Hypertrophic cardiomyopathy (HCM) is one of the most common inherited heart diseases, with an overall prevalence estimated to be 1:500 in the adult population, although only a minority of affected patients come to clinical recognition. It is also the most common cause of sudden cardiac death in young adults and a major cause of morbidity caused by chronic heart failure symptoms. However, more than half a century since the original description of the disease, there is no currently approved therapy for the treatment of patients with HCM, and to date there have been only 5 randomized studies of medical therapies in HCM. As such, unmet medical need in HCM has been highlighted by the National Heart, Lung, and Blood Institute (NHLBI) as a research priority. Encouragingly, the infrastructure needed to conduct rigorous clinical trials in HCM has recently emerged because of the heightened awareness and understanding of the disease, development of clinical centers of excellence, and advances in diagnostic imaging. In this article, we will discuss the complex pathophysiology of HCM, review the current therapeutic landscape, describe new mechanistic insights into the central role of the late sodium current in HCM, and introduce the scientific rationale and execution of the Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) trial, the largest randomized, double-blind, placebo controlled clinical trial, now underway, designed to evaluate the effect of a novel pharmacological approach in patients with symptomatic HCM.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02291237.

Key Words: cardiomyopathy, hypertrophic ▪ clinical trial ▪ death, sudden, cardiac ▪ diagnostic imaging ▪ morbidity
Pathophysiologic Targets and Limitations of Current Therapies

Heart Failure With Outflow Obstruction

The most important cause of heart failure symptoms in HCM is the mechanical resistance to LV outflow caused by the systolic anterior motion of the mitral valve with septal contact. LV outflow tract pressure gradients ≥30 mm Hg represent an independent determinant of progressive symptoms and death caused by heart failure or stroke. Outflow gradients can be present under resting conditions or be provoked with a variety of maneuvers or drugs, such as with exercise or infusion of dobutamine or isoproterenol. In patients with obstruction who develop limiting heart failure symptoms, the first option to control symptoms is pharmacological therapy with β-blockers or verapamil, which decrease outflow obstruction by reducing contractility, reduce myocardial oxygen demand, and enhance diastolic filling. Disopyramide, a class I antiarrhythmic, lowers gradients as well by way of its potent negative inotropic effects.

The modest efficacy and tolerability of these drugs remains a major limitation of pharmacotherapy in obstructive HCM, and a substantial proportion of these patients experience progressive heart failure requiring surgical septal myectomy or (when contraindicated) alcohol septal ablation. These septal reduction therapies can decrease the symptoms of heart failure by virtue of permanent reduction of mechanical obstruction to LV outflow, normalization of intraventricular pressures, and attenuation of mitral regurgitation. Although these invasive procedures are effective at improving heart failure symptoms, a subset of patients remain with some limitations after successful relief of obstruction, likely because of underlying diastolic heart failure.

Heart Failure Without Outflow Obstruction

One third of patients with HCM have the nonobstructive form of the disease without pressure gradients at rest or with provocation. Although the majority of patients with nonobstructive HCM have a stable clinical course, ≈10% experience progressive, limiting heart failure symptoms predominantly because of diastolic dysfunction (Figure 1). Disease progression often has a multifactorial cause, including abnormal myocardial blood flow at the microvascular level, myocardial fibrosis, abnormal cardiomyocyte energetics, increased diastolic tension caused by intracellular calcium dysregulation and atrial arrhythmias. Medical treatment is limited to negative chronotropic agents, such as β-blockers and nondihydropyridine calcium channel blockers, which may exert a beneficial effect on diastolic function by increasing myocardial blood flow and LV filling time, but have no proven benefit on outcome. About 5% of patients will proceed to overt systolic dysfunction subtended by extensive LV fibrosis, which is generally treated with standard heart failure drug regimens, and a smaller subset require advanced treatment options including heart transplant.

