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Advances in Clinical Trials

Novel Approach Targeting the Complex Pathophysiology of Hypertrophic Cardiomyopathy

Designing the Late Sodium Current Inhibition With Eleclazine on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy Trial

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Abstract—Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder, with an overall prevalence of at least 1:500 in the adult population although only a fraction 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 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 Eleclazine on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM), 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.

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Key Words: cardiomyopathy, hypertrophic ■ clinical trial ■ death, sudden, cardiac ■ diagnostic imaging ■ morbidity

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited heart diseases, with a prevalence estimated to be 1:500 in the adult population, but only a minority of these patients are diagnosed and present with symptoms.^{1,2} Mutations in genes encoding proteins of the cardiac sarcomere are responsible and contribute to the heterogeneity in clinical expression and natural history of HCM.² The clinical diagnosis is based on otherwise unexplained left ventricular (LV) hypertrophy identified by echocardiography or cardiovascular magnetic resonance. Although sudden death caused by malignant ventricular arrhythmias is the most serious complication of this disease, HCM is also responsible for heart failure and cardioembolic stroke.

Over the last half century, significant progress has been made in the treatment of patients with HCM, including (1)

implantable cardioverter-defibrillators (ICDs) for prevention of sudden death based on a risk stratification strategy using noninvasive clinical markers³; (2) utilization of surgical myectomy (or alternatively, alcohol septal ablation) for treatment of heart failure symptoms by abolishing outflow tract obstruction; and (3) drugs and transcatheter ablation for atrial fibrillation (AF) and prevention of embolic stroke. The implementation of these treatment strategies has resulted in a lower disease-related mortality, providing patients with the chance of achieving normal longevity.

Despite these advances, the availability of effective and specific pharmacological therapy for HCM remains an unmet need and a research priority, as recently highlighted in a consensus document by the NHLBI.⁴ Many barriers

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have in fact hindered the investigation of new therapeutic interventions in randomized controlled trials. However, most limitations have now been overcome by virtue of advances in cardiac imaging and genetic testing, which have improved diagnosis and heightened awareness of the disease and the establishment of international centers of excellence and registries, which have made it possible to recruit large cohorts of patients into clinical trials. Nevertheless, unique methodological aspects are involved in the design of trials in patients with HCM, yet to be tested in international multicenter studies. Taking into consideration the advances made in the diagnosis and pathophysiology of HCM, lessons learned from contemporary treatment strategies and encouraged by improvements in the infrastructure needed to conduct clinical trials in HCM, we designed the Eleclazine on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) trial. Here, we describe the first and largest randomized, double-blind, placebo-controlled multicenter clinical trial designed to test the effect of the novel late sodium current (I_{NaL}) inhibitor eleclazine in patients with symptomatic HCM. In addition, we review current therapies and their targets and discuss in detail the role of I_{NaL} in the pathophysiology of HCM, that is, the rationale of the LIBERTY-HCM trial.

Pathophysiologic Targets and Limitations of Current Therapies

Heart Failure With Outflow Obstruction

The most important cause of limiting 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.⁵ LV outflow tract pressure gradients ≥ 30 mm Hg represent an independent determinant of progressive symptoms and death caused by heart failure or stroke.⁶ 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.⁷ 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.⁸ Disopyramide, a class I antiarrhythmic, lowers gradients as well by way of its potent negative inotropic effects.⁹

The modest efficacy and tolerability of these drugs remains a major limitation of pharmacotherapy in obstructive HCM,⁹ and a substantial proportion of these patients experience progressive heart failure requiring surgical septal myectomy or (when contraindicated) alcohol septal ablation.¹⁰ These septal reduction therapies can reduce the symptoms of heart failure by virtue of permanent reduction of mechanical obstruction to LV outflow, normalization of intraventricular pressures, and decrease in mitral regurgitation.¹¹ 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.¹²

