CLINICAL STUDY PROTOCOL

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. 333 Lakeside Dr. Foster City, California 94404 United States
IND Number:	121806
EudraCT Number:	2013-004429-97
Clinical Trials.gov Identifier:	NCT02291237
Indication:	Hypertrophic Cardiomyopathy
Protocol ID:	GS-US-361-1157
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Protocol Version/Date:	Original: 01 April 2014 Amendment 1: 10 October 2014 Amendment 2: 10 February 2015 Amendment 3: 12 August 2016

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

TABLE OF CONTENTS 2
LIST OF IN-TEXT TABLES 5
LIST OF IN-TEXT FIGURES 5
PROTOCOL SYNOPSIS 6
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 16
1. INTRODUCTION 20
1.1. Background 20
1.2. GS-6615 21
1.2.1. General Information 21
1.2.2. Preclinical Pharmacology and Toxicology 22
1.2.3. Clinical Trials of GS-6615 22
1.3. Rationale for This Study 24
1.3.1. Rationale for Dose Selection 24
1.4. Compliance 26
2. OBJECTIVES 27
3. STUDY DESIGN 28
3.1. Endpoints 28
3.2. Study Design 28
3.3. Study Treatments 29
3.4. Duration of Treatment 29
3.5. Discontinuation Criteria 30
3.6. Source Data 30
3.7. Biomarker Testing 30
3.7.1. Biomarker Samples to Address the Study Objectives 30
3.7.2. Biomarker Samples for Optional Future Research 30
3.7.3. Biomarker Samples for Optional Pharmacogenomic Research 31
4. SUBJECT POPULATION 32
4.1. Number of Subjects and Subject Selection 32
4.2. Inclusion Criteria 32
4.3. Exclusion Criteria 33
5. INVESTIGATIONAL MEDICINAL PRODUCTS 35
5.1. Randomization, Blinding and Treatment Codes 35
5.1.1. Procedures for Breaking Treatment Codes 35
5.2. Description and Handling of GS-6615 36
5.2.1. Formulation 36
5.2.2. Packaging and Labeling 36
5.2.3. Storage and Handling 36
5.3. Dosage and Administration of GS-6615 or Placebo 37
5.3.1. Dose Modification for Adverse Events 38
5.3.2. Administration of GS-6615 or Placebo 38
5.4. Prior and Concomitant Medications 39
5.4.1. Other Protocol Restrictions 39
5.5. Study Drug Accountability 39
5.5.1. Investigational Medicinal Product Return or Disposal 39
6. STUDY PROCEDURES 40

6.1. Subject Enrollment and Treatment Assignment 40
6.2. Pretreatment Assessments 40
6.2.1. Screening Visit 40
6.3. Randomization (Day 1) 41
6.4. Treatment Assessments: Double-Blind Treatment Period 43
6.4.1. Week 1 Contact 43
6.4.2. Week 2 Visit 43
6.4.3. Week 6 Visit 44
6.4.4. Week 9 Contact 45
6.4.5. Week 12 Visit 45
6.4.6. Week 15 Contact 46
6.4.7. Week 18 Visit 46
6.4.8. Week 21 Contact 47
6.4.9. Week 24 Visit 48
6.4.10. Post Week 24 Double-Blind Treatment Period Visits 49
6.4.11. End of Double-Blind Treatment (EDBT) Period Visit 50
6.5. Treatment Assessments: Open-label Extension 51
6.5.1. Start of Open-label Extension Period (OLE) 52
6.5.2. Open-label Extension Period (OLE) Visits 52
6.5.3. OLE Week 1 Contact 53
6.6. Post-treatment Assessments 53
6.6.1. 30-day Follow-up Visit 53
6.7. Unscheduled Visits 54
6.8. Assessments for Premature Discontinuation from Study 54
6.8.1. Early Termination Visit 54
6.8.2. Vital Status 55
6.9. Criteria for Discontinuation of Study Treatment 55
6.10. End of Study 56
6.11. Cardiopulmonary Exercise Testing (CPET) 56
6.11.1. CPET Equipment Preparation 57
6.11.2. CPET Instructions for Subjects 57
6.11.3. CPET Conduct 58
6.12. Electrocardiogram (ECG) 60
6.13. ZIO® XT Patch 60
6.14. Echocardiogram (ECHO) 61
6.15. ICD Interrogation 61
6.16. Minnesota Living with Heart Failure Questionnaire (MLHFQ) 61
6.17. Perception of Treatment Assignment Questionnaire 62
6.18. Physical Examination 62
6.19. Vital Signs 63
6.20. Clinical Laboratory Assessments 63
6.20.1. Blood Samples 63
6.20.2. Urinalysis 64
6.20.3. Pregnancy Test 64
6.21. Pharmacokinetic (PK) Samples 64
6.21.1. Plasma PK Samples 64
6.21.2. Urine PK Samples 65
6.22. NT-proBNP and High-sensitivity Troponin T (hsTnT) Samples 65

7. ADVERSE EVENTS 66

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events 66
7.1.1. Adverse Events 66
7.1.2. Serious Adverse Events 66

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events 67
7.2. Assessment of Adverse Events and Serious Adverse Events 67
7.2.1. Assessment of Causality for Study Drugs and Procedures 67
7.2.2. Assessment of Severity 68
7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead 68
7.4. Gilead Reporting Requirements 70
7.5. Special Situations Reports 70
7.5.1. Definitions of Special Situations 70
7.5.2. Instructions for Reporting Special Situations 71

8. STATISTICAL CONSIDERATIONS 73

8.1. Analysis Objectives and Endpoints 73
8.1.1. Analysis Objectives 73
8.1.2. Primary Endpoint 73
8.1.3. Secondary Endpoint 73
8.1.4. Exploratory Endpoints 74
8.1.5. Safety Endpoints 75
8.2. Analysis Conventions 75
8.2.1. Analysis Sets 75
8.3. Data Handling Conventions 76
8.4. Demographic Data and Baseline Characteristics 77
8.5. Efficacy Analysis 77
8.5.1. Primary Analysis 78
8.5.2. Secondary Analyses 78
8.5.3. Exploratory Analyses 78
8.6. Safety Analysis 79
8.6.1. Extent of Exposure 79
8.6.2. Adverse Events 79
8.6.3. Laboratory Evaluations 79
8.6.4. Other Safety Evaluations 80
8.7. Pharmacokinetic Analysis 80
8.8. Biomarker Analysis 80
8.9. Sample Size 80
8.10. Data Monitoring Committee 80
8.11. Endpoint Adjudication 81

9. RESPONSIBILITIES 82

9.1. Investigator Responsibilities 82
9.1.1. Good Clinical Practice 82
9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval 82
9.1.3. Informed Consent 82
9.1.4. Confidentiality 83
9.1.5. Study Files and Retention of Records 83
9.1.6. Case Report Forms 84
9.1.7. Investigational Medicinal Product Accountability and Return 85
9.1.8. Inspections 85
9.1.9. Protocol Compliance 85
9.2. Sponsor Responsibilities 86
9.2.1. Protocol Modifications 86
9.2.2. Study Report and Publications 86
9.3. Joint Investigator/Sponsor Responsibilities 86

9.3.1. Payment Reporting 86
9.3.2. Access to Information for Monitoring 87
9.3.3. Access to Information for Auditing or Inspections 87
9.3.4. Study Discontinuation 87

10. REFERENCES 88

11. APPENDICES 90

Appendix 1. Investigator Signature Page 91
Appendix 2. Study Procedures Table 92
Appendix 3. Modified Naughton Protocol 95
Appendix 4. Predicted Peak VO_2 Equations 96
Appendix 5. Borg Perceived Exertion Scale 97
Appendix 6. Minnesota Living With Heart Failure Questionnaire 98
Appendix 7. Perception of Treatment Assignment Questionnaire 99
Appendix 8. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements 100
Appendix 9. Classification of Strong Inhibitors and Inducers of CYP3A 103

LIST OF IN-TEXT TABLES

Table 5-1. Study Drug Doses 37

LIST OF IN-TEXT FIGURES

Figure 1-1. Simulated PK Profile for Proposed Dosing Regimen 26
Figure 3-1. Study Schema 29

PROTOCOL SYNOPSIS

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

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
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	121806 2013-004429-97 NCT02291237
Study Centers Planned:	Approximately 40-50 centers worldwide
Objectives:	The primary objective of this study is to: • Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO_2 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. The exploratory objectives of this study are to: PPD [redacted]

	• Evaluate the effect of GS-6615 on prognostic biomarkers of myocardial wall stress (NT-proBNP) and microvascular ischemia (high-sensitivity Troponin T [hsTnT]). • Evaluate the effect of GS-6615 on electrocardiogram (ECG) parameters.
Study Design:	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. Eligible subjects will be randomized in a 1:1 ratio to either 30 mg single loading dose followed by 3 mg daily maintenance dose of GS-6615 until Week 12 then 6 mg daily maintenance dose of GS-6615 from Week 12 to at least Week 24, or matching placebo. Randomization will be stratified by sex and by age (≥ 50 years and < 50 years).
Number of Subjects Planned:	Approximately 180 subjects randomized (90 subjects per arm).
Target Population:	Subjects with symptomatic HCM
Duration of Treatment:	Minimum expected treatment duration is 24 weeks. In order to accumulate long-term safety data subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit. At the end of the double-blind, placebo-controlled treatment period, all subjects who complete the double-blind period (including study drug dosing) may continue in the study, at the discretion of the investigator, and receive GS-6615 in an open-label extension until this drug is commercially available for the treatment of patients with symptomatic HCM, or the investigator deems it no longer in the subject's best interests, or until Gilead terminates development of the study drug for the treatment of symptomatic HCM in the subject's home country. Subjects will continue to be followed for periodic assessments throughout the open-label period. The expected maximum treatment duration is approximately 52 months (assuming a 12 month enrollment period, double-blind treatment up to maximum of approximately 20 months, and open-label treatment up to maximum of approximately 32 months).

Diagnosis and Main Eligibility Criteria:

Subjects with symptoms (NYHA Class ≥ II dyspnea or CCS Class ≥ II angina) due to HCM (defined as a maximal LV wall thickness of ≥ 15 mm in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed) will be randomized.

Subjects with and without left ventricular outflow tract 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.

