Clinical trial results:
A Phase 3, Single-Blind Study to Evaluate the Effect of Eleclazine (GS-6615) on Shortening of the QT Interval, Safety, and Tolerability in Subjects with Long QT Syndrome Type 3

Summary

EudraCT number	2014-000042-30
Trial protocol	GB DE NL ES FI IT
Global end of trial date	15 February 2017

Results information

Result version number	v1 (current)
This version publication date	30 December 2017
First version publication date	30 December 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-372-1234

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02300558
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive , Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox , Gilead Sciences International Ltd , ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2016
Global end of trial reached?	Yes
Global end of trial date	15 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of oral eleclazine on mean daytime QTcF interval after 24 weeks of treatment with elecalzine in participants with long QT syndrome Type 3. During the single-blind treatment period (24 weeks), participants received eleclazine placebo on Day 1 and eleclazine from Day 2 to Week 24. Following the single-blind treatment period, participants who didn't permanently discontinue study drug were be eligible, at the discretion of the investigator, to continue receiving eleclazine during an open-label extension phase (OLE).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	41
EEA total number of subjects	26

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	38
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Asia. The first participant was screened on 17 December 2014. The last study visit occurred on 15 February 2017.

Pre-assignment

Screening details:

54 participants were screened.

Period 1

Period 1 title	Single Blind Phase (24 Weeks)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Eleclazine (Single-Blind Treatment Period)

Arm description:

Single oral loading dose of placebo to match eleclazine loading dose (8 x 6 mg placebo to match tablets) on Day 1; eleclazine 48 mg (8 x 6 mg tablets) on Day 2; followed by eleclazine 3 mg (1 x 3 mg tablet) once daily from Day 3 to the Week 12 Visit; then once daily maintenance dose of eleclazine 6 mg (1 x 6 mg tablet) from the day after the Week 12 Visit through Week 24

Arm type	Experimental
Investigational medicinal product name	Eleclazine
Investigational medicinal product code	
Other name	GS-6615
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single oral loading dose of placebo to match eleclazine loading dose (8 x 6 mg placebo to match tablets) on Day 1; eleclazine 48 mg (8 x 6 mg tablets) on Day 2; followed by eleclazine 3 mg (1 x 3 mg tablet) once daily from Day 3 to the Week 12 Visit; then once daily maintenance dose of eleclazine 6 mg (1 x 6 mg tablet) from the day after the Week 12 Visit through Week 24

Number of subjects in period 1	Eleclazine (Single-Blind Treatment Period)
Started	41
Completed	35
Not completed	6
Study Terminated by Sponsor	6

Period 2

Period 2 title	Open-Label Extension
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Eleclazine

Arm description:

Eleclazine 6 mg or 3 mg tablets orally once daily

Arm type	Experimental
Investigational medicinal product name	Eleclazine
Investigational medicinal product code	
Other name	GS-6615
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 mg or 3 mg tablets orally once daily

Number of subjects in period 2[1]	Eleclazine
Started	32
Completed	0
Not completed	32
Withdrew Consent	1
Study Terminated by Sponsor	29
Lack of efficacy	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 3 participants completed the single-blind phase (24 weeks) but did not continue to open-label extension phase.

Baseline characteristics

Reporting groups

Reporting group title	Single Blind Phase (24 Weeks)

Reporting group description: -

Reporting group values	Single Blind Phase (24 Weeks)	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46		
standard deviation	± 12.5	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	17	17	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	1	1	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	36	36	
Not Permitted	1	1	
Other	2	2	
Ethinicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	40	40	
Not Permitted	1	1	
Mean Daytime QTcF Lead V5 (Standard 12-Lead ECG)			
1) QTcF refers to QT interval corrected for heart rate using the Fridericia formula. QTcF = QT/cube root (RR), where RR is in seconds. 2) AUC0-6 for QTcF was calculated using the trapezoidal rule, mean of triplicate values, and actual time (latest of triplicate times). 3) Mean daytime QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from dosing to the 6 hour postdose time point.			
Units: msec			
arithmetic mean	507.5		
standard deviation	± 38.11	-	
Mean Daily QTcF in Lead V5 (Holter)			
1) AUC (0-6) was calculated using the trapezoidal rule, mean of triplicate vales, and nominal time. 2) Mean daytime QTcF (AUC 0-6/6) was computed by dividing AUC(0-6) by the time from the first nonmissing time^ to the last nonmissing time^, from predose to 6 hours postdose. 3) Mean nocturnal QTcF (AUC 0-6/6) was computed by dividing AUC(0-6) by the time from the first nonmissing time^ to the last nonmissing time^, from midnight to 6:00 AM.			