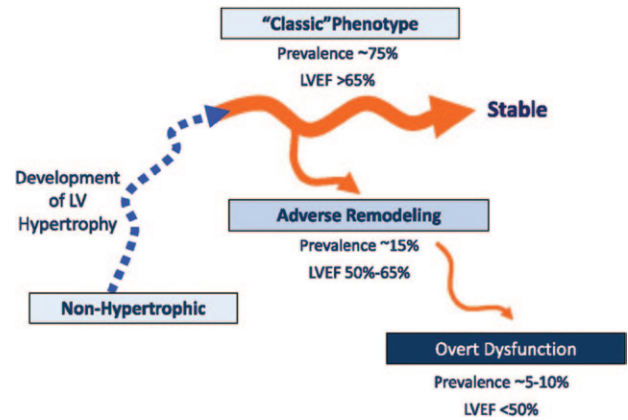


Figure 1. Stages of hypertrophic cardiomyopathy (HCM). Thickness of the orange lines reflects prevalence of each stage in HCM cohorts. Prevalence of nonhypertrophic HCM is unknown. LVEF indicates left ventricular ejection fraction. Reprinted from Olivotto et al¹⁴ with permission of the publisher. Copyright © 2012, Wolters Kluwer Health.

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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, $\approx 10\%$ experience progressive, limiting heart failure symptoms predominantly because of diastolic dysfunction (Figure 1).^{13–15} 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.¹⁶ 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.¹⁷

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Microvascular Dysfunction and Angina

Angina or atypical chest pain, in the absence of flow-limiting epicardial coronary artery disease, are common in patients with HCM with or without LV outflow obstruction.¹⁸ In a subgroup of patients with HCM chest pain represents the predominant disease manifestation associated with severe functional limitation.¹⁸ 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, 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).¹⁹ Although verapamil and β -blockers can be effective at improving chest pain, many patients remain symptomatic and significantly limit their daily activities.¹⁶

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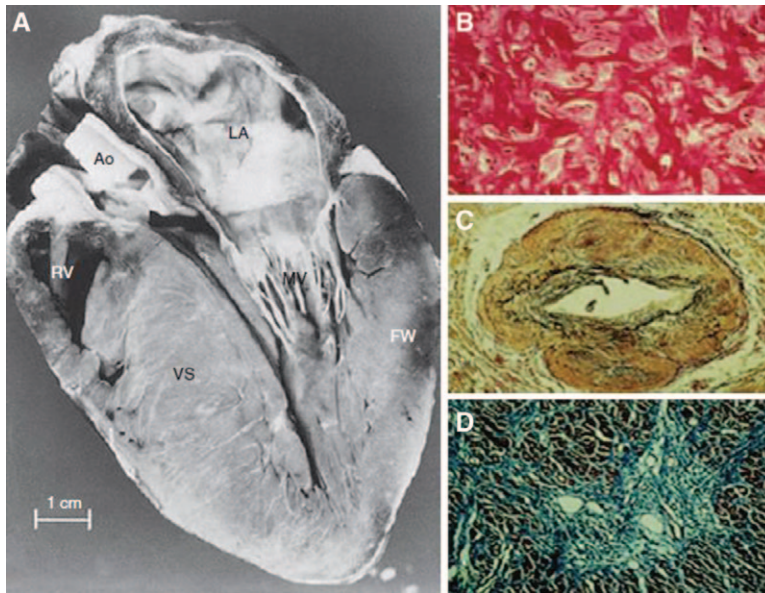


Figure 2. Histopathology of hypertrophic cardiomyopathy (HCM). **A**, Gross specimen of a heart from a patient with HCM demonstrating asymmetrical hypertrophy of the left ventricular (LV) wall. **B**, Histopathology of myocardium from a patient with HCM revealing myocyte disarray. **C**, Intramural coronary artery with medial thickening and **(D)** luminal obliteration. Ao indicates aorta; FW, free wall of LV; LA, left atrium; RV, right ventricle; and VS, ventricular septum. Reprinted from Maron¹⁹ with permission of the publisher. Copyright ©2009, Springer Publishing.

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.^{6,16} Amiodarone is the most effective agent for reducing AF recurrence, but its use is limited in younger patient population with HCM because of toxicity with its long-term use.^{7,16} The efficacy of other antiarrhythmic drugs in suppressing AF in HCM, such as sotalol or disopyramide, is considered limited.⁷

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 primary prevention, 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 in 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 the 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_i^+ overload and decreases the transmembrane electric gradient, which favors reverse mode action of the Na^+/Ca^{2+} exchanger (NCX) to bring calcium into the cell. The resultant cytosolic Ca_i^{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 \approx 2-fold greater in cardiomyocytes from patients with HCM than in control donor hearts.²⁴ The increased I_{NaL} and associated abnormalities in Ca_i^{2+} homeostasis ultimately were found to induce prolongation of the action potential duration, increase diastolic Na_i^+ and Ca_i^{2+} concentrations, exacerbate susceptibility to triggered arrhythmias, promote systolic hypercontractility, and increase diastolic tension. As shown in Figure 4, all of these electric 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

