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

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The primary objective of this study is to:* Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO2 achieved during cardiopulmonary exercise testing (CPET), in subjects with symptomatic hypertrophiccardiomyopathy (HCM).The...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON42173

Source
ToetsingOnline

Brief title
GS-US-361-1157

Condition

- Cardiac and vascular disorders congenital

Synonym
heart failure, heart muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: cardiac late inward, sodium current (INa) inhibitor, Symptomatic Hypertrophic Cardiomyopathy

Outcome measures

Primary outcome

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 VO2 between Screening

(baseline) and Week 24.

Secondary outcome

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 VO2 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:

* Changes in arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation) between the 14-day baseline period (prior to randomization) and post baseline periods (after randomization) (ZIO® XT Patch).

* Changes in diastolic function, systolic function,dynamic obstruction, and LV wall thickness between baseline and Week 12, and between baseline and Week 24.

* Changes in biomarkers of myocardial wall stress and microvascular ischemia between baseline and Week 12, and between baseline and Week 24.

- NT-proBNP

- High-sensitivity Troponin T (hsTnT)

* Changes in ECG parameters between baseline and Week 12, and between baseline and Week 24.

- QTc interval at rest and at Peak exercise

Study description

Background summary

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

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*.

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

The result of the study will determine if GS-6615 is effective and safe for the treatment of patients with symptomatic HCM.

Study objective

The primary objective of this study is to:
* Evaluate the effect of GS-6615 on exercise capacity, as measured by Peak VO2 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:
* Evaluate the effect of GS-6615 on arrhythmia burden (premature ventricular complexes, nonsustained ventricular tachycardia, paroxysmal atrial fibrillation).
* Evaluate the effect of GS-6615 on echocardiographic measures of diastolic function, systolic function, dynamic obstruction, and LV wall thickness.
* 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).

Intervention

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.

Study burden and risks

The subjects will need to undergo the following procedures:

- Physical exam and vital signs * all visits
- Questionnaire (MLHFQ) * 3x
- ECG * all visits
- Cardiopulmonal exercise test (CPET) * 2x
- Echo * 4x
- Blood sample * all visits
- Urine samples * all visits (except randomisation visit)
- Pregnancy test for all female subjects - all visits
- Optional blood sample for pharmacogenomic sample * 1x
- Placement of ZIO® XT Patch following 14 days * 3x

Side effects related to GS-6615 reported include abnormal dreams, drowsiness, increased urination at night, feeling tense, , fatigue (tiredness), sweats, headache, nausea (feeling sick to the stomach), vomiting diarrhea, dizziness, increased libido, upper respiratory tract infection and temporary increase in liver enzymes (blood tests related to the liver). There have been no reports of serious or severe side effects related to taking GS-6615.
Furthermore, the subjects have a small risk because of procedures they need to undergo: blood sampling,ECG, ECHO, ZIO® XT Patch, CPET.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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 VO2 < 75% of predicted for age, sex, and body size based on the Wasserman Hansen equation (Appendix 4), as confirmed by the investigator
6) Ability to perform an upright treadmill cardiopulmonary exercise test (CPET)
7) 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

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 FEV1 < 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/m2
10) Severe renal impairment at Screening (defined as an estimated GFR < 30 mL/min/1.73m2 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

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-09-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GS-6615
Generic name:	NA

Ethics review

Approved WMO Date:	17-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2015
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004429-97-NL
ClinicalTrials.gov	NCT02291237
CCMO	NL49071.018.14