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 65 years old, inclusive
3) Established diagnosis of Hypertrophic Cardiomyopathy defined by standard criteria as a maximal LV wall thickness ≥ 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 ≥ II Dyspnea
   B) Canadian Cardiovascular Society (CCS) Class ≥ II Angina
5) Screening (baseline) Peak VO_2 < 80% of predicted based on age, sex, and weight-adjusted equations (Appendix 4), as confirmed by the investigator
6) Ability to perform an upright treadmill cardiopulmonary exercise test (CPET)

7) Hemodynamically stable at both Screening and Randomization visits defined as: systolic blood pressure ≥ 90 mmHg, HR ≤ 100 beats/min, and not requiring mechanical circulatory support or intravenous treatment with diuretics or vasoactive drugs
8) 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 8

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 ≥ 50% stenosis in ≥ 1 epicardial coronary artery)
3) Left ventricular systolic dysfunction (ejection fraction < 50%), known or detected during Screening 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) Body mass index (BMI) ≥ 36 kg/m^2
10) Severe renal impairment at Screening (defined as an estimated GFR < 30 $mL/min/1.73m^2$ as calculated by the Modification of Diet in Renal Disease [MDRD] equation by the central laboratory)
11) Abnormal liver function tests at Screening, defined as ALT or AST > 2x ULN, or total bilirubin > 1.5x ULN
12) Known or suspected history of seizures or epilepsy

13) Use of Class I antiarrhythmic drugs, including disopyramide, within 7 days prior to Screening

14) Use of ranolazine within 7 days prior to Screening

15) Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A (see Appendix 9) within 5-half-lives prior to Screening

16) Known hypersensitivity to study drug (GS-6615 or placebo), its metabolites, or formulation excipient

17) 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 8 for definition of female of childbearing potential).

18) 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

19) Any condition that in the opinion of the investigator would preclude compliance with the study protocol

Study Procedures/ Frequency:

At minimum, subjects will be seen in the clinic for a Screening visit (within 14 to 28 days prior to Randomization), a Randomization visit, and during the treatment period at Week 2, 6, 12, 18, and 24 visits. For subjects screening under Protocol Amendment 1 (10 October 2014), the Screening visit will be within 14-60 days prior to Randomization. Subjects will be contacted between study visits for assessment of adverse events and concomitant medications. In order to accumulate additional long-term safety in this population, subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit. At the end of the double-blind, placebo-controlled treatment period, all subjects who complete the double-blind period (including study drug dosing) may continue in the study, at the discretion of the investigator, to receive GS-6615 in an open-label extension. During the open-label extension period subjects will continue to undergo periodic required assessments. A 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), echocardiography (ECHO), and screening labs. Subjects who are eligible to continue with the screening process will be required to wear a noninvasive cardiac rhythm monitoring patch (ZIO® XT Patch) for 14 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 < 80% of predicted based on age, sex, and weight-adjusted equations (Appendix 4). Subjects whose Screening (baseline) Peak VO_2 is ≥ 80% of predicted will not be eligible to continue.

Prior to the Randomization visit the investigator will review the Screening visit assessments (ECG, ECHO, vital signs, 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 14-28 days after the Screening visit (or within 14-60 days for subjects screening under Protocol Amendment 1). At the end of the Randomization visit, eligible subjects will be randomly assigned to GS-6615 or matching placebo.

At Randomization and every post randomization visit, 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. At Screening, Week 2, 12 and 24 visits subjects will undergo ECHO. At Screening, Week 12 and 24 visits subjects will undergo NT-proBNP and hsTnT testing. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) will be completed at Randomization, Week 12 and 24 visits. At Week 24 visit, subjects will also complete the Perception of Treatment Assignment Questionnaire. Subjects with ICDs will undergo ICD interrogation at the Randomization, Week 12 and 24 visits.

At Randomization, Week 6, and Week 18 visits, subjects will be provided with another noninvasive cardiac rhythm monitoring patch (ZIO® XT Patch) that will record heart rhythm for 14 days.

At the end of the double-blind, placebo-controlled treatment period, all subjects who complete the double-blind period (including study drug dosing) may continue in the study, at the discretion of the investigator, and receive GS-6615 in an open-label extension. Open-label extension visits will occur at Weeks 12, 24, 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. Two plasma PK samples (predose and postdose) and a predose urine PK sample (starting at Week 2) will be collected at Randomization and every post randomization study visit through OLE Week 24. A single plasma PK sample will be collected at each open-label extension visit starting at OLE Week 48 and at the 30-day Follow-up visit or ET, if applicable. 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_2). 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). For subjects with ICDs, a core electrophysiology laboratory will collect and read ICD interrogation data and provide centralized blinded adjudication of the ICD-related safety endpoints.
Test Product, Dose, and Mode of Administration:	**Day 1 through End of Double-Blind Treatment (GS-6615 treatment arm):** Oral single loading dose of 30 mg GS-6615 (5 x 6 mg tablets) on Day 1, followed by daily maintenance dose of 3 mg GS-6615 (1 x 3 mg GS-6615 tablet) until Week 12 then daily maintenance dose of 6 mg GS-6615 (2 x 3 mg GS-6615 tablets) from Week 12 to at least Week 24 visit. **Open-label extension period (all subjects):** Oral single double-blind loading dose of GS-6615 or matching placebo (5 tablets) on day of EDBT visit (to maintain retrospective blinding to double-blind study treatment assignment), followed by maintenance dose of 6 mg open-label GS-6615 (2 x 3 mg GS-6615 tablets) once daily through the end of the open-label extension.

Reference Therapy, Dose, and Mode of Administration:	**Day 1 through End of Double-Blind Treatment (Placebo treatment arm):** Oral single loading dose of placebo to match GS-6615 (5 x placebo tablets) on Day 1, followed by daily maintenance dose of matching placebo (1 x placebo tablet) until Week 12 then daily maintenance dose of matching placebo (2 x placebo tablets) from Week 12 to at least Week 24 visit.

Criteria for Evaluation:

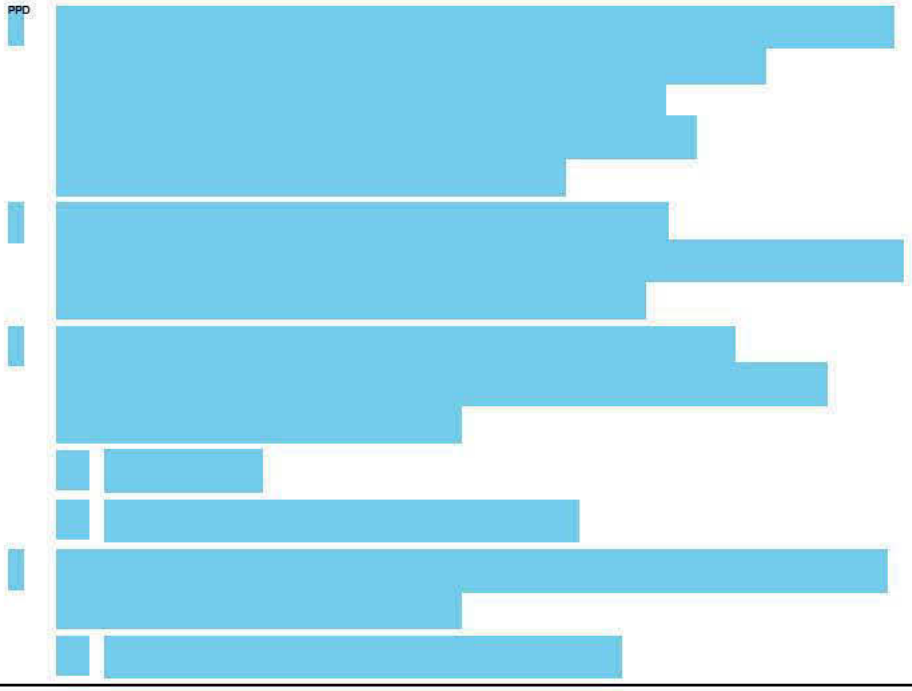
Safety: Safety will be assessed by the incidence of treatment-emergent AEs, (including physical exam findings new from baseline), death, appropriate ICD interventions (shock or anti-tachycardia pacing) in subjects with ICDs, and clinically significant abnormalities in vital signs, laboratory parameters, arrhythmia burden, and ECG variables.

Efficacy: The primary endpoint of this study is the change in Peak VO_2 between Screening (baseline) and Week 24.

The secondary endpoints of this study include:

- Change in MLHFQ from baseline to Week 24.
- Change in treadmill exercise time from baseline and to Week 24.
- Change in Peak VO_2 from baseline to Week 12.
- Change in the MLHFQ from baseline to Week 12.
- Change in treadmill exercise time from baseline to Week 12.

The exploratory endpoints of this study include:



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 3 mg maintenance dose of GS-6615 until Week 12 then 6 mg daily maintenance dose of GS-6615 from Week 12 to at least Week 24, or matching placebo. Randomization will be stratified by sex and by age (≥ 50 years and < 50 years).

Timing of Analyses:

After all subjects have completed the double-blind treatment period (including the 30-day follow-up visit for subjects not continuing in the open-label extension), the database will be cleaned and locked for the primary analysis of efficacy and safety for the double-blind treatment period.

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 24 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 12, MLHFQ, treadmill 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 may be used as a sensitivity analysis for continuous variables. Mixed models repeated measurement (MMRM) analyses will also be performed.

The primary endpoint (change in Peak VO_2 between Screening and Week 24) 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 ($p < 0.01$), the secondary endpoints will be analyzed in an alpha-controlled sequential step-down manner as follows, using a significance level of 5%:

1) Change in MLHFQ from baseline to Week 24
2) Change in treadmill exercise time from baseline to Week 24
3) Change in Peak VO_2 from baseline to Week 12
4) Change in MLHFQ from baseline to Week 12
5) Change in treadmill exercise time from baseline to Week 12

All other 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.

Numbers of subjects who die or have appropriate ICD interventions will be summarized by treatment group.

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.

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 95% power assuming a treatment difference of 3 mL/kg/min in the primary endpoint (Peak VO_2), a standard deviation of 4 mL/kg/min, and a two-sided alpha of 0.01.