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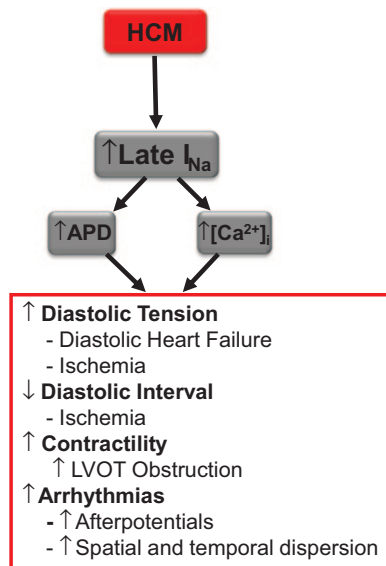


Figure 3. Adverse consequences of enhanced I_{NaL} in hypertrophic cardiomyopathy (HCM). APD indicates action potential duration; and LVOT, left ventricular outflow tract.

obtained from a large family with HCM, ranolazine restored normal rhythmic beat frequency.²⁹

Altogether, these findings suggest that inhibition of I_{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 virtue of mild negative inotropism). Figure 3 depicts the many adverse consequences of enhanced I_{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_{NaL} Inhibitors

Eleclazine (GS-6615; Gilead Sciences, Foster City, CA) is a new selective inhibitor of I_{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_{NaL} but also late I_{Ca} , peak I_{Ca} , I_{Na-Ca} , and I_{Ks} ,³² eleclazine is more potent and selective in inhibiting I_{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 its in vivo selectivity and inhibition of I_{NaL} .³³ Because the magnitude of pathologically enhanced I_{NaL} (roughly a 2-fold increase versus normal) is similar in HCM and long-QT syndrome type 3,²⁴ eleclazine is expected to show efficacy in mitigating or reversing the electromechanical abnormalities that are mediated by an

increased I_{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 $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 permuted 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 an oral single 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 visit. 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 maximum of ≈ 20 months, and open-label treatment up to 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 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