Microvascular Dysfunction and Angina

Angina or atypical chest pain, in the absence of flow-limiting epicardial coronary artery disease, is common in patients with HCM with or without LV outflow obstruction. In a subgroup of patients with HCM chest pain represents the predominant disease manifestation associated with severe functional limitation. The mechanism of HCM-related chest pain is likely caused by the failure of the microvasculature to meet the increased myocardial oxygen demand with effort, which is because of not only an increase in LV wall thickness and extravascular compression caused by increased diastolic tension and reduced capillary density but also marked microvascular remodeling leading to luminal obliteration of the coronary arterioles (Figure 2). Although verapamil and β-blockers can be effective at improving chest pain, many patients remain symptomatic and significantly limited in their daily activities.
Atrial and Ventricular Arrhythmias

AF is the most common sustained arrhythmia in HCM, occurring in nearly one quarter of patients.20 AF is poorly tolerated and associated with worsening heart failure symptoms, particularly in patients with outflow tract obstruction.20 Cardioembolic risk is high irrespective of the calculated CHA2DS2-VASc score.6,18 Amiodarone is the most effective agent for reducing AF recurrence, but its use is limited in younger patient populations with HCM because of toxicity with its long-term use.7,16 The efficacy of other antiarrhythmic drugs in suppressing AF recurrence, but its use is limited in younger patient populations with HCM because of toxicity with its long-term use.7,16

Finally, sudden cardiac death caused by ventricular tachyarrhythmias remains the most serious consequence of HCM, for which the ICD is the only effective means of protection.21 Although the current risk stratification algorithm for the use of ICDs in HCM, based on many noninvasive risk markers, has been a highly effective strategy at reliably identifying patients for primary prevention ICD, some high-risk patients are not identified with this strategy.3 Antiarrhythmic drugs such as amiodarone or β-blockers do not reduce the risk of sudden death, and their value in reducing appropriate ICD interventions is uncertain.7

More than half a century since the original description of the disease,22 there is no currently approved therapy for the treatment of patients with HCM.9 Indeed, in the past 60 years, there have been only 5 randomized studies of medical therapies in HCM.9 This limited clinical trial experience has been attributed to the rarity of the disease, the geographic dispersion of patients, and low event rates limiting the ability to identify hard end points, all of which present major challenges to successful recruitment of subjects to such trials. For all the above reasons, the development of novel drug therapies that can be effective at treating the complex pathophysiology underlying the heterogeneous clinical manifestations of HCM would represent an important advancement for the treatment of patients with HCM.

Role of the Enhanced Cardiac Late Sodium Current (I_{NaL}) in the Pathophysiology of HCM

Recent studies have provided new insights into the central role of I_{NaL} in the complex pathophysiology of HCM. I_{NaL} is an inward ion current, carried by Na^+ ions, that flows primarily during the plateau (phase 2) of the cardiac action potential and thereby contributes to the duration of phase 2 and early phase 3 of repolarization.23 In normal myocardium, the magnitude of I_{NaL} is small relative to peak I_{Na} (<1%), and hence its contribution to the duration of the action potential is minimal or not discernible. However, in disease states such as HCM I_{NaL} is increased 2 to 3-fold in magnitude.24 The adverse consequences of increased I_{NaL} include abnormalities in repolarization and LV function (Figure 3).25-28 An enhanced I_{NaL}, such as that observed in cardiomyocytes from patients with HCM,24 causes intracellular Na^+ overload and decreases the transmembrane electrical gradient, which favors reverse mode action of the Na^+/Ca^{2+} exchanger (NCX) to bring calcium into the cell. The resultant cytosolic Ca^{2+} overload causes sustained activation of Ca^{2+}/calmodulin kinase II (CaMKII) with subsequent increased phosphorylation of its downstream targets, including the Ca^{2+} channel, ryanodine receptor, phospholamban, and the Na^+ channel itself in a positive feedback cycle.24

In a recent study of LV tissue retrieved during septal myectomy from 26 patients with symptomatic HCM, the magnitude of I_{NaL} was found to be 2-fold greater in cardiomyocytes from patients with HCM than in control donor hearts.24 The increased I_{NaL} and associated abnormalities in Ca^{2+} homeostasis ultimately were found to induce prolongation of the action potential duration, increase diastolic Na^+ and Ca^{2+} concentrations, exacerbate susceptibility to triggered arrhythmias, promote systolic hypercontractility, and increase diastolic tension. As shown in Figure 4, all of these electrical and intracellular Na^+ and Ca^{2+} abnormalities were significantly reduced or abolished by the I_{NaL} inhibitor ranolazine. Furthermore, in a study of arrhythmic, stem cell–derived cardiomyocytes...
obtained from a large family with HCM, ranolazine restored normal rhythmic beat frequency.29