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
µg	microgram
µM	micrometer
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
BMI	body mass index
BTPS	body temperature and pressure, saturated
BUN	blood urea nitrogen
Ca^{2+}	calcium
CBC	complete blood count
CCS	Canadian Cardiovascular Society
cECG	continuous ECG
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
cm	centimeters
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PMBC) concentration of drug
CNS	central nervous system
CO_2	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
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECHO	echocardiography
eCRF	electronic case report form
EDBT	end of double-blind treatment
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ER	emergency room
ET	early termination
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
H0	null hypothesis
H1	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
HR	heart rate
hsTnT	high-sensitivity Troponin T
ICD	implantable cardioverter-defibrillator
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
I_{Na}	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
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
ng	nanogram
NOAEL	no observed adverse effect level
nsVT	non-sustained ventricular tachycardia
NT-proBNP	N-terminal-pro-brain natriuretic peptide
NYHA	New York Heart Association
O_2	oxygen
OLE	open-label extension
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
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
ST	electrocardiographic interval between the termination of the S wave and the beginning of the T wave representing the interval between ventricular depolarization and repolarization
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 {Maron et al 2013}. The disease is usually caused by autosomal-dominant mutations in genes encoding contractile components of the cardiac sarcomere {Maron et al 2012b}.

Clinically, HCM is recognized as unexplained left ventricular (LV) hypertrophy (typically ≥ 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 {Gersh et al 2011}. 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 {Elliott et al 2006}.

HCM may present at any time from infancy to old age. It is most commonly diagnosed in the third and fourth decades of life, although the majority of patients who may satisfy the morphologic criteria for diagnosis are never brought to medical attention {Maron et al 2012a}. It is estimated that just over half of all patients clinically diagnosed with HCM present with symptoms that include shortness of breath and chest pain with exertion, palpitations, fatigue and syncope {Adabag et al 2006} In the subset of patients who are symptomatic, the disease can progress along several discrete, but not mutually exclusive pathways {Maron 2002}:

- 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” {Force et al 2010}.

Empirical medical therapy is considered first-line, and is based on using agents that decrease cardiac contractility {Spoladore et al 2012}. 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 {Melacini et al 2007}. 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 {Rothman et al 2012}. 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 {van Dockum et al 2004}. In patients at high risk for sudden cardiac death, placement of an ICD is standard of care {Maron 2010}.

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 {Morrow et al 1959}. 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 {Zaza et al 2008}, {Shryock et al 2008}. 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

Safety pharmacology studies conducted to examine the potential effects of GS-6615 on the respiratory, gastrointestinal (GI), central nervous and cardiovascular systems had the following observations: reduction in grip strength, a trend toward reduced cardiovascular contractility, reduced tidal volume and minute volume and delayed gastric emptying with no effect on intestinal transit time. These effects appeared to be dose related, but none were substantial in magnitude. All of the observed effects in these safety pharmacology studies can be readily evaluated in the clinical setting, and most have good margins of exposure relative to the projected clinically efficacious concentration.

The primary target organ of toxicity for GS-6615 in rats, rabbits and dogs is the central nervous system (CNS). In all species studied, ataxia and/or tremors/convulsions consistent with seizures were observed in the highest tested doses and were significant enough to warrant early termination of several animals. In general, CNS effects in toxicity studies were observed at or above group mean C_{max} values of 3-4 μg/mL. There were no CNS-related anatomic or clinical pathology correlates associated with the observed CNS effects in rats, rabbits or dogs. Additionally, no effects on embryo-fetal development were observed in rats or rabbits at exposure levels up to and including those that caused maternal toxicity. No evidence of genotoxicity has been observed.

In rats that received GS-6615 daily for 26 weeks (TX-279-2023) mortality, ataxia, and hypoactivity were observed at 25 mg/kg/day, necessitating a dosing holiday and reduction of dose levels to 10 mg/kg/day for the remainder of the study. The 15 mg/kg/day dose was tolerated throughout the study and was considered the no observed adverse effect level (NOAEL). This dose level corresponded to mean GS-6615 C_{max} and AUC_{24hr} values of 4020 ng/mL and 76,900 ng·hr/mL, respectively, during Week 26 of the dosing phase. A 39 week study in dogs at doses up to 5 mg/kg/day (TX-279-2024) showed no effects on any evaluated endpoint; the 5 mg/kg/day dose was considered the NOAEL for the study. This dose level corresponded to a mean GS-6615 C_{max} and AUC_{24hr} values of 3440 ng/mL and 55,400 ng·hr/mL, respectively, during Week 39 of the dosing phase.

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 95 subjects have been exposed to GS-6615 across four 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 in any of the recently completed or ongoing studies.

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 and has been completed. 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. In general, GS-6615 was well tolerated, and no clinically significant adverse events (AEs) or laboratory findings were observed except for AEs involving transient transaminase elevations in 2 subjects. An alanine aminotransferase (ALT) value of 4 times the upper limit of normal (ULN) was reported in one subject receiving the 30 mg dose of GS-6615. This subject also had symptoms of fatigue, sweats, nausea, and vomiting, which resolved after one day without treatment. An ALT increase > 3x ULN was observed in a second subject receiving placebo who was otherwise asymptomatic. In both subjects, bilirubin levels were normal and ALT returned to baseline within the next few days without clinical sequelae.

- 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. All AEs were reported as mild in severity except for severe appendicitis (not related to study drug) and moderate headache. Treatment related AEs included abnormal dreams (Cohort 2), nocturia (Cohort 2), headache (Cohort 2 and 3), and somnolence (Cohort 3). Overall, 4 subjects in Cohort 2 reported vivid dreams or nightmare (preferred terms of abnormal dreams or nightmare). Of these, 3 subjects had nocturia or pollakuria. The AEs of abnormal dreams started during the first week of dosing, gradually tapered off, and stopped by Day 17.

- 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 34 subjects with LQT3 identified from the LQTS registry with proven mutations in the cardiac sodium channel and QTc > 460 msec will be enrolled. This study is being performed in six sequential cohorts; four single dose cohorts followed by two 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 and Cohort 6: Day 1 – 50 mg, Days 2-3 – 10 mg, Days 4-7 - 20 mg). All single dose cohorts (ie, Cohorts 1-4) and Cohort 5 are now completed, with a total of 19 subjects (10 unique) enrolled. Cohort 6 is ongoing. All AE's reported in this study to date were assessed as mild and not related to study drug. No clinically significant trends were seen in vital signs or laboratory indices.

- GS-US 356-1308: This Phase 1 study was a single blind, randomized, placebo-controlled study designed to assess the safety, tolerability and PK profile of GS-6615 administered as multiple oral doses to elderly healthy subjects aged 65-80 years. Subjects were randomized 5:1 (active:placebo) to receive a single oral loading dose of GS-6615/placebo followed by 6 mg GS-6615/placebo once daily for 20 days. Twenty two subjects were enrolled and completed the study. Preliminary safety data show no clinically significant findings or trends in ECG parameters or laboratory results. All AEs reported were assessed as mild in severity with 3 AEs (lightheadedness, increased libido, loose stools) reported as related to study drug. Small fluctuations in vital signs were observed in both the GS-6615 and placebo groups, and were assessed as not clinically significant.

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 {Coppini et al 2013}, 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 {Lan et al 2013}. 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

The pharmacokinetics (PK) of GS-6615 is characterized by fast absorption, low apparent clearance, modest apparent volume of distribution, and a long terminal half-life resulting in significant accumulation at steady-state. In younger , healthy subjects (age 18-65), the GS-6615 median terminal half-life was 8.9 days (Q1-Q3, 5.5-16.4 days, N=30) and 11.9 days (Q1-Q3, 6.4-22.3 days, N=29) in the single ascending dose (SAD) study,

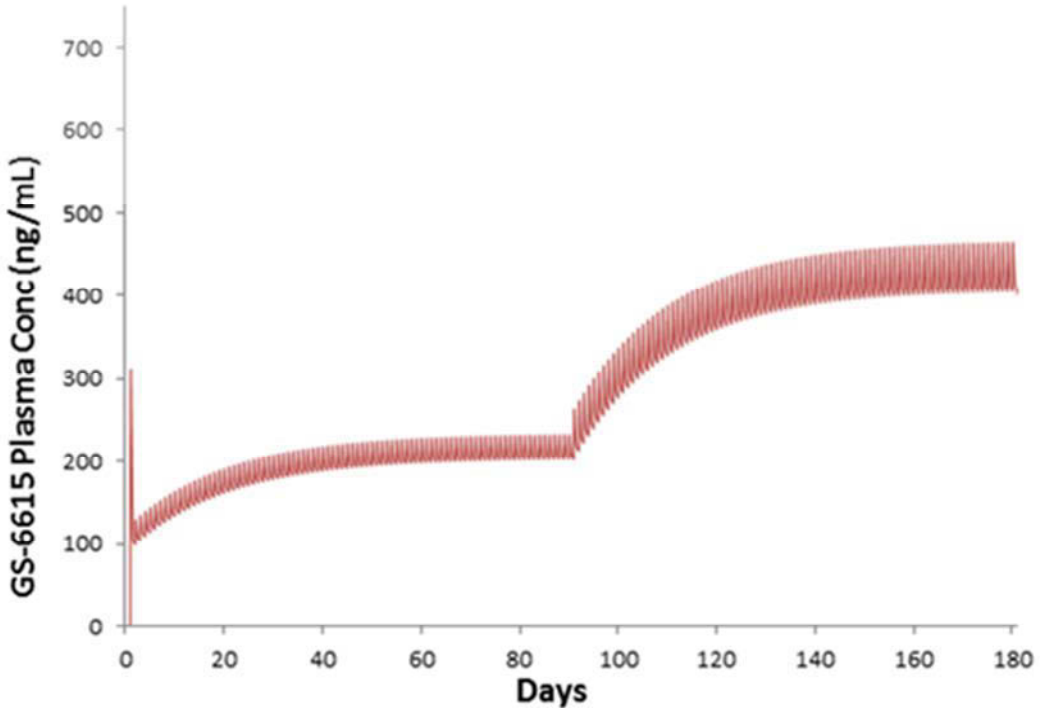
GS-US-279-0101, and the multiple ascending dose (MAD) study, GS-US-279-0102, respectively. To date, the highest observed mean C_{max} values of GS-6615 were 655 ng/mL (1.58 μM) after a single 60 mg dose and 590 ng/mL (1.44 μM) after 7 days of 20 mg followed by 14 days of 9 mg. The highest observed individual Cmax values were 900 ng/mL in the SAD study and 765 ng/mL in the MAD study. The observed variability (%CV) in GS-6615 C_{max} ranged from 15% to 23% after a single dose to 19% to 45% on Day 21 after multiple doses. The ongoing elderly PK study, GS-US-356-1308, (age 65-80 years, N=19) revealed a median terminal half-life of 20 days (Q1-Q3, 12.7-30.5 days; through at least 30 days after last dose) with corresponding higher steady-state exposures (~1.5x higher) at an equal dose.