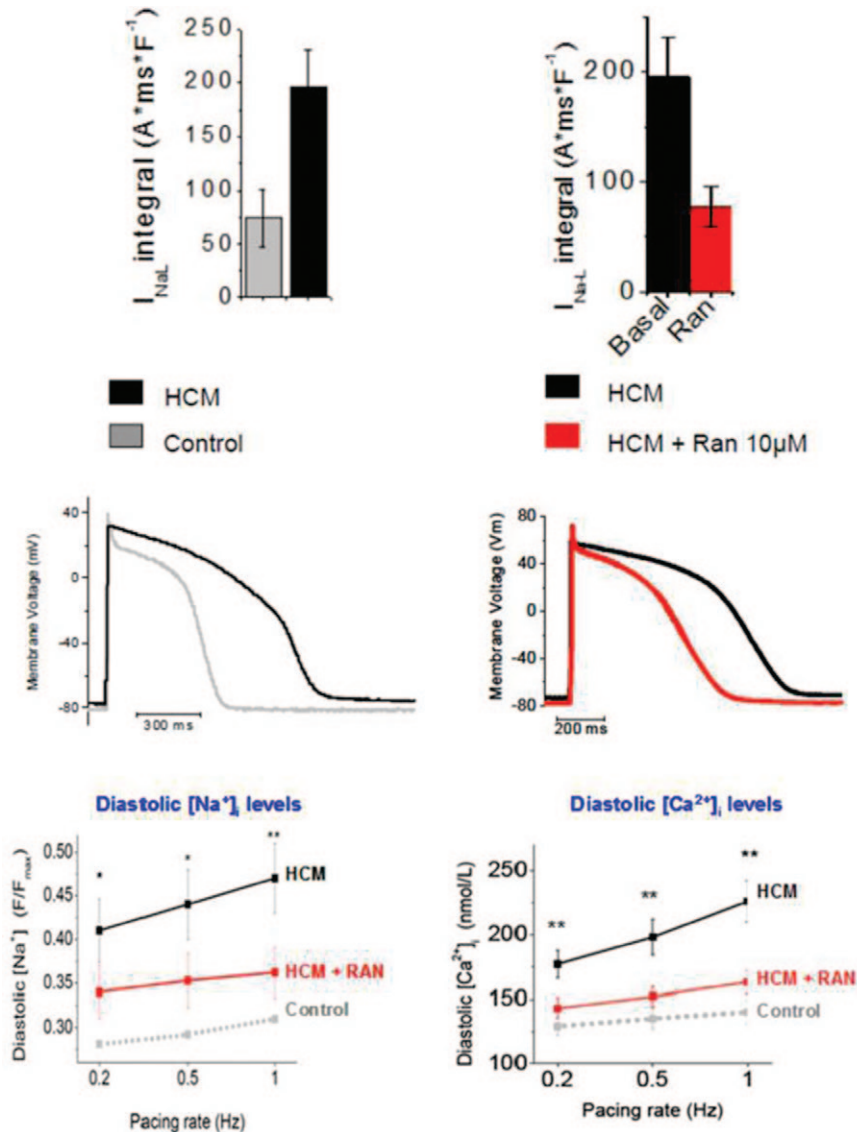


Figure 4. I_{NaL} -induced abnormalities in hypertrophic cardiomyopathy (HCM) abolished with ranolazine. **A**, Magnitude of I_{NaL} in HCM myocytes compared with controls (**left**). Exposure to ranolazine (10 μM /L) reduces the magnitude of I_{NaL} to control levels (**right**). **B**, Action potential duration (APD) at baseline measured at a pacing rate of 1 Hz was 598 ms (± 29 ; $n=24$) in the HCM myocytes and 351 ms (± 28 ; $n=8$) in the control myocytes (**left**). Exposure to ranolazine (10 μM /L) shortened the APD in HCM myocytes from 659 ms (± 46 ; $n=12$) to 536 ms (± 28 ; $n=12$; **right**). **C**, Diastolic Na^+ (**left**) and calcium (**right**) concentrations are significantly increased in HCM myocytes compared with controls. Ranolazine (10 μM /L) reduces both significantly across a range of pacing frequencies. Reprinted from Coppini et al²⁴ with permission of the publisher. Copyright ©2013, Wolters Kluwer Health.

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 repeat cardiopulmonary exercise testing, ECG, echo, MLHFQ, and pharmacokinetic laboratory draws are repeated at weeks 12 and 24.

Rationale for Primary End Point: The Role of V_{O_2} Max

In LIBERTY-HCM, the individual change in peak V_{O_2} between screening and week 24 will serve as the primary study end point (Figure 6).^{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.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 transmitral peak inflow velocities and LV isovolumic relaxation time.^{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 V_{O_2} is the peak oxygen uptake achieved during the performance of dynamic exercise and is equal to the product

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Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<p>Have the ability to understand and sign a written informed consent form, which must be obtained before initiation of study procedures</p> <p>Men and women 18- to 65-y old, inclusive</p> <p>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</p> <p>Exertional symptoms including at least one of the following:</p> <ul style="list-style-type: none"> New York Heart Association class \geq II dyspnea Canadian Cardiovascular Society class \geq II angina <p>Screening (baseline) peak $\dot{V}O_2$ $< 80\%$ of predicted based on age, sex, and weight-adjusted equations</p> <p>Ability to perform an upright treadmill cardiopulmonary exercise test</p>	<p>Known aortic valve stenosis (moderate or severe)</p> <p>Known coronary artery disease ($\geq 50\%$ stenosis in ≥ 1 epicardial coronary artery)</p> <p>LV ejection fraction $< 50\%$, known or detected during Screening visit</p> <p>Known moderate or severe chronic obstructive pulmonary disease (FEV1 $< 80\%$ predicted)</p> <p>Known moderate or severe restrictive lung disease (total lung capacity $< 70\%$ predicted)</p> <p>Recent septal reduction procedure within 6 mo before screening or such a procedure scheduled to occur during the study</p> <p>Atrial fibrillation on 12-lead ECG at screening or detected during randomization visit</p> <p>Known or suspected infiltrative myocardial disease or glycogen storage disorder.</p> <p>Body mass index ≥ 36 kg/m²</p> <p>Severe renal impairment at screening (GFR < 30 mL/min per 1.73 m²)</p> <p>Abnormal liver function tests at screening, defined as ALT or AST $> 2 \times$ ULN, or total bilirubin $> 1.5 \times$ ULN</p> <p>Known or suspected history of seizures or epilepsy</p> <p>Use of class I antiarrhythmic drugs within 7 d before screening</p> <p>Use of ranolazine within 7 d before screening</p> <p>Use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A</p> <p>Known hypersensitivity to study drug (eleclazine or placebo), its metabolites, or formulation excipient</p> <p>Women who are pregnant or breastfeeding.</p> <p>Any clinically significant ongoing medical condition that might jeopardize the subject's safety or interfere with the study</p> <p>Any condition that would preclude compliance with the study protocol</p>