Altogether, these findings suggest that inhibition of \( I_{\text{NaL}} \) has the potential to counter several adverse features of HCM pathophysiology. These include the following: (1) diastolic dysfunction (by restoring intracellular calcium homeostasis), (2) microvascular ischemia (by reducing diastolic tension and increasing microvascular coronary perfusion), (3) ventricular arrhythmias (by improving repolarization and suppressing triggers), and (4) LV outflow tract (LVOT) obstruction (by improving diastolic filling and relaxation). Figure 3 depicts the many adverse consequences of enhanced \( I_{\text{NaL}} \) in HCM. Therefore, inhibition of this current is expected to attenuate the phenotype of HCM via a multifactorial cascade.

Eleclazine (GS-6615): Introducing a Novel Class of \( I_{\text{NaL}} \) Inhibitors

Eleclazine (GS-6615; Gilead Sciences, Foster City, CA) is a new selective inhibitor of \( I_{\text{NaL}} \),30 whose molecular structure is not related to ranolazine. Although ranolazine has been described in population-based analyses to cause modest QTc prolongation31 through its inhibition of not only \( I_{\text{NaL}} \) but also late \( I_{\text{Ca,L}} \), peak \( I_{\text{Ca,L}} \), \( I_{\text{NaCa}} \), and \( I_{\text{Ks}} \),32 eleclazine is more potent and selective in inhibiting \( I_{\text{NaL}} \). In addition, eleclazine has a longer half-life that allows daily dosing regimens. In a recent phase I study (Clinicaltrials.gov NCT01849003) eleclazine significantly shortened the QTc interval in subjects with long-QT syndrome type 3, a monogenic disease caused by a gain-of-function mutation in the gene (SCN5A) that encodes for the cardiac sodium channel, thereby confirming that are mediated by an increased \( I_{\text{NaL}} \) in patients with HCM, and thereby improve their symptoms and functional status.

LIBERTY-HCM Study Design and Rationale

The ongoing LIBERTY-HCM study (Clinicaltrials.gov NCT02291237) will test the hypothesis that eleclazine (GS-6615), when compared with placebo, improves exercise capacity as measured by peak VO\(_2\) during cardiopulmonary exercise testing in subjects with symptomatic HCM. The LIBERTY-HCM study is an international double-blind, placebo-controlled, randomized clinical trial—the largest ever undertaken in patients with HCM—and the first including >40 centers in the United States, Europe, Israel, and Australia. LIBERTY-HCM will enroll a total of 180 patients with symptomatic HCM, as defined as at least New York Heart Association class 2 dyspnea or Canadian Cardiovascular Society class 2 angina, and peak VO\(_2\) of <80% of the predicted based on age- and sex-adjusted equations. Subjects both with or without LVOT obstruction are eligible, irrespective of genetic background. Specific inclusion and exclusion criteria are listed in Table 1. Eligible subjects will be randomized 1:1 to receive either eleclazine or matching placebo added to standard background therapy for 24 weeks, based on a permutated block randomization scheme stratified by sex and age (≥50 and <50 years) and performed using an automated Web-based system. Patients in the eleclazine treatment arm will receive a single oral loading dose of 30 mg on day 1, followed by daily maintenance dose of 3 mg until week 12 and then daily maintenance dose of 6 mg from week 12 to week 24. All subjects (including those of the placebo arm) will have the option to subsequently continue treatment through an open-label extension period where they will receive a single oral double-blind loading dose of eleclazine (if previously on placebo) or matching placebo (if already on active treatment) followed by a maintenance dose of 6 mg of eleclazine. The expected maximum treatment duration is ≈58 months (assuming an 18-month enrollment period, double-blind treatment up to a maximum of ≈20 months, and open-label treatment up to a maximum of ≈32 months). All patients are allowed to continue background optimal open-label therapy for HCM with the exception of ranolazine and class I antiarrhythmic drugs.

