Clinical trial results:
A Phase 1b/2, Multicenter, Open-Label, Dose-Escalation Study of Ribociclib (LEE011) in Combination with Binimetinib (MEK162) in Adult Patients with NRAS Mutant Melanoma

Summary

EudraCT number	2012-004104-35
Trial protocol	NL IT DE NO
Global end of trial date	22 February 2018

Results information

Result version number	v1 (current)
This version publication date	24 August 2019
First version publication date	24 August 2019

Trial information

Trial identification

Sponsor protocol code	CMEK162X2114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01781572
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Array BioPharma Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, Colorado 80301, United States,
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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	31 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2018
Global end of trial reached?	Yes
Global end of trial date	22 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Phase 1b: To estimate the maximum tolerated dose(s) [MTD(s)] and/or identify the recommended Phase 2 dose (RP2D) and schedule of ribociclib and binimetinib in combination.
• Phase 2: To describe the antitumor activity of the ribociclib and binimetinib in combination at the RP2D.

Protection of trial subjects:

This study was conducted according to International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines concerning Good Clinical Practice (GCP), the European Union Clinical Trials Directive (2001/20/EC), Title 21 of the US Code of Federal Regulations (21CFR) and the practices and regulations of each participating nation.
At each site, the Investigator or a medically qualified member of the study team was required to provide each patient with a full explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The study protocol, the informed consent form (ICF), and printed patients' information materials were reviewed and approved by the independent ethics committee (IEC) and/or institutional review board (IRB) for each site before any study procedures were performed.

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	27 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Netherlands: 18
Worldwide total number of subjects	102
EEA total number of subjects	52

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)	54
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Upon study entry, all patients were required to provide either an archival tumor biopsy with the corresponding pathology report or a newly obtained tumor biopsy. Both parts of the study were limited to patients aged 18 or older with metastatic or locally advanced NRAS-mutant melanoma.

Pre-assignment

Screening details:

Screening assessments were performed within 14 days prior to the first dose of ribociclib and binimetinib except for the pretreatment tumor biopsy, which was performed within 28 days before dosing. A total of 23 patients were screened but not enrolled.

Period 1

Period 1 title	Phase 1b (dose-escalation phase)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	28-day schedule

Arm description:

A combined total of 61 patients were treated in the 28-day (n=29) and 21-day (n=32) treatment cycles, and all patients discontinued treatment. The starting dose in the 28-day schedule was binimetinib 45 mg BID + ribociclib 200 mg QD.
28-Day Schedule: ribociclib was taken (QD) for 21 consecutive days followed by a 7-day planned break. Binimetinib was taken (BID) on a continuous dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two treatment regimens were evaluated in the dose-escalation phase. A complete treatment cycle was defined as 28 days or 21 days of treatment with the study drug combinations. Cycle 1 Day 1 was defined as the day that the first dose of the ribociclib + binimetinib combination was administered.
The starting dose levels for dose escalation for ribociclib and binimetinib were as follows:
• Ribociclib: 200 mg QD
• Binimetinib: 45 mg BID
28-Day Schedule: ribociclib was taken QD for 21 consecutive days followed by a 7-day planned break. Binimetinib was taken BID on a continuous dosing schedule.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Two treatment regimens were evaluated in the dose-escalation phase. A complete treatment cycle was defined as 28 days or 21 days of treatment with the study drug combinations. Cycle 1 Day 1 was defined as the day that the first dose of the ribociclib + binimetinib combination was administered.
The starting dose levels for dose escalation for ribociclib and binimetinib were as follows:
• Ribociclib: 200 mg QD

• Binimetinib: 45 mg BID
28-Day Schedule: ribociclib was taken QD for 21 consecutive days followed by a 7-day planned break. Binimetinib was taken BID on a continuous dosing schedule.

Arm title	21-day schedule

Arm description:

A combined total of 61 patients were treated in the 28-day (n=29) and 21-day (n=32) treatment cycles, and all patients discontinued treatment. The starting dose in the 21-day schedule was binimetinib 30 mg BID + ribociclib 200 mg QD.
21-Day Schedule: ribociclib QD and binimetinib BID were taken QD for 14 consecutive days followed by a 7-day planned break.