GFR, glomerular filtration rate; and LV, left ventricular.

of maximum cardiac output and maximum arteriovenous oxygen difference. It is widely considered the best measure of cardiovascular fitness and exercise capacity.³⁹ In the majority of patients with HCM from referral populations, peak $\dot{V}O_2$ is significantly reduced,⁴⁰ and its value correlates with New York Heart Association class and quality of life measures.⁴¹ As a clinical trial end point, peak $\dot{V}O_2$ 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

$\dot{V}O_2$ has been recommended in intervention studies to reduce the 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 $\dot{V}O_2$ 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 $\dot{V}O_2$ was found to be an independent predictor of a composite end point of death, ICD discharge, or witnessed revival from

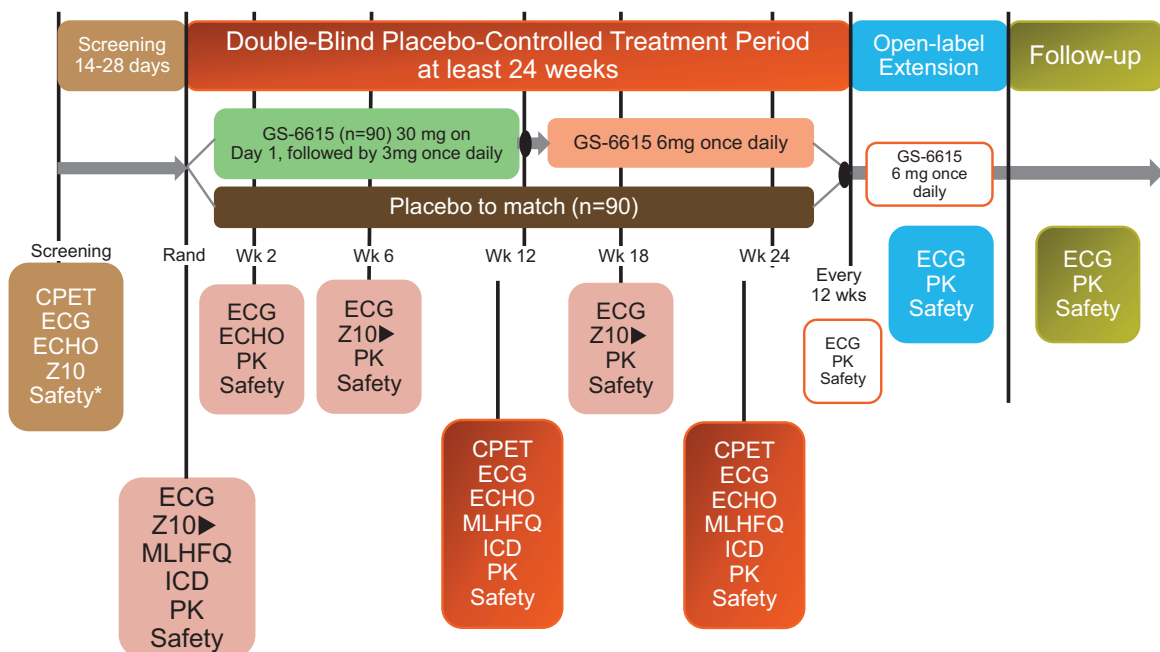


Figure 5. Eleclazine on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) study patient flow diagram. *Safety assessments include physical examination vital signs, clinical assessments, pregnancy testing, concomitant medication review, and adverse event review.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

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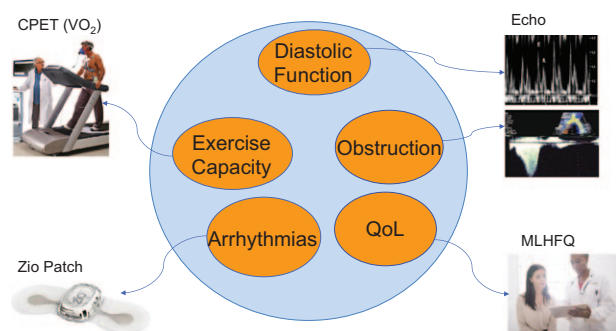