LIBERTY-HCM Study Assessments

As shown in Figure 5, the study includes 4 periods: screening, double-blind, placebo-controlled treatment (minimum of 24 weeks), open-label extension, and follow-up (30 days after last dose). After consent, patients undergo baseline screening procedures of history and physical, measurement of vital signs, measurements of biomarkers, including high-sensitivity troponin T, N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) and electrolytes, baseline cardiopulmonary exercise testing, ECG, echocardiogram, and arrhythmic burden assessment using the ZIO XT Patch. Eligible patients are then randomized within 4 weeks of screening and undergo repeat ECG and ZIO XT Patch, quality of life assessment by completion of the Minnesota Living with Heart Failure Questionnaire (MLHFQ), ICD interrogation, where applicable, and measurement of plasma drug levels to generate pharmacokinetic data. Safety assessments of physical examination, vital signs, laboratories, and pregnancy tests are repeated at weeks 2, 6, 12, 18, and 24 and every 12 weeks into the open-label extension period. Study assessments of cardiopulmonary exercise testing, ECG, echo, MLHFQ, and pharmacokinetic laboratory draws are repeated at weeks 12 and 24.

Figure 3. Adverse consequences of enhanced \( I_{\text{NaL}} \) in hypertrophic cardiomyopathy (HCM). APD indicates action potential duration; and LVOT, left ventricular outflow tract.
Rationale for Primary End Point: The Role of VO\textsubscript{2} Max

In LIBERTY-HCM, the individual change in peak VO\textsubscript{2} between screening and week 24 will serve as the primary study end point (Figure 6).\textsuperscript{34,35} This choice reflects the idea that the principal goal of treatment with eleclazine in HCM is to relieve congestive symptoms and improve exercise tolerance. With a cardiac mortality of <1\% per year as well as the small size and geographic dispersion of the HCM population, rates of hard events (eg, sudden cardiac death) in HCM cohorts are too low to be used as outcome end points, because of the prohibitively large sample sizes required to achieve statistical power.\textsuperscript{2} Instead, surrogate end points have traditionally been used in studies of HCM, including peak exercise workload, change in LVOT gradient, symptom questionnaires, or indices of cardiac performance, such as transmirtal peak inflow velocities and LV isovolumic relaxation time.\textsuperscript{36–38} However, the use of such soft end points may be problematic because they do not always relate closely to the underlying disease process or its clinical outcome and may lack reproducibility.

Peak VO\textsubscript{2} is the peak oxygen uptake achieved during the performance of dynamic exercise and is equal to the product of maximum cardiac output and maximum arteriovenous oxygen difference. It is widely considered the best measure of cardiovascular fitness and exercise capacity.\textsuperscript{39} In the majority of patients with HCM from referral populations, peak VO\textsubscript{2} is significantly reduced,\textsuperscript{40} and its value correlates with New York Heart Association class and quality of life measures.\textsuperscript{41} As a clinical trial end point, peak VO\textsubscript{2} has several statistical
advantages over end points such as treadmill time or 6-minute walk distance, which include high reproducibility, low variance, and a narrow dynamic range at maximal effort. As such peak VO₂ has been recommended in intervention studies to reduce the standard deviation (SD) of the end point measurement and minimize sample size requirements and has been endorsed for the clinical evaluation of the efficacy of therapeutic intervention in patients with HCM.40

The prognostic value of peak VO₂ in HCM has consistently been reported from major referral centers. In a study of 1017 patients with HCM followed up for a mean of 6 years, peak VO₂ was found to be an independent predictor of a composite end point of death, ICD discharge, or witnessed revival from sudden death.42 After multivariable adjustment, each 1-mL/kg per minute increase in peak VO₂ was associated with a 9% reduction in the composite primary end point.

### Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tr>
<td>Have the ability to understand and sign a written informed consent form, which must be obtained before initiation of study procedures</td>
<td>Known aortic valve stenosis (moderate or severe)</td>
</tr>
<tr>
<td>Men and women 18- to 65-y old, inclusive</td>
<td>Known coronary artery disease (≥50% stenosis in ≥2 epicardial coronary artery)</td>
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| 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 Exertional symptoms including at least one of the following: New York Heart Association class ≥II dyspnea Canadian Cardiovascular Society class ≥II angina | LV ejection fraction <50%, known or detected during Screening visit Known moderate or severe chronic obstructive pulmonary disease (FEV1<80% predicted) Known moderate or severe restrictive lung disease (total lung capacity <70% predicted) Recent septal reduction procedure within 6 mo before screening or such a procedure scheduled to occur during the study Atrial fibrillation on 12-lead ECG at screening or detected during randomization visit Known or suspected infiltrative myocardial disease or glycogen storage disorder Body mass index ≥ 36 kg/m² Severe renal impairment at screening (GFR <30 mL/min per 1.73 m²) Abnormal liver function tests at screening, defined as ALT or AST >2×ULN, or total bilirubin >1.5×ULN Known or suspected history of seizures or epilepsy Use of class I antiarrhythmic drugs within 7 d before screening Use of ranolazine within 7 d before screening Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A Known hypersensitivity to study drug (eleclazine or placebo), its metabolites, or formulation excipient Women who are pregnant or breastfeeding Any clinically significant ongoing medical condition that might jeopardize the subject’s safety or interfere with the study Any condition that would preclude compliance with the study protocol

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; LV, left ventricular; and ULN, upper limit of normal.

**Figure 5.** Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) study patient flow diagram. *Safety assessments include physical examination, vital signs, clinical assessments, pregnancy testing, concomitant medication review, and adverse event review. CPET indicates cardiopulmonary exercise testing; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; MLHFQ, Minnesota Living with Heart Failure Questionnaire; PK, pharmacokinetic; and ZIO, ZIOPatch.
Subgroup Analyses

Subgroup analyses of potential interest include those based on the presence or absence of resting LVOT obstruction (gradient > 30 mm Hg under resting conditions), provocable obstruction (gradient ≤ 30 mm Hg under resting conditions but > 30 mm Hg during the strain phase of the Valsalva maneuver), and nonobstructive (baseline LVOT gradient < 30 mm Hg under resting conditions and during the strain phase of the Valsalva maneuver) as measured during the screening echocardiogram. Subgroup analyses will also be considered using the presence or absence of a known sarcomeric mutation, age subgroup, sex, baseline Peak VO₂ (above or below median), maximal LV wall thickness (> 25 mm or ≤ 25 mm), baseline ejection fraction (> 60% or ≤ 60%), baseline QTcB (above and below median), presence or absence of symptoms of angina pectoris (Canadian Cardiovascular Society class ≥ II), and use of β-blockers and calcium channel blockers at baseline.

Core Laboratories and Committees

Each site will submit study data for standardized and blinded adjudication of the primary, secondary, and exploratory end points by the respective LIBERTY-HCM core laboratories (Table 2). A data and safety monitoring board comprised of 2 independent expert cardiologists, and an independent statistician will review unblinded results for adverse events and other safety signals after the first 25 subjects enrolled have completed their week 2 visit and at subsequent intervals. The data and safety monitoring board will have the authority to recommend stopping the study early or modifying the study design for safety concerns weighing risks and benefits at any time during the course of the study. No formal interim analyses for superiority or futility are planned, and no prespecified stopping rules will be implemented.

Table 2. Eleclazine on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) Core Laboratories

<table>
<thead>
<tr>
<th>Study Data</th>
<th>Core Laboratories</th>
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<tbody>
<tr>
<td>CPET</td>
<td>Core exercise physiology laboratory at Stanford University</td>
</tr>
<tr>
<td>Functional capacity (VO₂)</td>
<td>ECG laboratory at BioTelemetry, Inc. (formerly Cardiocore)</td>
</tr>
<tr>
<td>Exercise hemodynamics</td>
<td></td>
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<tr>
<td>Echocardiography</td>
<td>Core echo laboratory at Brigham and Women’s Hospital</td>
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<tr>
<td>Diastolic function</td>
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<tr>
<td>Systolic function</td>
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<tr>
<td>Dynamic obstruction</td>
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<tr>
<td>LV wall thickness</td>
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<tr>
<td>Electrocardiography</td>
<td>iRhythm Technologies, Inc.</td>
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<tr>
<td>ECG intervals and segments</td>
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<tr>
<td>ZIOPatch ambulatory cardiac rhythm data</td>
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<tr>
<td>Premature ventricular complexes</td>
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<tr>
<td>Nonsustained ventricular tachycardia</td>
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<tr>
<td>Paroxysmal atrial fibrillation burden</td>
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<tr>
<td>ICD interrogation</td>
<td>Core electrophysiology laboratory at the University of Rochester</td>
</tr>
<tr>
<td>Arrhythmia burden</td>
<td></td>
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<tr>
<td>ICD interventions</td>
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CPET indicates cardiopulmonary exercise testing; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; and LV, left ventricular.
Statistical Considerations

