A Phase 3, Single-Blind Study to Evaluate the Effect of Eleclazine on Shortening of the QT Interval, Safety, and Tolerability in Subjects with Long QT Syndrome type 3.

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The primary objective of this study is to evaluate in subjects with LQT3:- The effect of oral eleclazine on mean daytime QTcF interval (in msec) after 24 weeks of treatment with eleclazine (based on standard 12-lead electrocardiogram [ECG] data)The...

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

Summary

ID

NL-OMON41816

Source
ToetsingOnline

Brief title
Gilead GS-US-372-1234

Condition

- Cardiac and vascular disorders congenital

Synonym
Congenital Long QT 3 syndrome, Heart rhythm disorder

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Sponsor/ farmaceut

Intervention

Keyword: Long QT Syndrome type 3, LQT3, QTc interval shortening

Outcome measures

Primary outcome

Safety will be assessed by the incidence of treatment-emergent AEs (including new from baseline PE findings and medical history), clinically significant abnormalities in vital signs, laboratory parameters, ECG variables, ACAs, CV deaths, SCDs, CV hospitalizations, seizures, and other relevant events to be described in detail in the CEC charter.

The primary efficacy endpoint is the difference between mean daytime QTcF interval (in msec) (AUC0-6/6) at baseline and at Week 24 (based on standard 12 lead ECG data).

Secondary outcome

The secondary endpoints include:

* The difference between the mean daytime QTcF interval (in msec) (AUC0 6/6) at baseline and at Week 12 (based on standard 12 lead ECG data)

* The difference between the mean daily (daytime and nocturnal) QTcF interval (in msec) at baseline and at Week 24 (based on Holter data)

* The difference between the mean nocturnal (midnight to 6:00 AM study center local time) QTcF interval (in msec) at baseline and at Week 24 (based on Holter data)

The additional endpoints include:

* The difference between the mean daily (daytime and nocturnal) QTcF interval (in msec) at baseline and at Week 12 (based on Holter data)

* The difference between the mean nocturnal QTcF interval (in msec) (midnight to 6:00 AM study center local time) at baseline and at Week 12 (based on Holter data)

* The maximal reduction of QTcF interval between predose (T = 0) and any time within 24 hours post loading dose of eleclazine on Day 2 (based on standard 12-lead ECG)

* The maximal reduction in time-matched QTcF interval (in msec) from baseline to Day 2, Week 12, and Week 24 (based on standard 12 lead ECG or Holter data). Baseline for each time point is the value at the nominal time point on Day 1 corresponding to the postdose nominal time point

* Proportion of subjects who have a mean daytime QTcF interval (in msec) (AUC0-6/6) of * 500 msec vs < 500 msec at baseline vs Week 12 and at baseline vs Week 24 (based on standard 12 lead ECG data)

* Changes in other markers of ventricular repolarization from baseline to Week 12 and baseline to Week 24 (based on Holter* data)

Study description

Background summary

The congenital long QT syndrome (LQTS) represents a group of diverse genetic disorders characterized by a prolonged QT interval on a 12-lead electrocardiogram (ECG). The common pathogenesis of LQTS involves prolongation of the ventricular action potential, caused either by

decreases in the outward potassium current or increases in the late inward sodium or calcium current, leading to QT prolongation, increased susceptibility to early afterdepolarizations (EADs), and sustained polymorphic ventricular tachycardia (VT) (torsade de pointes). The disease clinically manifests as syncope and cardiac arrest. While LQTS is relatively rare, with an estimated prevalence of 1 in 2000-5000 individuals, it is highly lethal, with greatly increased mortality rates relative to the general population. It has been well established that the risk of sudden cardiac death (SCD) is directly related to the QTc interval, and preliminary data suggest that shortening of the QTc interval reduces this risk.