Data from Study GS-US-279-0102 and Study GS-US-356-1308 were used to simulate the expected steady-state exposures of a proposed GS−6615 dosing regimen of a single 30 mg load followed by a daily dose of 6 mg in subjects with typical exposures (younger, age 18-65 years) or a single 30 mg load followed by a daily dose of 3 mg in subjects with higher exposures (elderly, age 65-80 years). The proposed dosing regimen is expected to a yield mean steady-state C_{max} of 467 ng/ mL (1.1 μM) and 353 ng/ mL (0.84 μM) in younger and elderly populations, respectively. These exposures, in comparison with the C_{max} value (3440 ng/mL) at the no-observed-adverse-effect level (NOAEL) from the 9 month dog toxicity study provide a 7-10-fold margin. The maximum absolute steady-state C_{max} is estimated to be 1020 ng/mL (2.4 μM) based upon the subject with lowest clearance in the elderly PK study, GS-US-356-1308, yielding a safety margin of ~3.4-fold.

HCM is an inherited disease of young and middle-aged adults, and is most commonly diagnosed in the third and fourth decades of life. Given the relatively young age distribution expected in this study, the proposed dosing regimen for this study is based on the pharmacokinetic data from the MAD study of healthy adults (GS-US-279-0102). In view of the relative rarity of symptomatic HCM, which limits the number of subjects available for enrollment, a single arm will be randomized to a sequence of two escalating doses of GS-6615 which will be compared to a parallel placebo arm. Upon randomization subjects will receive a 30 mg loading dose followed by a 3 mg/day maintenance dose for 12 weeks. After 12 weeks, all subjects who tolerate the 3 mg dose once daily will have the maintenance dose increased to 6 mg once daily. Down-titration of the maintenance dose to 3 mg will be permitted in the event of intolerance to the 6 mg dose. The anticipated mean steady state C_{max} at the 3 mg maintenance dose is 234 ng/mL; and the anticipated mean steady state C_{max} at the 6 mg maintenance dose is 465 ng/mL (see Figure 1-1).

Dose selection for this trial is also informed by preliminary data from the ongoing Study GS-US-279-0110 which showed that oral doses of GS-6615 caused sustained QTc interval shortening in subjects with LQT3. In the multiple dose cohort (Cohort 5), GS-6615 at a mean C_{max} of 362 ng/mL (on Day 7, the last day of dosing) was associated with an average daytime QTc interval shortening of 30 msec and a maximal QTc interval shortening of 51 sec. This suggests that C_{max} of 362 ng/mL is within the effective concentration of QTc interval shortening. Since the magnitude of pathologically enhanced late I_{Na} is similar in patients with LQT3 and with symptomatic HCM, it is expected that exposures comparable to those that cause QTc shortening in LQT3 will be efficacious in symptomatic HCM. These exposures are achieved by the 6 mg maintenance doses selected in the present study.

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 3 mg maintenance dose for 12 weeks followed sequentially by a 6 mg maintenance dose for an additional 12 weeks, at minimum. At the steady state concentrations anticipated with these doses, GS-6615 has been well-tolerated with no exposure-related safety signals identified to date.

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_2 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.

The exploratory objectives of this study are to:

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.

At minimum, subjects will be seen in the clinic for a Screening visit, Randomization visit, and at Week 2, 6, 12, 18 and 24 visits. Subjects will be contacted between study visits for assessment of adverse events (AEs) and concomitant medications.

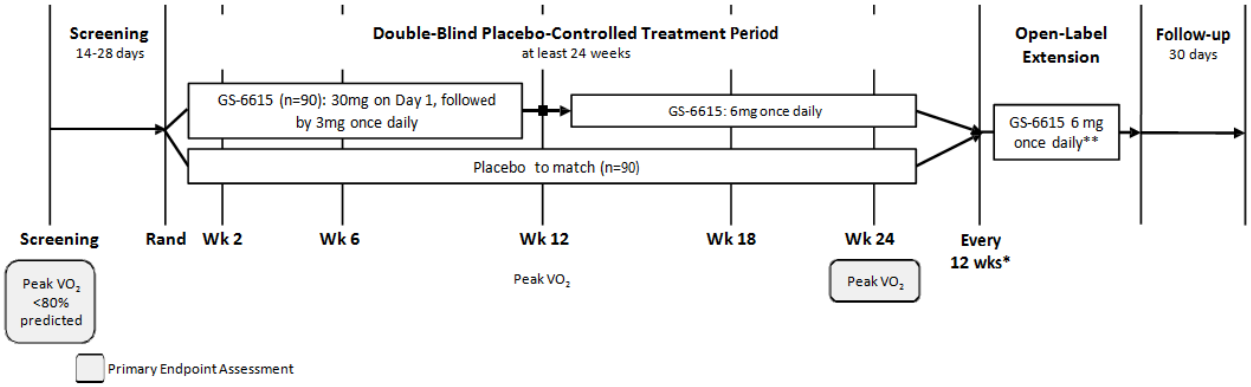
In order to accumulate additional long-term safety in this population, subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit.

All subjects who complete the double-blind treatment period (including study drug dosing) may continue in the study, at the discretion of the investigator, and receive GS-6615 in an open-label extension until this drug is commercially available for the treatment of patients with symptomatic HCM, or the investigator deems it no longer in the subject's best interests, or until Gilead terminates development of the study drug for the treatment of symptomatic HCM in the subject's home country. Subjects will complete a safety follow-up visit 30-days after last dose of study drug.

The expected maximum treatment duration is approximately 52 months (assuming a 12 month enrollment period, double-blind treatment up to maximum of approximately 20 months, and open-label treatment up to maximum of approximately 32 months).

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_2 of < 80% of predicted based on age, sex, and weight-adjusted equations (Appendix 4).

Figure 3-1. Study Schema



* Subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit.

** Subjects who complete double-blind treatment period 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 3 mg daily maintenance dose of GS-6615 until Week 12 then 6 mg daily maintenance dose of GS-6615 from Week 12 to at least Week 24, or matching placebo. Randomization will be stratified by sex and by age (≥ 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 at least 24 weeks.

In order to accumulate additional long-term safety in this population, subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit.

All subjects who complete the double-blind treatment period (including study drug dosing) may continue in the study, at the discretion of the investigator, and receive GS-6615 in an open-label extension until this drug is commercially available for the treatment of patients with symptomatic HCM, or the investigator deems it no longer in the subject's best interests, or until Gilead terminates development of the study drug for the treatment of symptomatic HCM in the subject's home country. Subjects will continue to be followed for periodic assessments

throughout the open-label extension. The expected maximum treatment duration is approximately 52 months (assuming a 12 month enrollment period, double-blind treatment up to maximum of approximately 20 months, and open-label treatment up to maximum of approximately 32 months).

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.

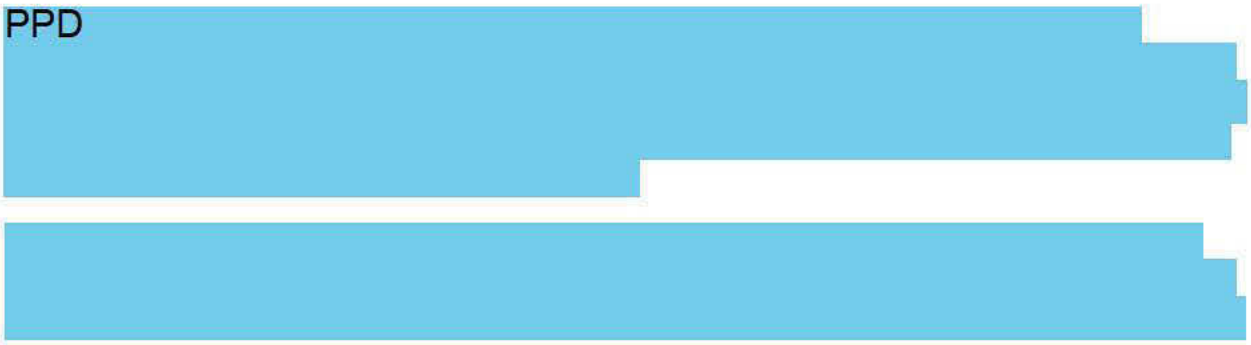
3.7. Biomarker Testing

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 Screening, 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 {Coats et al 2013}, {Kubo et al 2013}.

3.7.2. Biomarker Samples for Optional Future Research



PPD

3.7.3. Biomarker Samples for Optional Pharmacogenomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

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

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 65 years old, inclusive
3) Established diagnosis of Hypertrophic Cardiomyopathy defined by standard criteria as a maximal LV wall thickness ≥ 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 ≥ II Dyspnea
   b) Canadian Cardiovascular Society (CCS) Class ≥ II Angina
5) Screening (baseline) Peak VO_2 < 80% of predicted based on age, sex, and weight-adjusted equations (Appendix 4), as confirmed by the investigator
6) Ability to perform an upright treadmill cardiopulmonary exercise test (CPET)
7) Hemodynamically stable at both Screening and Randomization visits defined as: systolic blood pressure ≥ 90 mmHg, HR ≤ 100 beats/min, and not requiring mechanical circulatory support or intravenous treatment with diuretics or vasoactive drugs
8) 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 8

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 ≥ 50% stenosis in ≥ 1 epicardial coronary artery)

3) Left ventricular systolic dysfunction (ejection fraction < 50%), known or detected during Screening 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) Body mass index (BMI) ≥ 36 kg/m^2

10) Severe renal impairment at Screening (defined as an estimated GFR < 30 $mL/min/1.73m^2$ as calculated by the Modification of Diet in Renal Disease [MDRD] equation by the central laboratory)

11) Abnormal liver function tests at Screening, defined as ALT or AST > 2xULN, or total bilirubin > 1.5x ULN

12) Known or suspected history of seizures or epilepsy

13) Use of Class I antiarrhythmic drugs, including disopyramide, within 7 days prior to Screening

14) Use of ranolazine within 7 days prior to Screening

15) Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A (see Appendix 9) within 5- half-lives prior to Screening

16) Known hypersensitivity to study drug (GS-6615 or placebo), its metabolites, or formulation excipient

17) 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 8 for definition of female of childbearing potential).