4) Daily was computed as the average of daytime AUC(0-6/6) and nocturnal AUC (0-6/6), when both values are not missing. 5) ^ = nominal time point			
Units: msec			
arithmetic mean	514.7		
standard deviation	± 45.76	-	
Nocturnal QTcF in Lead V5 (Holter)			
Units: msec			
arithmetic mean	530.6		
standard deviation	± 52.25	-	

End points

End points reporting groups

Reporting group title	Eleclazine (Single-Blind Treatment Period)
Reporting group description:	
Single oral loading dose of placebo to match eleclazine loading dose (8 x 6 mg placebo to match tablets) on Day 1; eleclazine 48 mg (8 x 6 mg tablets) on Day 2; followed by eleclazine 3 mg (1 x 3 mg tablet) once daily from Day 3 to the Week 12 Visit; then once daily maintenance dose of eleclazine 6 mg (1 x 6 mg tablet) from the day after the Week 12 Visit through Week 24	
Reporting group title	Eleclazine
Reporting group description:	
Eleclazine 6 mg or 3 mg tablets orally once daily	

Primary: Change From Baseline in Mean Daytime QT Interval in Lead V5 Corrected for Heart Rate Using the Fridericia Formula (QTcF) Interval to Week 24 (Based on Standard 12-Lead ECG Data)

End point title	Change From Baseline in Mean Daytime QT Interval in Lead V5 Corrected for Heart Rate Using the Fridericia Formula (QTcF) Interval to Week 24 (Based on Standard 12-Lead ECG Data)[1]

End point description:

1) Baseline was the Day 1 value.
2) QTcF is corrected QT interval using Fridericia's formula. QTcF = QT/cube root (RR), where RR is in seconds.
3) AUC0-6 for QTcF was calculated using the trapezoidal rule, mean of triplicate values, and actual time (latest of triplicate times).
4) Mean daytime QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from dosing to the 6 hour postdose time point.
5) Participants in Full Analysis Set (FAS) with available data were analyzed. Full Analysis Set was defined as all enrolled participants who have confirmed LQT3 genotype, do not have confirmed LQT1 or LQT2 mutations, received at least 1 dose of active eleclazine, and have both a baseline and at least 1 postbaseline mean daytime QTcF interval (standard 12-lead).

End point type	Primary

End point timeframe:

Baseline; Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis of this primary endpoint is provided in the attachment.

End point values	Eleclazine (Single-Blind Treatment Period)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: msec				
arithmetic mean (standard deviation)	-8.5 (± 18.03)			

Attachments (see zip file)	Primary_Endpoint_StatsAnalysis.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Daytime QTcF Interval (AUC0-6/6) to Week 12 (Lead V5; Standard 12-Lead ECG)

End point title	Change From Baseline in Mean Daytime QTcF Interval (AUC0-6/6) to Week 12 (Lead V5; Standard 12-Lead ECG)

End point description:

1) Baseline was the Day 1 value.
2) QTcF is corrected QT interval using Fridericia's formula. QTcF = QT/cube root (RR), where RR is in seconds.
3) AUC0-6 for QTcF was calculated using the trapezoidal rule, mean of triplicate values, and actual time (latest of triplicate times) .
4) Mean daytime QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from dosing to the 6 hour postdose time point.
5) Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Eleclazine (Single-Blind Treatment Period)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: msec				
arithmetic mean (confidence interval 95%)	2.2 (-4.7 to 9.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Mean Daily (Daytime and Nocturnal) QTcF interval to Week 24 (Lead V5; Holter)