Depending on the molecular and genotypic basis of the action potential prolongation, 13 subtypes of LQTS have been identified to date. Among them, long QT types 1, 2, and 3 are the most common, with 30-35%, 25-40%, and 5-10% of cases, respectively. Types 1 and 2 LQTS (LQT1 and LQT2) are both characterized by loss-of-function mutations involving potassium channels; the affected genes are KCNQ1 and KCNH2, respectively. These mutations result in decreases in either the slowly activating (IKs; LQT1) or the rapidly activating (IKr; LQT2) component of the outward-rectifying potassium current. Type 3 LQTS (LQT3) is caused by mutations in the gene encoding the cardiac sodium channel Nav1.5 (SCN5A), which results in impaired inactivation of the channel and a consequent increase in the late inward sodium current (late INa). LQT3 is distinguished by greater lethality, even within the broader context of LQTS. While the overall frequency of cardiac events in LQT1 and LQT2 is typically greater than that of LQT3, the events that occur in LQT3 are often more malignant, with an approximately 5-fold risk of mortality relative to both LQT1 and LQT2.

As with the clinical course and prognosis, the relative efficacy of available treatment options is dependent on genotype. Because cardiac events in LQT1 are typically triggered by exercise, beta-blockers are considered the mainstay of prophylactic pharmacotherapy in these patients.

However, in contrast to LQT1, cardiac events in LQT3 occur more frequently at rest in the absence of adrenergic stimulation. Moreover, patients with LQT3 shorten their QT intervals with tachycardia. These data therefore suggest that beta-blockers would have diminished utility in LQT3. Indeed, observational data have borne this out, with consistently lower efficacy rates of beta-blockers in patients with LQT3.

Moreover, the well-described association between LQT3 and sinus node dysfunction presents an additional potential limitation to the use of beta-blockers in patients with this genotype.

As the mechanism of QT lengthening in LQT3 involves an increase in late INa, it has been postulated that medications that target the sodium channel would be particularly effective in such patients. To this end, several Class I antiarrhythmic medications, including mexiletine and flecainide, have been observed to shorten the QTc interval in patients with LQT3.

Additionally, more selective inhibition of late INa by the piperazine derivative ranolazine was demonstrated to reduce QTc in a

concentration-dependent manner in patients with LQT3. Despite the attractiveness of this mechanistically-based strategy, however, full adoption of this approach is limited by concerns over IKr inhibition and tolerability in currently available agents.

Study objective

The primary objective of this study is to evaluate in subjects with LQT3:
- The effect of oral eleclazine on mean daytime QTcF interval (in msec) after 24 weeks of treatment with eleclazine (based on standard 12-lead electrocardiogram [ECG] data)

The secondary objectives of this study are to evaluate in subjects with LQT3:
- The effect of oral eleclazine on mean daytime QTcF interval (in msec) after 12 weeks of treatment with eleclazine (based on standard 12-lead ECG data)
- The effect of oral eleclazine on mean daily (daytime and nocturnal) QTcF interval (in msec) after 24 weeks of treatment with eleclazine (based on Holter data)
- The effect of oral eleclazine on mean nocturnal QTcF interval (in msec) after 24 weeks of treatment with eleclazine (based on Holter data)

The additional objectives of this study are to evaluate:
- The effect of oral eleclazine on the mean daily (daytime and nocturnal) QTcF interval (in msec) after 12 weeks of treatment with eleclazine (based on Holter data)
- The effect of oral eleclazine on the mean nocturnal QTcF interval (in msec) after 12 weeks of treatment with eleclazine (based on Holter data)
- The effect of oral eleclazine on the maximal reduction in QTcF interval (in msec) (based on standard 12 lead ECG and Holter data)
- The effect of oral eleclazine on changes in other markers of ventricular repolarization from baseline to Week 12 and baseline to Week 24 (based on Holter data)
- The safety and tolerability of oral eleclazine in subjects with LQT3
- The pharmacokinetic (PK) profile of oral eleclazine in subjects with LQT3

Study design

A single-arm, single-blind, multi-center study.