18) 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

19) 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 may continue in the study, at the discretion of the investigator, and receive GS-6615 in an open-label extension.

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 3 mg daily maintenance dose of GS-6615 until Week 12 then 6 mg daily maintenance dose of GS-6615 from Week 12 to at least Week 24, or matching placebo. Randomization will be stratified by sex and by age (≥ 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 24 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

During the double-blind treatment period, GS-6615 will be supplied as 3 mg or 6 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 6 mg GS-6615 white film-coated tablets and contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

During the Open-Label Extension period, GS-6615 will be supplied as 3 mg pink film-coated instead of the white film-coated tablets. The 3 mg tablets are round, pink, biconvex, film-coated tablets debossed with a “3” on one side and “GSI” on the other. In addition to the active ingredient, GS-6615 3 mg pink film-coated tablets contain the following commonly used excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide, and red iron oxide.

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 treatment period, followed by an open-label extension in which all subjects (assigned to both GS-6615 and matching placebo treatment arms) 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 through Week 12 visit**	**Day after Week 12 visit through End of Double-Blind Treatment visit**	**End of Double-Blind Treatment (EDBT) visit (start of OLE)**	
GS-6615 treatment arm	30 mg GS-6615 (5 x 6 mg GS-6615 tablets)	3 mg GS-6615 (1 x 3 mg GS-6615 tablet) once daily	6 mg GS-6615 (2 x 3 mg GS-6615 tablets) once daily	**Start of visit:** 6 mg GS-6615 (2 x 3 mg GS-6615 tablets) **End of visit**: Matching placebo (5 placebo tablets)	6 mg GS-6615 (2 x 3 mg GS-6615 tablets) once daily
Placebo treatment arm	Matching placebo (5 placebo tablets)	Matching placebo (1 placebo tablet) once daily	Matching placebo (2 placebo tablets) once daily	**Start of visit**: Matching placebo (2 placebo tablets) **End of visit:** 30 mg GS-6615 (5 x 6 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.

All subjects who complete the double-blind treatment period (including study drug dosing) may continue in the study, at the discretion of the investigator and receive GS-6615 in an open-label extension until this drug is commercially available for the treatment of patients with symptomatic HCM, or the investigator deems it no longer in the subject's best interests, or until Gilead terminates development of the study drug for the treatment of symptomatic HCM in the subject's home country.

On the day of the End of Double-Blind Treatment Period (EDBT) 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 will take a double-blind loading dose of study drug on site at the EDBT visit. The double-blind loading dose on the day of the EDBT visit will ensure that all subjects entering the open-label extension receive the appropriate loading dose and will maintain retrospective blinding to double-blind study treatment assignment.

During the open-label extension period, all subjects will receive a maintenance dose of 6 mg GS-6615 once daily (2 x 3 mg GS-6615 tablets) starting the day after the EDBT visit.

Subjects who turn 66 years of age during the study will undergo a blinded review of safety and the benefit of continuing blinded study drug at 6 mg versus down titration to 3 mg will be reviewed by the investigator in consultation with the Medical Monitor.

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 possible.

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.

Subjects who complete the Week 12 visit but are unable to consistently tolerate 1 tablet once daily should continue on no more than 1 tablet of blinded study drug once daily after Week 12. After a period of consistent tolerability at the dose of one tablet once daily, the subject may attempt to up-titrate to the target dose of 2 tablets once daily, at the discretion of the investigator and in consultation with the Medical Monitor.

Subjects who complete the double-blind treatment period at a down-titrated dose of 1 tablet of blinded study drug once daily may continue into the open-label extension at 3 mg once daily of GS-6615. After a period of consistent tolerability at the dose of 3 mg once daily, the subject may attempt to up-titrate to the target dose of 6 mg once daily, at the discretion of the investigator and in consultation with the Medical Monitor.

5.3.2. Administration of GS-6615 or Placebo

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.

5.4. 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 9) 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 14-28 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. For subjects screening under Protocol Amendment 1 (10 October 2014), the Screening visit will be within 14-60 days prior to Randomization.

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 8.
- Complete physical examination including vital signs, body weight, and height, as described in Sections 6.18 and 6.19. Calculate BMI to confirm eligibility using body weight and height measurements.
- 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_2 of < 80% of predicted based on age, sex, and weight-adjusted equations (Appendix 4). Subjects whose baseline Peak VO_2 is ≥ 80% of predicted will not be eligible to continue.

- ECHO as described in Section 6.14, including measurement of left ventricular ejection fraction to confirm eligibility

- Collect blood and urine samples for Clinical Laboratory Assessments as described in Section 6.20

- Collect blood sample for serum pregnancy testing for females of childbearing potential only

- Blood sample collection for NT-proBNP and hsTnT testing

- ZIO® XT Patch wear starts at the end of the Screening visit and continues for 14 days. Subjects will be provided with instructions for wear and removal of the patch. The ZIO® 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 14-28 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 14-28 days after the Screening visit on Day 1 (or within 14-60 days for subjects screening under Protocol Amendment 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 blood sample collection for plasma PK sample as described in Section 6.21 before the subject has taken the first dose of study drug
- PPD
- Urine pregnancy test for females of childbearing potential only
- Abbreviated physical examination including vital signs as described in Sections 6.18 and 6.19
- MLHFQ administration as described in Section 6.16
- Standard 12-lead resting ECG as described in Section 6.12
- For subjects with ICDs, perform ICD interrogation as described in Section 6.15
- Collect ZIO® XT Patch
- ZIO® XT Patch wear starts during the Randomization visit and continues for 14 days. Subjects will be provided with instructions for wear and removal of the patch. The ZIO® XT Patch will be collected at the Week 2 visit.
- 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.
- Second blood sample collection for plasma PK sample as described in Section 6.21. 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 second 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 2 visit so subject can take the study drug while on site.

6.4. Treatment Assessments: Double-Blind Treatment Period

6.4.1. Week 1 Contact

Subjects will be contacted on Day 7 ±3 days to review ongoing ZIO® XT Patch wear, 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 2 Visit

The Week 2 visit will occur on Day 14 (±3 days). On the day of the visit, subjects should take study drug on site.

The following will be performed and documented at the Week 2 visit:

- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.20
- 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 6.18 and 6.19
- Standard 12-lead resting ECG as described in Section 6.12
- ECHO as described in Section 6.14
- Collect ZIO® XT Patch
- 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 blood sample collection for plasma PK sample as described in Section 6.21. 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 6 Visit

The Week 6 visit will occur on Day 42 (±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 6 visit:

- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.

- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.20

- 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 6.18 and 6.19

- Standard 12-lead resting ECG as described in Section 6.12

- ZIO® XT Patch wear starts at any time during the Week 6 visit and continues for 14 days. Subjects will be provided with instructions for wear and removal of the patch. The ZIO® XT Patch will be collected at the Week 12 visit.

- 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 blood sample collection for plasma PK sample as described in Section 6.21. 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.

6.4.4. Week 9 Contact

Subjects will be contacted on Day 63 ±3 days to review ZIO® XT Patch wear/removal, adverse events and concomitant medications, 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, and review the CPET restrictions for the next visit.

6.4.5. Week 12 Visit

The Week 12 visit will occur on Day 84 (±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 6.18 and 6.19
- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.16
- Standard 12-lead resting ECG as described in Section 6.12
- For subjects with ICDs, perform ICD interrogation as described in Section 6.15
- 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 6.20
- 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 ZIO® XT Patch
- Collect and review used and unused study drug for accountability and calculate compliance
- Dispense study drug
- Second blood sample collection for plasma PK sample as described in Section 6.21. 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.

6.4.6. Week 15 Contact

Subjects will be contacted on Day 105 (±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.

6.4.7. Week 18 Visit

The Week 18 visit will occur on Day 126 (±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 blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.20
- 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 6.18 and 6.19
- Standard 12-lead resting ECG as described in Section 6.12
- ZIO® XT Patch wear starts at any time during the Week 18 visit and continues for 14 days. Subjects will be provided with instructions for wear and removal of the patch. The ZIO® XT Patch will be collected at the Week 24 visit.
- 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 blood sample collection for plasma PK sample as described in Section 6.21. 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.

6.4.8. Week 21 Contact

Subjects will be contacted on Day 147 (±3 days) to review ZIO® XT Patch wear/removal, adverse events and concomitant medications, 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, and review CPET restrictions for the next visit.

6.4.9. Week 24 Visit

The Week 24 visit will occur on Day 168 (±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.

In order to accumulate additional long-term safety in this population, subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period (EDBT) visit. For some subjects the Week 24 visit may also serve as the EDBT visit, see Section 6.4.11 for further detail.

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 6.18 and 6.19
- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.16
- Perception of Treatment Assignment Questionnaire administration as described in Section 6.17
- Standard 12-lead resting ECG as described in Section 6.12
- For subjects with ICDs, perform ICD interrogation as described in Section 6.15
- 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 6.20
- 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
- Collect ZIO® XT Patch
- Second blood sample collection for plasma PK sample as described in Section 6.21. 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 in the open-label extension, the second PK sample must be collected before the subject takes the blinded loading dose.
- 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.

6.4.10. Post Week 24 Double-Blind Treatment Period Visits

Post Week 24 Double-Blind Treatment Period Visits will occur every 12 weeks (± 7 days) until the last subject has been followed up for approximately 24 weeks.

At each post Week 24 double-blind treatment period visit the following will be performed and documented:

- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.20
- 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 6.18 and 6.19
- 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 blood sample collection for plasma PK sample as described in Section 6.21. 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.

