 hours	7.5 – 25 hours