Intervention

Single-Blind Treatment Period: Oral single loading dose of 48 mg of eleclazine (8 x 6 mg eleclazine tablets) on Day 2, followed by a daily maintenance dose of 3 mg of eleclazine (1 x 3 mg eleclazine tablet) from Day 3 through the Week 12 Visit, followed by a daily maintenance dose of 6 mg of eleclazine (1 x 6 mg eleclazine tablet) from the day after the Week 12 Visit through Week 24

Open-Label Extension: Oral daily maintenance dose of 6 mg of GS 6615 (1 x 6 mg eleclazine tablet) through the end of the OLE

Reference Therapy, Dose, and Mode of Administration:
Single-Blind Treatment Period: Oral single loading dose of placebo to match eleclazine loading dose (8 x 6 mg matching placebo tablets) on Day 1

Study burden and risks

De patients will undergo the following procedures:
* Physical exam and vital signs * each visit, except week 2
* ECG * each visit, except week 2
* Holter-ECG * during 48 hours after each visit
* Placement of ZIO® XT Patch * 2x
* Blood- en urine sample * each visit, except week 2
* Pregnancy test (only womenthat can get pregnant) - each visit, except week 2
* Blood sample for pharmacokinetic - each visit, except screening and week 2
* Blood sample for pharmacogenomic research * 1x

As of 15 September 2014, 95 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 5 different research studies.
This study can have the following side-effects: abnormal dreams, drowsiness, increased urination at night, feeling tense, headache, fatigue (tiredness), sweats, 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 functions). There have been no reports of serious or severe side effects related to taking eleclazine.
Furthemore the study procedures, like blood draws, ECGs and ZIO® XT Patch, may cause discomfort.

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 70 years old, inclusive, at time of Screening
3) Subjects with an established diagnosis of LQT3 (by genotype testing).
4) Mean (of triplicate) QTc interval * 480 msec (or * 460 msec, for subjects who are currently taking ranolazine or Class I antiarrhythmic drugs such as mexiletine) at 3 or more time points, determined by standard 12-lead ECG, at Screening
5) Subjects with an implanted cardiac device (eg, pacemaker, implantable cardioverter defibrillator [ICD], implantable loop monitor) may participate in the study, provided that they are not predominantly ventricular paced, in the judgment of the investigator
6) 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 3
7) Willing and able to comply with the requirements of the protocol and directions from the clinic staff

Exclusion criteria

1) Known pathogenic mutations associated with Long QT 1 syndrome (LQT1) or Long QT 2 syndrome (LQT2)
2) Known or suspected history of seizures or epilepsy
3) History of heart failure defined as New York Heart Association (NYHA) Class IV and/or known left ventricular ejection fraction (EF) * 45%
4) Known severe obstructive sleep apnea that is not treated. Known untreated moderate sleep apnea may be included after discussion with the medical monitor

5) Body mass index (BMI) * 40 kg/m2 at Screening
6) Any abnormal laboratory value or physical examination (PE) finding at Screening, judged by the investigator to preclude enrollment in the study
7) Severe renal impairment at Screening (defined as an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m2, using the 4 Variable Modification of Diet in Renal Disease [MDRD] equation [see Appendix 6 and {8057}]), as determined by the study center
8) Abnormal liver function tests at Screening, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2x upper limit of normal (ULN), or total bilirubin > 1.5x ULN
9) Current treatment with drugs known to prolong the QT interval (not including beta-blockers)
10) Current use of Class I and Class III antiarrhythmic drugs other than amiodarone (see Appendix 5). Such medications should be discontinued for at least 5 half lives prior to Day 1.
11) Current use of amiodarone. Chronic use of amiodarone should be discontinued for at least 3 months prior to Day 1.
12) Current use of ranolazine. Ranolazine should be discontinued for at least 3 days prior to Day 1.
13) Current use of drugs or products that are strong inhibitors or inducers of CYP3A (see Appendix 4). Such medications should be discontinued 5 half-lives prior to Day 1.
14) Participation in prior clinical studies of eleclazine is not exclusionary, however subjects must have completed dosing of eleclazine in the prior study at least 60 days prior to Screening into this study.
15) Known hypersensitivity to eleclazine, its metabolites, or formulation excipients

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-08-2015

Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	eleclazine
Generic name:	N/A

Ethics review

Approved WMO Date:	07-01-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2016
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	EUCTR2014-000042-30-NL
ClinicalTrials.gov	NCT02300558
CCMO	NL49681.018.14