6.4.11. End of Double-Blind Treatment (EDBT) Period Visit

Subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit. At this time, subjects due for their Week 24 visit should perform all Week 24 assessments and do not require an End of Double-Blind Treatment Period visit in addition. Subjects will continue to receive blinded study drug through the End of Double-Blind Treatment Period visit. On the day of the visit, subjects should take the daily maintenance dose of double-blind study drug at the site.

Subjects who have already discontinued treatment but who are continuing the study will also be contacted for the End of Double-Blind Treatment Period visit when the last subject is anticipated to complete the Week 24 visit.

The following procedures will be performed and documented at the End of Double-Blind Treatment Period visit:

- Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
- Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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 6.20
- 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 6.18 and 6.19
- 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
- Second blood sample collection for plasma PK sample as described in Section 6.21. 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 in the open-label extension, the second PK sample must be collected before the subject takes the blinded loading dose.
- If subject will participate in the open-label extension period, perform and document open-label entry procedures described in Section 6.5.1.

At the end of the double-blind treatment period, all subjects who complete the treatment period (including study drug dosing), may continue in the study at the discretion of the investigator, and receive GS-6615 in an open-label extension until this drug is commercially available for the treatment of patients with symptomatic HCM, or the investigator deems it no longer in the subject's best interests, or until Gilead terminates development of the study drug for the treatment of symptomatic HCM in the subject's home country. The expected maximum treatment duration is approximately 52 months (assuming a 12 month enrollment period, double-blind treatment up to maximum of approximately 20 months, and open-label treatment up to maximum of approximately 32 months).

6.5. Treatment Assessments: Open-label Extension

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

6.5.1. Start of Open-label Extension Period (OLE)

At the end of the EDBT visit, subjects continuing into the open-label extension period the following will be performed and documented:

- Dispense study drug. Provide subject with dosing instructions for GS-6615 open-label extension.
- All subjects will take a blinded loading dose of study drug (GS-6615 or matching placebo) on site.
- Instruct the subject to hold the GS-6615 dose on the day of the next visit so the subject can take the study drug while on site.

6.5.2. Open-label Extension Period (OLE) Visits

GS-6615 open-label extension period visits will occur at the following time points: OLE Week 12 (OLE Day 84 ±7 days), OLE Week 24 (OLE Day 168 ±7 days), and every 24 weeks (±14 days) thereafter (ie, OLE Week 48 and so on).

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

- PK sample collection at OLE Week 12 and OLE Week 24 visits:
  - Predose blood sample collection for plasma PK sample as described in Section 6.21. The first PK sample should be collected before the subject has taken the daily study drug dose at the site.
  - Predose urine sample collection for urine PK as described in Section 6.21. The urine sample for PK 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
  - Second blood sample collection for plasma PK sample as described in Section 6.21. 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.
- PK sample collection from OLE Week 48 visit through last OLE visit:
  - Plasma PK sample collection at a single timepoint at each visit as described in Section 6.21
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.20

- Urine pregnancy test for females of childbearing potential only
- Abbreviated physical examination including vital signs, as described in Sections 6.18 and 6.19
- 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

6.5.3. OLE Week 1 Contact

Subjects will be contacted at OLE Week 1 (OLE Day 7 ±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 and continue to attend normal study visits (at minimum one visit at least 30 days after last dose) after study drug discontinuation are not required to compete 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 6.18 and 6.19
- Standard 12-lead resting ECG as described in Section 6.12
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.20
- Urine pregnancy test for females of childbearing potential only
- Plasma PK sample collection at a single timepoint as described in Section 6.21
- 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. 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 during the double-blind treatment period, 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. If appropriate, discuss options for study drug dose modification per Section 5.3.1.

- Obtain consent for vital status collection to occur every 3 months until end of double-blind treatment period as described in Section 6.8.2

- Abbreviated physical examination including vital signs, as described in Sections 6.18 and 6.19

- Standard 12-lead resting ECG as described in Section 6.12

- For subjects with ICDs, perform ICD interrogation as described in Section 6.15
- Complete Cardiopulmonary Exercise Testing (CPET) using the Modified Naughton Protocol as described in Section 6.11 and according to the study-specific CPET Manual if subject prematurely discontinued prior to Week 24 study visit
- MLHFQ administration as described in Section 6.16 if subject prematurely discontinued prior to Week 24 visit
- Perception of Treatment Assignment Questionnaire administration as described in Section 6.17 if subject prematurely discontinued prior to Week 24 visit
- ECHO as described in Section 6.14
- Blood and urine sample collection for Clinical Laboratory Assessments as described in Section 6.20
- Urine pregnancy test for females of childbearing potential only
- Plasma and urine PK sample collection at a single timepoint as described in Section 6.21
- Review of concomitant medications
- Review of adverse events
- Collect and review used and unused study drug for accountability and calculate compliance, if applicable

6.8.2. Vital Status

Subjects who terminate the study early, are lost to follow-up, or withdraw consent from the study, will continue to be followed by the site for vital status collection after consent for this has been given. If the subject or a family member cannot be contacted, vital status should be obtained, if possible, from public records such as government vital statistics in countries where such a registry exists or obituaries. Vital status should be obtained every 3 months from the date of the subject's early study termination, loss to follow-up, or withdrawal of consent with last collection at the end of the double-blind treatment period.

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. Refer to Section 5.3.2, Prior and Concomitant Medications, for list of allowed and prohibited concomitant medications.
- 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 8
- 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). The expected maximum treatment duration is approximately 52 months (assuming a 12 month enrollment period, double-blind treatment up to maximum of approximately 20 months, and open-label treatment up to maximum of approximately 32 months).

6.11. Cardiopulmonary Exercise Testing (CPET)

Subjects will undergo an upright treadmill CPET using the Modified Naughton Protocol (Appendix 3) at Screening, Week 12, Week 24 study visits, and if applicable, Early Termination visit. 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_2 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_2) and related secondary endpoints.

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, should 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, Week 24 visits, and if applicable, Early Termination visit.

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, Week 24 visits, and if applicable, Early Termination visit, 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, and if applicable, Early Termination visit. 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 or sit in a chair next to the treadmill and acclimate to the gas exchange equipment. Record the resting CPET data for a minimum of two minutes (and ideally until the subject's RER is between 0.70 and 0.85) prior to beginning 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). At the time the exercise test is stopped (maximum exercise), a 12-lead ECG should be printed manually if the system does not print one automatically.

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
  - — Fatigue or exhaustion
- 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 (≥ 250 mmHg)
  - — Severely increased in diastolic blood pressure (≥ 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 ≥ 2.0 mm of horizontal or downsloping ST depression below the resting ST segments, or ≥ 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, as outlined in Section 6 and in Appendix 2.

A core ECG laboratory will collect ECG data and provide centralized blinded adjudication of ECG parameters for ECGs collected through the end of the double-blind treatment period. Instructions for the collection of ECGs and transmittal of ECGs to the core laboratory will be provided in the ECG study manual.

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

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® XT Patch

The ZIO® XT Patch will be worn for 14 day periods throughout the study as outlined in Section 6 and in Appendix 2.

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

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

The site staff will apply the ZIO® 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 14 day wear period, the subject will remove the ZIO® XT Patch at home and will return it to the site at the next scheduled study visit. Based on individual wear experiences actual wear time may be less than 14 days in some subjects (eg, due to intolerable skin irritation). If a subject is unable to wear the patch for the full 14 day period due to poor wear practices (eg, taking long showers or doing activities that cause excessive sweating), the subject should be re-trained on proper wear practices when the next patch is applied.

6.14. Echocardiogram (ECHO)

Subjects will undergo echocardiogram as outlined in Section 6 and in Appendix 2. 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 echocardiographic 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. ICD Interrogation

Subjects with ICD will undergo ICD interrogation at the Randomization, Week 12 and Week 24 visits, and if applicable, Early Termination visit. ICD interrogation data at Randomization will be used to verify programming parameters. If ICD interrogation was not performed or was not possible, a follow-up visit was not completed, or supplemental monitoring was indicated, remote monitoring interrogation data may be collected. The core electrophysiology laboratory will collect and read ICD interrogation data and provide centralized blinded adjudication of the ICD-related safety endpoints. Instructions for the collection and transmittal of ICD interrogation data to the core laboratory will be provided in a separate manual.

6.16. Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The MLHFQ (Appendix 6) will be administered at Randomization, Week 12, and Week 24 study visits and if applicable, Early Termination visit.

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 summating the responses to all 21 questions.

6.17. Perception of Treatment Assignment Questionnaire

The Perception of Treatment Assignment Questionnaire (Appendix 7) will be administered at Week 24 visit only after completion of the MLHFQ and if applicable, Early Termination visit.

Subjects should complete the questionnaire after all other assessments and interactions that may bias their responses. The subject should answer the question without being influenced by others such as their spouse or family members. The questionnaire may be read directly to the subject if one is careful not to influence responses by verbal or physical cues.

6.18. Physical Examination

A complete physical examination (PE), including vital signs as described in Section 6.19, 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, weight, and BMI should also be recorded.

An abbreviated PE, including vital signs as described in Section 6.19, 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.

6.19. 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.

6.20. 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.

6.20.1. 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 8)

6.20.2. 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.

6.20.3. Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential (as defined in Appendix 8) 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 8, 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.

6.21. Pharmacokinetic (PK) Samples

Plasma and urine PK samples will be collected as described below for assessment of GS-6615 concentrations and metabolites for PK characterization and future population PK studies of GS-6615 in the HCM population.

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

6.21.1. Plasma PK Samples

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 the end of the double-blind treatment period and during the open-label extension period at the OLE Week 12 and OLE Week 24 visits. 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 starting at each open-label extension visit starting at OLE Week 48 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.

6.21.2. Urine PK Samples

A single urine PK sample will be collected predose at all visits starting at Week 2 visit through the end of the double-blind treatment period and during the open-label extension period at the OLE Week 12 and OLE Week 24 visits. For subjects who have discontinued study treatment but who are continuing in the study, urine PK samples will continue to be collected at each follow-up visit.

A single urine 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.

6.22. NT-proBNP and High-sensitivity Troponin T (hsTnT) Samples

Blood samples for analysis of NT-proBNP and hsTnT prognostic biomarkers will be collected at Screening, 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.

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.

Refer to Appendix 8.