Sample Size
A difference of 3 mL/kg per minute in peak VO\textsubscript{2} is considered clinically meaningful based on previously published studies of change in peak VO\textsubscript{2} after therapeutic interventions in HCM.\textsuperscript{47-49} Thus, based on a 2-sided, 2-sample \( t \) test (\( \alpha = 0.01 \)), and a SD of 4 mL/kg per minute, a sample size of 90 subjects per arm provides >95% power to detect a change in peak VO\textsubscript{2} of 3 mL/kg per minute.

Analysis of Primary and Secondary End Points
The primary analysis will be conducted on an intention-to-treat basis. The primary efficacy end point, change in peak VO\textsubscript{2} between screening and week 24, will be compared between the eleclazine treatment group and the placebo group at a significance level of 0.01. If the comparison is statistically significant (\( P \leq 0.01 \)), the secondary end points will be analyzed in an \( \alpha \)-controlled sequential step-down manner as follows, using a significance level of 0.05. These end points include (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\textsubscript{2} from baseline to week 12; (4) change in MLHFQ from baseline to week 12; and (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 eleclazine and placebo. In that case, subsequent analyses will be considered exploratory only. All other secondary and exploratory end points will be tested at a 2-sided nominal significance level of 5%, with no adjustment for multiple testing. Subgroup analyses will be performed if at least 10 subjects per treatment group are in the subgroup.

Conclusions
There are currently no approved therapies for the treatment of symptomatic patients with HCM. Based on strong preclinical rationale, the LIBERTY-HCM study will determine whether the selective and potent late sodium current inhibitor eleclazine improves exercise capacity and related symptoms in subjects with symptomatic HCM. The study includes >40 centers in the United States, Europe, Israel, and Australia. It has several strengths, including stringent entry criteria and a robust primary end point, and it is the largest double-blind, randomized, placebo-controlled multicenter trial undertaken in patients with HCM to date. Furthermore, the study will rigorously capture and centrally assess many objective and subjective end points, such as quality of life, arrhythmic burden, and echocardiographic measures of diastolic function. It is hoped that this study will generate new insights into the pathophysiology of HCM and set the standard for future clinical investigations into this complex disease.

Sources of Funding
Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) is funded by Gilead Sciences, Inc. Dr Olivotto was supported by the Italian Ministry of Health (RF 2010–2313451 Hypertrophic cardiomyopathy: new insights from deep sequencing and psychosocial evaluation) and NET-2011-02347173 (mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy).

Disclosures
Dr Olivotto had received research grants and honoraria from Gilead Sciences, Inc, Menarini International and Genzyme and was supported by the Italian Ministry of Health (RF 2010–2313451 Hypertrophic cardiomyopathy: new insights from deep sequencing and psychosocial evaluation) and NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy). Dr Hellawell is an employee of Gilead Sciences, Inc and holds stock in the company. Dr Farzaneh-Far is a former employee of Gilead Sciences, Inc and holds stock in the company. C. Blair is an employee of Gilead Sciences, Inc and holds stock in the company. Dr Maron is a consultant for Gilead Sciences, Inc, Dr Belardinelli is an employee of Gilead Sciences, Inc and holds stock in the company. Dr Myers is a consultant for Gilead Sciences, Inc and holds stock in the company.

References
9 Olivotto et al Novel Approach Targeting HCM Pathophysiology


Novel Approach Targeting the Complex Pathophysiology of Hypertrophic Cardiomyopathy: The Impact of Late Sodium Current Inhibition on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) Trial

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Circ Heart Fail. 2016;9:e002764
doi: 10.1161/CIRCHEARTFAILURE.115.002764

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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