End point title	Change From Baseline Mean Daily (Daytime and Nocturnal) QTcF interval to Week 24 (Lead V5; Holter)

End point description:

1) Baseline was the Day 1 value.
2) QTcF is corrected QT interval using Fridericia's formula. QTcF = QT/cube root (RR), where RR is in seconds.
3) Mean daytime QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from the first nonmissing nominal time
point to the last nonmissing nominal time point, from predose to 6 hours postdose.
4) Mean nocturnal QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from the first nonmissing nominal time point to the last nonmissing nominal time point, from midnight to 6:00 AM. Daily was computed as the average of daytime (AUC0-6/6) and nocturnal (AUC0-6/6), with both values required to compute the average.
4) Participants in the the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Eleclazine (Single-Blind Treatment Period)			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: msec				
arithmetic mean (confidence interval 95%)	-1.8 (-13.6 to 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Nocturnal QTcF Interval to Week 24 (Lead V5; Holter)

End point title	Change From Baseline in Mean Nocturnal QTcF Interval to Week 24 (Lead V5; Holter)

End point description:

1) Baseline was the Day 1 value.
2) QTcF is corrected QT interval using Fridericia's formula. QTcF = QT/cube root (RR), where RR is in seconds.
3) Mean nocturnal QTcF (AUC0-6/6) was computed by dividing AUC0-6 by the time from the first nonmissing nominal time point to the last nonmissing nominal time point, from midnight to 6:00 AM.
4) Participants in the the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Eleclazine (Single-Blind Treatment Period)			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: msec				
arithmetic mean (confidence interval 95%)	-3.0 (-17.1 to 11.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 to the last dose date plus 30 days (median exposure to eleclazine: 396 days)	
Adverse event reporting additional description:	
Safety Analysis Set: participants who received at least 1 dose of study drug (either active or placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Single oral loading dose of placebo to match eleclazine loading dose (8 x 6 mg placebo to match tablets) on Day 1	
Reporting group title	Eleclazine Loading Dose (LD) 48 mg
Reporting group description:	
Eleclazine 48 mg (8 x 6 mg tablets) administered orally on Day 2	
Reporting group title	Eleclazine Maintenance Dose (MD) 3 mg
Reporting group description:	
Eleclazine 3 mg (1 x 3 mg tablet) administered once daily from Day 3 to the Week 12 Visit	
Reporting group title	Eleclazine MD 6 mg
Reporting group description:	
Eleclazine 6 mg (1 x 6 mg tablet) administered orally from the day after the Week 12 Visit through Week 24 and open-label extension.	
Reporting group title	All Eleclazine
Reporting group description:	
• Loading Dose: Eleclazine 48 mg (8 x 6 mg tablets) administered on Day 2 and 3 mg (1 x 3 mg tablet) once daily from Day 3 to the Week 12 Visit • Maintenance dose: Eleclazine 6 mg (1 x 6 mg tablet) from the day after the Week 12 Visit through Week 24 and open-label extension. • Adverse events in this reporting group include those that occurred any time during the study by participants while receiving loading dose or maintenance dose of eleclazine.	

Serious adverse events	Placebo	Eleclazine Loading Dose (LD) 48 mg	Eleclazine Maintenance Dose (MD) 3 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Eleclazine MD 6 mg	All Eleclazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Eleclazine Loading Dose (LD) 48 mg	Eleclazine Maintenance Dose (MD) 3 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 41 (12.20%)	5 / 41 (12.20%)	17 / 41 (41.46%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	2 / 41 (4.88%)
occurrences (all)	2	1	2
Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	2 / 41 (4.88%)
occurrences (all)	1	0	2
Ear and labyrinth disorders			

Vertigo labyrinthine			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	0 / 41 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	3 / 41 (7.32%)
occurrences (all)	0	1	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2