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

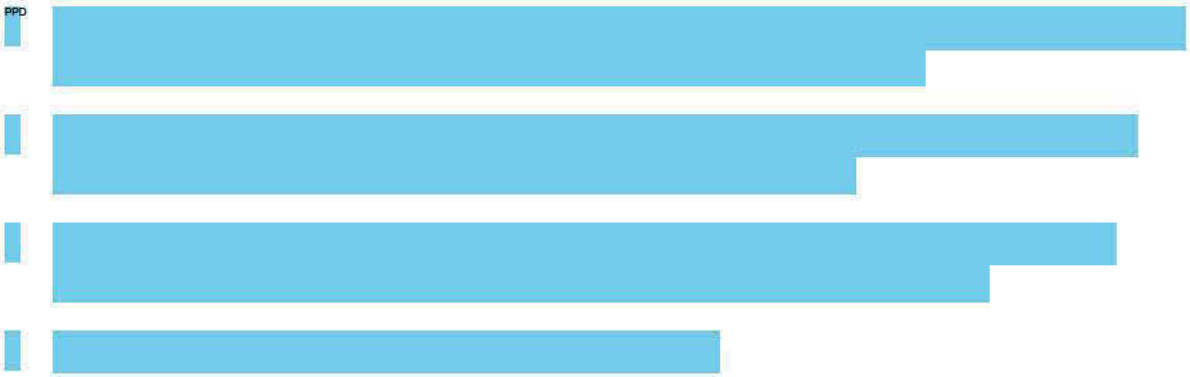
The primary objective of this study is to:

- Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO_2 achieved during CPET, in subjects with symptomatic 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.

The exploratory objectives of this study are to:



8.1.2. Primary Endpoint

The primary efficacy endpoint is the change in Peak VO_2 from baseline (Screening) to Week 24. 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

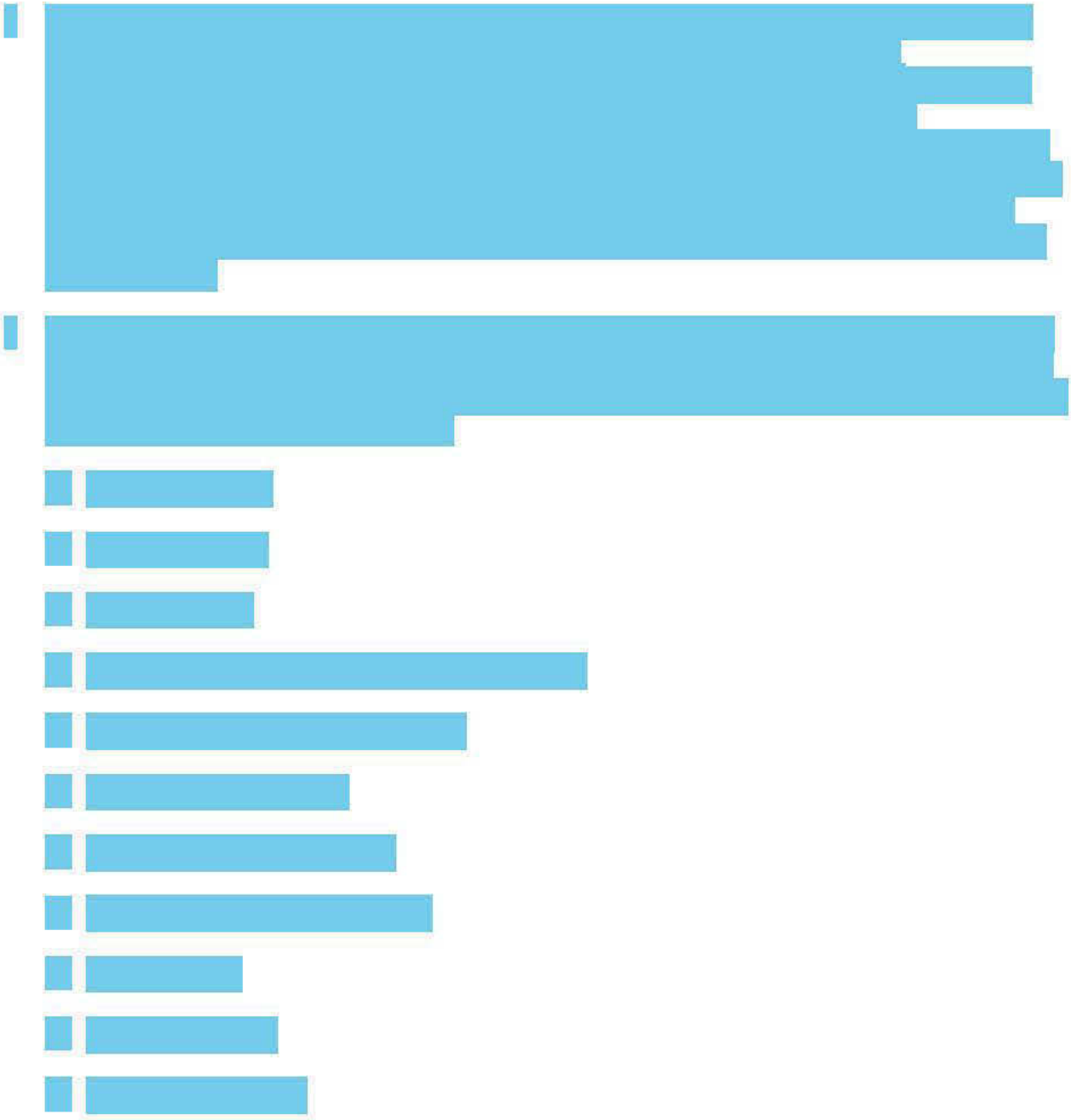
The secondary efficacy endpoints are:

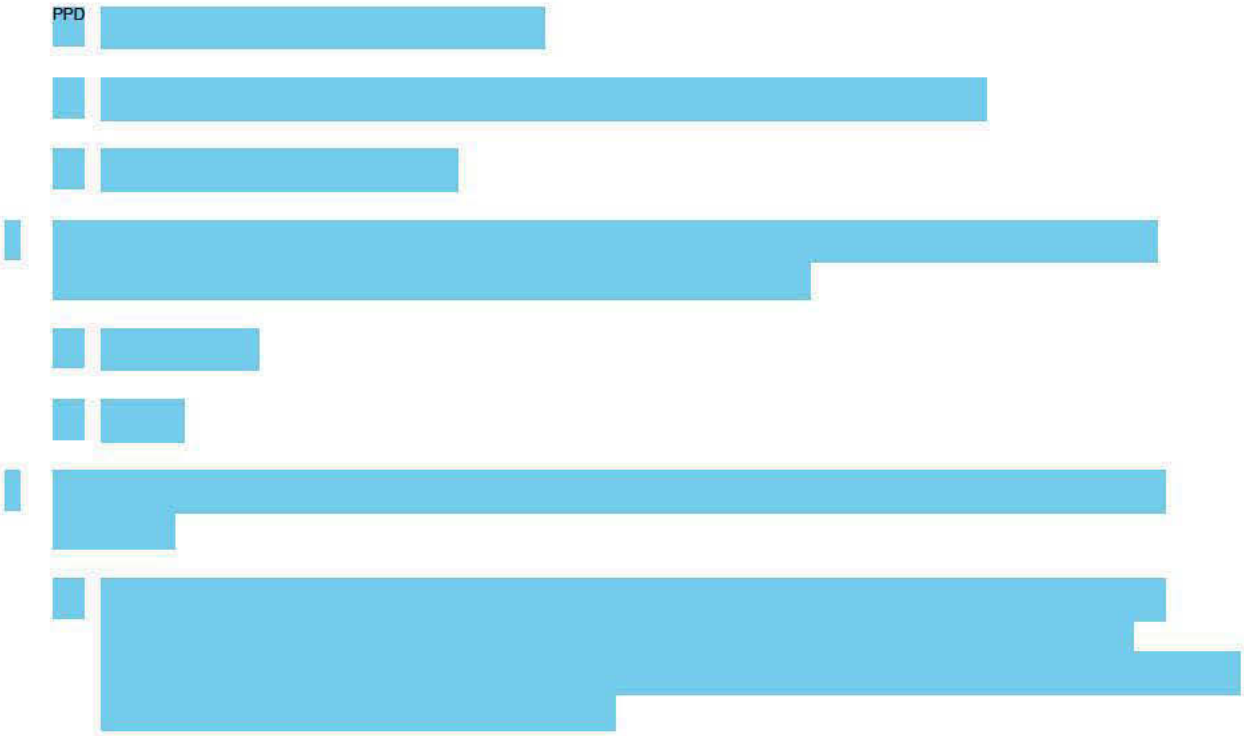
- Change in MLHFQ from baseline to Week 24.
- Change in treadmill exercise time from baseline to Week 24.

- Change in Peak VO_2 from baseline to Week 12.
- Change in the MLHFQ from baseline to Week 12.
- Change in treadmill exercise time from baseline to Week 12.

8.1.4. Exploratory Endpoints

PPD





8.1.5. Safety Endpoints

The safety endpoints include:

- Mortality and Appropriate ICD interventions (Shock or Anti-Tachycardia Pacing)
- AEs
- Vital Signs
- Clinical Laboratory Tests
- 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. This will be the primary analysis set for evaluation of efficacy. Subjects will be analyzed according to the randomized treatment.

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.

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

After all subjects have completed the double-blind treatment period (including the 30-day follow-up visit for subjects not continuing in the open-label extension), the database will be cleaned and locked for the primary analysis of efficacy and safety.

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.

Missing values for efficacy endpoints will be imputed by methods to be specified in the statistical analysis plan.

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_2 between Screening and Week 24) 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 ($p < 0.01$), the secondary endpoints will be analyzed in an alpha-controlled sequential step-down manner as follows, using a significance level of 5%:

1) Change in MLHFQ from baseline to Week 24

2) Change in treadmill exercise time from baseline to Week 24

3) Change in Peak VO_2 from baseline to Week 12

4) Change in MLHFQ from baseline to Week 12

5) Change in treadmill exercise time from baseline to Week 12

Sequential testing for statistical significance will stop after the first failure to reject the null hypothesis of no difference between active drug and placebo. In that case any subsequent analyses will be considered exploratory only.

