A Phase 2, Double-Blind, Randomized, Placebo Controlled, Dose Ranging, Parallel Group Study to Evaluate the Effect of GS-6615 on Ventricular Arrhythmia in Subjects with Implantable Cardioverter-Defibrillator (ICD) or Cardiac Resynchronization Therapy-Defibrillator (CRT-D)

Published: 25-09-2014
Last updated: 20-04-2024

The primary objective of this study is as follows:* To evaluate the effect of GS-6615 compared to placebo on the overall occurrence of appropriate ICD interventions (antitachycardia pacing [ATP] or shock) in subjects with ICD or CRT-D during the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON42304

Source
ToetsingOnline

Brief title
GS-US-356-0101

Condition

- Cardiac arrhythmias

Synonym
Subjects with an ICD or CRT-D implanted for primary or secondary prevention;Subjects with Implantable Cardioverter Defibrillator (ICD) or Cardiac Resynchronization Therapy-Defibrillator (CRT D)

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Cardiac Resynchronization Therapy-Defibrillator (CRT-D), Implantable Cardioverter-Defibrillator (ICD), Ventricular Arrhythmia

Outcome measures

Primary outcome

Criteria for Evaluation:

Safety:

Safety will be assessed by collecting AEs, clinical laboratory tests, vital

signs, PE findings, and ECG data (PR, RR, QRS, and QT interval).

PE findings before the first dose of the study drug will be captured as medical

history and post dose events will be AEs.

Safety endpoints will include:

* The time from the first dose of study drug to death due to any cause

* The time from the first dose of study drug to the first occurrence of an

appropriate ICD shock

Efficacy:

The primary endpoint is the overall occurrence (total number) of appropriate ICD interventions (ATP or shock) through Week 24.

Pharmacokinetics:

PK analysis of GS-6615 and metabolites will be performed by a designated central laboratory.

Secondary outcome

Secondary endpoints include:

* Overall occurrence (total number) of appropriate ICD interventions (ATP or shock) through the end of the study
* The change in PVC (count/48 hours) from Screening to Week 12
* The change in nsVT (number of episodes/48 hours) from Screening to Week 12
* Overall occurrence (total number) of VT/VF (treated and untreated) through Week 24 and through the end of the study
* The time from randomization to the first occurrence of appropriate ICD interventions (ATP or shock) or CV death
* Overall occurrence (total number) of electrical storm through Week 24 and through the end of the study
* Overall occurrence (total number) of inappropriate ICD interventions through Week 24 and through the end of the study
* Time from randomization to the first occurrence of CV hospitalization, CV ER visit, or CV death
* Change in LV systolic and diastolic function as assessed by ECHO at Week 12

and Week 24

Study description

Background summary

GS-6615, being a potent and selective inhibitor of a highly arrhythmogenic late INa current, is expected to reduce ventricular arrhythmia and may provide a safer alternative to currently used adjuvant AAD therapy in patients with ICDs/CRT-Ds.
The current study is designed to evaluate whether treatment with GS-6615 compared to placebo reduces the overall occurrence of appropriate ICD interventions (ATP or shocks) in subjects

Study objective

The primary objective of this study is as follows:
* To evaluate the effect of GS-6615 compared to placebo on the overall occurrence of appropriate ICD interventions (antitachycardia pacing [ATP] or shock) in subjects with ICD or CRT-D during the first 24 weeks of treatment

The secondary objectives of this study are to evaluate the effect of GS-6615 compared to placebo on the following:
* The overall occurrence of appropriate ICD interventions (ATP or shock) in subjects with ICD or CRT-D through the end of the study
* Premature ventricular complex (PVC) count/48 hours after 12 weeks of treatment (cECG monitoring)
* Nonsustained ventricular tachycardia (nsVT) episodes/48 hours after 12 weeks of treatment (cECG monitoring)
* The overall occurrence of VT/VF (treated and untreated) during the first 24 weeks and through the end of the study
* The time from randomization to the first occurrence of appropriate ICD interventions (ATP or shock) or cardiovascular (CV) death
* The overall occurrence of electrical storm during the first 24 weeks and through the end of the study; electrical storm is defined as * 3 separate episodes of ventricular arrhythmia within a 24 hour period terminated by ICD
* The occurrence of inappropriate ICD interventions during the first 24 weeks and through the end of the study
* Time from randomization to the first CV hospitalization, CV emergency room (ER) visit, or CV death
* Left ventricular (LV) systolic and diastolic function as assessed by echocardiography (ECHO)
* Safety and tolerability

Study design

This is a randomized, double-blind, two cohort, placebo-controlled, dose ranging, parallel group study

Intervention

GS-6615 3mg Arm: Oral single loading dose of 30 mg GS-6615 (3 x 10 mg tablets) on Day 1, followed by maintenance dose of 3 mg GS 6615 (1 x 3 mg GS-6615 tablet and 1 x 3 mg matching placebo tablet) once daily for the remainder of the treatment period

GS-6615 6mg Arm: Oral single loading dose of 30 mg GS-6615 (3 x 10 mg tablets) on Day 1, followed by maintenance dose of 6 mg GS 6615 (2 x 3 mg GS-6615 tablets) once daily for the remainder of the treatment period.