Non-serious adverse events	Eleclazine MD 6 mg	All Eleclazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 41 (34.15%)	24 / 41 (58.54%)	
Investigations			
Weight increased			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 41 (9.76%)	6 / 41 (14.63%)	
occurrences (all)	4	7	
Dizziness			

subjects affected / exposed	0 / 41 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)	5 / 41 (12.20%)	
occurrences (all)	2	5	
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Ear and labyrinth disorders			
Vertigo labyrinthine			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Arthralgia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 41 (7.32%)	6 / 41 (14.63%)	
occurrences (all)	4	7	
Nasopharyngitis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2014	1) Updated information from phase 1 studies in healthy volunteers and subjects with LQT3. 2) Revised Inclusion Criteria 4 to include QTc interval measurement criteria for subjects who are currently taking ranolazine or Class I antiarrhythmic drugs such as mexiletine. 3) Revised Exclusion Criteria 2 to strengthen language regarding seizures. 4) Revised Exclusion Criteria 11 to reflect the ranolazine half-life. 5) Revised the study design and study procedures to incorporate the addition of Week 2 Monitoring, the Week 18 Visit, and the open-label extension. 6) Revised the duration (length), windows, and timing of study visits. 7) Revised to clarify that subjects taking ranolazine or Class I antiarrhythmic drugs such as mexiletine may be hospitalized, at the discretion of the investigator, to allow for washout of the aforementioned medications. 8) Revised collection of DNA for the LQTS sequencing test to only occur on Day 1 of the Enrollment Visit. 9) Specified guidance to investigators for subjects who may experience a seizure. 10) Added use of a cardiac rhythm monitoring device (eg, ZIO® XT Patch). 11) Added predose urine PK collection from Day 1 through the OLE, and also at the Follow-up and Early Termination Visits. 12) Revised the dosing regimen of the single-blind treatment period; initiating the maintenance dose of 3 mg GS-6615 once daily for 12 weeks, followed by a fixed up-titration to 6 mg GS-6615 once daily for the next 12 weeks. 13) Added the formulation of 6 mg GS-6615 supplied during the single blind treatment period and also the formulation of GS-6615 supplied during the open-label extension. 14) Added guidance regarding review of safety data and consultation with the Gilead medical monitor regarding dose adjustment for subjects who turn 66 years of age during the study. 15) Revised the instructions for dose modification. 16) Updated to reflect change of primary endpoint to Week 24, consistent with revised dosing regimen.
13 November 2015	1) Updated the protocol title to reflect the name change of GS-6615 to eleclazine 5) Updated objectives and study endpoints to align with what was agreed to with the FDA and in the current Statistical Analysis Plan dated 06 February 2015 6) Revised Inclusion Criteria 2 to increase the age limit to 70 (inclusive) 7) Revised Inclusion Criteria 3 to remove the 6 month genotype requirement 8) Revised Inclusion Criterion 4 to reflect the decreased ECG collection time points 9) Added new exclusion criteria to exclude subjects with known severe obstructive sleep apnea that is not treated 10) Revised Exclusion Criteria 5 to increase the BMI to 40 kg/m2 (inclusive) 11) Revised Exclusion Criteria 17 to clarify that clinically significant planned elective invasive surgeries or procedures should be avoided during the single blind treatment period only 12) Modified the number of ECG collection time points at the screening visit 13) Updated Holter monitor recording requirements from 48 hours to 24 hours for each study visit 14) Revised the window for when plasma predose PK sample is to be collected for each visit 15) Revised PK sampling time points at each visit 16) Revised language in Section 8 regarding presentation of PK parameters in population PK report 17) Removed language referencing ZIO® XT Patch country restrictions 18) Corrected GFR MDRD equation in Appendix 6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 December 2016	A letter was sent to all Study GS-US-372-1234 participating investigators on 18 November 2016, advising them of an important finding identified in a Phase 2 study in subjects with ventricular tachycardia/ventricular fibrillation (VT/VF) and implantable cardioverter-defibrillator (ICDs) (Study GS-US-356-0101, TEMPO) in which the rate of ICD shocks was higher in subjects who received eleclazine compared with placebo. Another letter was sent to all Study GS-US-372-1234 participating investigators on 13 December 2016, advising them of Gilead's decision to discontinue the development of eleclazine and terminate this study. In light of the discontinuation of the VT/VF development program and based on the data from Study GS-US-356-0101, the totality of the data did not support continuation of the eleclazine development program for all other indications.	-

Notes:

Limitations and caveats

None reported