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.
Mixed Models Repeated Measures (MMRM) analyses will also be performed for selected endpoints as specified below.

8.5.1. Primary Analysis

The change in Peak VO_2 from baseline (Screening) to Week 24 for the GS-6615 treatment group will be compared to that of the placebo treatment group using ANCOVA including terms for baseline Peak VO_2, sex, and age in the model.

Missing values will be imputed by methods to be specified in the statistical analysis plan.

A MMRM analysis will also be performed without any data imputation.

The null hypothesis is that there is no difference between the mean change in Peak VO_2 between the GS-6615 treatment group and the placebo treatment group.

8.5.2. Secondary Analyses

Changes in Peak VO_2 at Week 12, MLHFQ at Week 12 and Week 24, and treadmill exercise time at Week 12 and Week 24, for the GS-6615 treatment group will be compared to those of the placebo treatment group using ANCOVA (including terms for baseline value, sex and age in the model), Sensitivity analyses will be performed using the stratified Wilcoxon rank sum test. MMRM analyses will also be performed.

Missing values will be imputed by methods to be specified in the statistical analysis plan.

Correlations between efficacy endpoints will be explored.

Pre-specified subgroup analyses will be performed, including subgroup analyses for subjects with baseline resting obstruction (defined as LVOT gradient > 30 mmHg under resting conditions), provocable obstruction (defined as LVOT gradient < 30 mmHg under resting conditions but > 30 mmHg during the strain phase of the Valsalva maneuver),and nonobstructive (defined as LVOT gradient < 30 mmHg under resting conditions and during the strain phase of the Valsalva maneuver), as measured during the screening 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 end of the double-blind treatment period (including the 30-day follow-up visit for subjects 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 from the start of the open-label extension 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 the 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 scheduled time points will be summarized.

Laboratory data will be listed. In addition, a separate listing of treatment-emergent laboratory abnormalities will be provided. Laboratory abnormalities will be defined relative to the normal range.

8.6.4. Other Safety Evaluations

The number of subjects who die or have appropriate ICD interventions will be summarized by treatment group.

Vital signs and 12-lead ECG data will be summarized by treatment group. Data and change from baseline at 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 ANCOVA with terms for sex, age, and baseline value as a covariate. MMRM analyses will also be performed with terms for sex, age and baseline value as a covariate, and time point in the model. Values will be log-transformed prior to analysis.

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 95% power assuming a treatment difference of 3 mL/kg/min in the primary endpoint (Peak VO_2). This treatment difference is clinically significant and similar to that seen with alcohol septal ablation {Firoozi et al 2002}.

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.

8.11. Endpoint Adjudication

A core exercise physiology laboratory will collect cardiopulmonary data and provide centralized blinded adjudication of the primary endpoint (Peak VO_2) and related secondary endpoints. 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). In subjects with ICDs, a core electrophysiology laboratory will collect and read ICD interrogation data and provide centralized blinded adjudication of the ICD-related safety endpoints. All core lab adjudications will be blinded to treatment assignment.

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

The study monitor will provide instructions for return to the designated disposal site. 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.

10. REFERENCES

Adabag AS, Kuskowski MA, Maron BJ. Determinants for clinical diagnosis of hypertrophic cardiomyopathy. The American journal of cardiology 2006;98 (11):1507-11.

Chikamori T, Counihan PJ, Doi YL, Takata J, Stewart JT, Frenneaux MP, et al. Mechanisms of exercise limitation in hypertrophic cardiomyopathy. J Am Coll Cardiol 1992;19 (3):507-12.

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11. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table
Appendix 3. Modified Naughton Protocol
Appendix 4. Predicted Peak VO_2 Equations
Appendix 5. Borg Perceived Exertion Scale
Appendix 6. Minnesota Living With Heart Failure Questionnaire
Appendix 7. Perception of Treatment Assignment Questionnaire
Appendix 8. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
Appendix 9. Classification of Strong Inhibitors and Inducers of CYP3A

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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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, Amendment 3, 12 August 2016

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

Jennifer Hellawell

PPD

Jennifer Hellawell, MD, FACC
Medical Monitor

16 Aug 2016
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 Treatment Period						OLE	Follow-up
	Screening Visit	Randomization Visit	Week 2 Visit	Week 6 Visit	Week 12 Visit[a]	Week 18 Visit	Week 24 Visit[a]	Every 12 weeks after Week 24 through EDBT visit	Visits at OLE Weeks 12, 24, & then every 24 weeks	30-day Follow-up Visit -or- ET Visit[b]
	Day -28 to Day -14	Day 1	Day 14 ±3 days	Day 42 ±7 days	Day 84 ±7 days	Day 126 ±7 days	Day 168 ±7 days			
Written Informed Consent	X									ET only[b]
Inclusion/Exclusion Criteria Review	X	X								
Medical History	X									
Physical Exam[c]	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Study drug dosing during visit[d]		X	X	X	X	X	X	X	OLE Wk 12 & OLE Wk 24 only	
MLHFQ[e]		X			X		X			ET only[g]
Perception of Treatment Assignment Questionnaire[f]							X			ET only[g]
12-Lead resting ECG	X	X	X	X	X	X	X	X	X	X
CPET/Peak VO_2 measurement	X				X		X			ET only[g]
Echocardiogram	X		X		X		X			ET only
ICD interrogation		X			X		X			ET only[g]
Clinical Laboratory Assessments[h]	X		X	X	X	X	X	X	X	X
Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X
PK sample collection		X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[kl]	X[l]

	Screening Period		Double-Blind Treatment Period						OLE	Follow-up
	Screening Visit	Randomization Visit	Week 2 Visit	Week 6 Visit	Week 12 Visit[a]	Week 18 Visit	Week 24 Visit[a]	Every 12 weeks after Week 24 through EDBT visit	Visits at OLE Weeks 12, 24, & then every 24 weeks	30-day Follow-up Visit -or- ET Visit[b]
	Day -28 to Day -14	Day 1	Day 14 ±3 days	Day 42 ±7 days	Day 84 ±7 days	Day 126 ±7 days	Day 168 ±7 days			
NT-proBNP & hsTnT	X				X		X			
Optional PG sample collection[m]		X								
Start ZIO® XT Patch (14 day wear)	X	X		X		X				
Collect ZIO® XT Patch		X	X		X		X			
Dispense Study Drug		X	X	X	X	X	X	X	X	
Study Drug Accountability & Compliance			X	X	X	X	X	X	X	X[n]
Contact Subject[o]									X[p]	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	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. For Week 24 visit only: For some subjects, Week 24 visit is the same as the End of Double-Blind Treatment Period Visit

b If a subject prematurely discontinues study participation before completing the 24 Week treatment period, the subject will be asked to return to the study center for the Early Termination (ET) Visit. The ET Visit should be performed as soon as possible. Informed consent for future contact and collection of vital status will be obtained.

c Complete PE including body weight and height measurements, and BMI calculation at Screening, abbreviated PE at all other visits.

d 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.

e It is very important that MLHFQ administration occurs prior to CPET.

f The Perception of Treatment Assignment Questionnaire will be administered only after completion of MLHFQ. Subjects should complete the questionnaire after all other assessments and interactions that may bias their responses.

g Complete at Early Termination visit for subjects who prematurely discontinued prior to Week 24 visit

h 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.

i Females of Child-Bearing Potential only. Serum pregnancy test at Screening and urine pregnancy test at all other visits.

j 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

k At all post randomization visits through OLE Week 24, plasma and urine PK samples are collected predose and plasma PK sample is 3 hours postdose, if 3 hours postdose is not possible postdose plasma PK sample should be collected as late as possible before subject leaves the site

l Single PK sample collected at each open-label extension visit starting at OLE Week 48 and at the 30-day Follow-up visit or ET visit, if applicable.

m 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

n ET visit only, when applicable

o Contact subject at Week 1 (Day 7 ±3), Week 9 (Day 63 ±3), Week 15 (Day 105 ±3 days), Week 21 (Day 147 ±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. During Week 1 contact, also review ongoing ZIO® XT Patch wear. During Week 9 and Week 21 contacts, also review ZIO® XT Patch use/removal and remind the subject of the CPET restrictions on the day of the next visit.

p Contact subject at OLE Week 1 to review adverse events and concomitant medications. Additional subject contacts between OLE visits are at investigator discretion.

Appendix 3. Modified Naughton Protocol

Stage	Speed (mph)	Elevation (%)	Duration (min)	(METs)
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. Predicted Peak VO_2 Equations

Sex	Predicted Peak VO_2 mL/kg/min
Male	60 – (Age* x 0.55)
Female	48 – (Age* x 0.37)

* Age in years

References:

{Myers 1996} Essentials of Cardiopulmonary Exercise Testing Chapter 6, p.133. Myers J, 1996. ISBN 0-87322-636-4.
{Chikamori et al 1992} Mechanisms of Exercise Limitation in Hypertrophic Cardiomyopathy. Chikamori T, et al. J Am Coll Cardiol 1992;507-512.

Appendix 5. Borg Perceived Exertion Scale

Score	Perceived Exertion
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.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little				Very Much
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

11/10/04

Appendix 7. Perception of Treatment Assignment Questionnaire

In which arm of the study do you think you have been participating?

. Active arm (GS-6615)

□ Placebo arm (sugar pill)

Appendix 8. 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 ≥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

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(use both OR choose one and use with a hormone method)</th></tr>
<tr><td rowspan="2">Intrauterine Devices (IUDs)
- Copper T 380A IUD
- LNg 20 IUD

Tubal Sterilization</td><td>Estrogen and Progesterone
- Oral contraceptives
- Transdermal patch
- Vaginal ring
Progesterone
- Injection
- Implant</td><td>- Diaphragm with spermicide
OR
- Cervical cap with spermicide
- Male condom
(with or without spermicide)</td></tr>
<tr><td colspan="2">Partner’s vasectomy must be used with a hormone or barrier method.</td></tr>
</table>

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 9. Classification of Strong Inhibitors and Inducers of CYP3A

Strong CYP 3A Inhibitors[a]		
Drug	**Half-life**	**Time to 5 half-lives**
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 ≥ 5-fold increase in the plasma AUC values or more than 80% decrease in clearance

Strong CYP 3A Inducers		
Drug	**Half-life**	**Time to 5 half-lives**
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