Placebo Arm: Oral single loading dose of placebo to match GS 6615 (3 x 10 mg placebo tablets) on Day 1, followed by maintenance dose of matching placebo (2 x 3 mg matching placebo tablets) once daily for the remainder of the treatment period

Study burden and risks

There are assessments like blood tests, ECG, ECHO that are done more often or more extensively than if subjects would receive regular treatment.
Holter monitoring will be done for 48 hours continuously at Screening and then at the Week 12 visit. Subjects will be able to go home with the Holter monitor. Subjects will not be able to shower or take a bath while having the Holter monitor hooked up.

To date, 85 healthy subjects and 10 subjects with Long QT-3 syndrome have taken single doses and multiple doses of GS-6615 ranging from 3 mg to 60 mg in 4 different clinical research studies. GS-6615 has not been studied in patients with ICD*s or CRT-D*s and who have episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF), or reduced heart function.

Side effects reported as related to GS-6615 include abnormal dreams, drowsiness, increased urination at night, feeling tense, fatigue (tiredness), sweats, headache, nausea (feeling sick to the stomach), vomiting, 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.

In animal studies, decreased grip strength, unsteady gait (difficulty walking), tremors (shaking), and convulsions were observed when there were high amounts of GS-6615 in the blood, about 9-10 times higher than the amount of GS-6615 in the blood that is expected in subjects in this study (in subjects 65 years or

older, the amount of GS-6615 in the blood may only be 4-5 times higher). There is a possibility that GS-6615 may cause seizures, dizziness, tremors, and unsteady gait (difficulty walking) in humans.

There is no guarantee that subjects will receive personal benefit from taking part in this study. The study drugs are not expected to cure subjects of VT/VF. However, clinical research studies such as this are a way for doctors to determine if a drug is useful in fighting a disease. By taking part in this study, subjects and the Sponsor, Gilead Sciences, Inc., may benefit if GS-6615 is effective in preventing heart rhythm problems in patients with an ICD or CRT-D. Subjects taking part in this study may benefit the community, scientists and doctors who work with heart rhythm problems by providing increased knowledge and information about the treatment of the disease.

Contacts

Public
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US
Scientific
Gilead Sciences

Lakeside Drive 333
Foster City CA 94404
US

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) Between 18 and 80 years of age (inclusive)
3) Implanted ICD or CRT-D for primary or secondary prevention
a) ICD or CRT-D must have capabilities of counting device interventions and storing electrograms
b) Subjects with ICD or CRT-D implanted for primary prevention must have at least one ICD intervention for VT/VF (shock or ATP) within 60 days prior to Screening
c) Subjects with ICD or CRT-D implanted for secondary prevention must have at least one ICD intervention for VT/VF (shock or ATP) or a documented VT/VF episode (prior to implantation) within 60 days prior to Screening
4) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use the protocol specified method(s) of contraception
5) Subjects must be hemodynamically stable at both Screening and Randomization visits.

Exclusion criteria

1) New York Heart Association (NYHA) Class IV heart failure
2) Myocardial infarction, unstable angina, coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within 4 weeks prior to Screening or during the screening period before Randomization
3) Hemodynamically significant primary obstructive valvular disease
4) History of congenital heart disease
5) Inherited arrhythmia such as Brugada syndrome. Subjects with LQT-3 or HCM may be considered.
6) Subjects who are being considered for cardiac transplantation and are on a cardiac transplant list. Subjects who are not expected to have a transplant during the study can be considered for the study after consultation with the Gilead Medical Monitor.
7) Known or suspected history of seizures or epilepsy
8) Cardiac ablation within 3 months prior to Screening or planned cardiac ablation during the course of the study
9) Severe renal impairment at Screening (defined as an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease [MDRD] equation by the central laboratory)
10) Abnormal liver function test defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2xULN at Screening, or bilirubin > 1.5xULN at Screening
11) Current use of Class I and Class III antiarrhythmic drugs; such medications should be discontinued > 5 half-lives (or > 28 days for chronic use of amiodarone) prior to Randomization.
12) Current use of concomitant treatment with drugs or products that are strong inhibitors or inducers of CYP3A; such medications should be discontinued at least 5 half lives prior to Randomization.

13) Current use of concomitant treatment with ranolazine. Ranolazine should be discontinued at least 7 days prior to Randomization.
14) Previous exposure to GS-6615
15) Known hypersensitivity to the study drug, its metabolites, or formulation excipient
16) Females who are pregnant or are 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 are required for female subjects of childbearing potential.
17) Subjects with a subcutaneous ICD
18) Any ICD/CRT-D -related technical issue, malfunction, or potential malfunction which in the judgment of the investigator would disrupt adequate data collection or interpretation
19) 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 previous 30 days with potential residual effects that might confound the results of this study
20) Any condition that in the opinion of the investigator would preclude compliance with the study protocol
21) Body mass index (BMI) * 36 kg/m2

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):	01-07-2015
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	25-09-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-004430-15-NL
ClinicalTrials.gov	NCT02104583
CCMO	NL48714.060.14