Figure 6. End points of the LIBERTY-HCM trial target the pathophysiology of hypertrophic cardiomyopathy. Cardiopulmonary exercise testing (CPET) (VO_2) image © COSMED. Echocardiographic images reprinted from Oh et al³⁴ with permission of the publisher, Copyright ©2011, Wolters Kluwer Health and reprinted from Nagueh et al³⁵ with permission of the publisher, Copyright ©2011 Elsevier. MLHFQ image ©Getty Images. Zio Patch image ©iRhythm.

sudden death.⁴² After multivariable adjustment, each 1-mL/kg per minute increase in peak VO_2 was associated with a 9% reduction in the composite primary end point. Smaller studies have yielded similar results.^{43,44} These findings mirror the robust prognostic significance of peak VO_2 in the broader heart failure population.^{45,46} Furthermore, peak VO_2 is sensitive to therapeutic interventions leading to symptomatic relief and increased functional capacity in patients with HCM, as shown by the significant increases observed after surgical myectomy⁴⁷ and percutaneous alcohol septal ablation.⁴⁸ Peak VO_2 has also been shown to be sensitive to pharmacological therapies in HCM. In a recent phase 2 study of perhexiline, a carnitinepalmitoyltransferase inhibitor, 46 patients with symptomatic nonobstructive HCM were randomized to treatment with perhexiline or matching placebo for 3 to 6 months.⁴⁹ Subjects randomized to perhexiline had a significant increase in peak VO_2 during exercise when compared with those on placebo (22.2 ± 0.2 – 24.3 ± 0.2 versus 23.6 ± 0.3 – 22.3 ± 0.2 mL/kg per minute). At the same time, peak VO_2 has been effective in disputing nonefficacious therapies in HCM, such as dual chamber pacing for relief of dynamic obstruction.^{50–55} Taken together, these data provide compelling evidence in favor of peak VO_2 as a meaningful (and as yet unsurpassed) end point to evaluate the status of the disease in patients with HCM and the efficacy of therapeutic interventions.

Secondary End Points

Secondary end points include safety and tolerability of eleclazine, the effect on quality of life as measured by the MLHFQ and the effect on treadmill exercise time during cardiopulmonary exercise testing (Figure 6). Exploratory end points include change in arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, and paroxysmal AF) and change in echocardiographic measures of diastolic function, systolic function, dynamic obstruction, and LV wall thickness. Additional exploratory end points include change in biomarkers of myocardial wall stress (N-terminal of the prohormone brain natriuretic peptide) and microvascular ischemia (high-sensitivity troponin T) and changes in ECG parameters.

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), provokable 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) 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 VO_2 (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 $\geq \text{II}$), 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

Study Data	Core Laboratories
CPET	Core exercise physiology laboratory at Stanford University
Functional capacity (VO_2)	
Exercise hemodynamics	
Echocardiography	Core echo laboratory at Brigham and Women's Hospital
Diastolic function	
Systolic function	
Dynamic obstruction	
LV wall thickness	
Electrocardiography	ECG laboratory at BioTelemetry, Inc. (formerly Cardiacore)
ECG intervals and segments	
ZioPatch ambulatory cardiac rhythm data	iRhythm Technologies, Inc.
Premature ventricular complexes	
Nonsustained ventricular tachycardia	
Paroxysmal atrial fibrillation burden	
ICD interrogation	Core electrophysiology laboratory at the University of Rochester
Arrhythmia burden	
ICD interventions	

CPET indicates cardiopulmonary exercise testing; ICD, implantable cardioverter-defibrillator; and LV, left ventricular.

Statistical Considerations

Sample Size

A difference of 3 mL/kg per minute in peak Vo_2 is considered clinically meaningful based on previously published studies of change in peak Vo_2 after therapeutic interventions in HCM.^{47–49} Thus, based on a 2-sided, 2-sample *t* test ($P=0.01$), 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_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_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 α -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_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 the active drug 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 pre-clinical 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 to future clinical investigations into this complex disease.

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and NET-2011-02347173 (mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy).

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