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Two treatment regimens were evaluated in the dose-escalation phase. A complete treatment cycle was defined as 28 days or 21 days of treatment with the study drug combinations. Cycle 1 Day 1 was defined as the day that the first dose of the ribociclib + binimetinib combination was administered.
The starting dose levels for dose escalation for ribociclib and binimetinib were as follows:
• Ribociclib: 200 mg QD
• Binimetinib: 45 mg BID
21-Day Schedule: ribociclib QD and binimetinib BID were taken QD for 14 consecutive days followed by a 7-day planned break.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Two treatment regimens were evaluated in the dose-escalation phase. A complete treatment cycle was defined as 28 days or 21 days of treatment with the study drug combinations. Cycle 1 Day 1 was defined as the day that the first dose of the ribociclib + binimetinib combination was administered.
The starting dose levels for dose escalation for ribociclib and binimetinib were as follows:
• Ribociclib: 200 mg QD
• Binimetinib: 45 mg BID
21-Day Schedule: ribociclib QD and binimetinib BID were taken QD for 14 consecutive days followed by a 7-day planned break.

Number of subjects in period 1	28-day schedule	21-day schedule
Started	29	32
Completed	20	21
Not completed	29	32
Patient decision	2	-
Physician decision	-	2
Adverse event, non-fatal	9	3
Death	1	-
Progressive disease	17	27

Joined	20	21
In Phase 2 additional patients were enrolled	20	21

Period 2

Period 2 title	Phase 2 (dose-expansion phase)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Arm title	Binimetinib plus Ribociclib

Arm description:

The dose-expansion phase was initiated with a newly recruited group of patients.
Binimetinib 45 mg BID + ribociclib 200 mg QD on 28-day schedule

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One treatment regimen was chosen and evaluated in the dose-expansion phase: a 28-day schedule of 200 mg oral ribociclib QD for 21 days with 45 mg oral binimetinib BID for 28 days.

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ribociclib, supplied as hard gelatin capsules for oral use of dosage strengths of 50 and 200 mg.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is dose escalation part only (61 patients enrolled) to estimate the MTD(s) and/or to identify the RP2D and schedule of ribociclib and binimetinib in combination. In Phase 2 additional patients were enrolled (41).

Number of subjects in period 2[2]	Binimetinib plus Ribociclib
Started	41
Completed	0
Not completed	41
Physician decision	4

Patient decision	2
Death	1
Adverse event	11
Progressive disease	23

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: This study was a multi-center, open-label, dose-finding escalation study comprising 2 parts: Phase 1b was the dose escalation part, and it was followed by a Phase 2 clinical efficacy evaluation. In the first part 61 patients have been enrolled. They discontinued the treatment and 41 patients in the second part have been enrolled to a total of 102 patients globally included.

Baseline characteristics

Reporting groups

Reporting group title	Phase 2 (dose-expansion phase)

Reporting group description:

Phase 2: To describe the antitumor activity of the ribociclib and binimetinib in combination at the RP2D (binimetinib 45 mg BID and ribociclib 200 mg QD).
A total of 41 patients were treated, and all patients (100%) discontinued treatment. Based on the recommendations of the dose-escalation meetings between the Sponsor and the Investigators, the RP2D and schedule for the combination of binimetinib and ribociclib to be used for the dose-expansion phase of the study was binimetinib 45 mg BID + ribociclib 200 mg QD on the 28-day schedule.

Reporting group values	Phase 2 (dose-expansion phase)	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	22	22	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	15	15	
Male	26	26	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) includes all patients who received at least one dose of LEE011 (QD) or MEK162 (BID). Patients will be analyzed according to the planned treatment combination.

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	102		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	54		
From 65-84 years	48		
85 years and over	0		
Gender categorical Units: Subjects			
Female	41		
Male	61		

End points

End points reporting groups

Reporting group title	28-day schedule

Reporting group description:

A combined total of 61 patients were treated in the 28-day (n=29) and 21-day (n=32) treatment cycles, and all patients discontinued treatment. The starting dose in the 28-day schedule was binimetinib 45 mg BID + ribociclib 200 mg QD.
28-Day Schedule: ribociclib was taken (QD) for 21 consecutive days followed by a 7-day planned break. Binimetinib was taken (BID) on a continuous dosing schedule.

Reporting group title	21-day schedule

Reporting group description:

A combined total of 61 patients were treated in the 28-day (n=29) and 21-day (n=32) treatment cycles, and all patients discontinued treatment. The starting dose in the 21-day schedule was binimetinib 30 mg BID + ribociclib 200 mg QD.
21-Day Schedule: ribociclib QD and binimetinib BID were taken QD for 14 consecutive days followed by a 7-day planned break.

Reporting group title	Binimetinib plus Ribociclib

Reporting group description:

The dose-expansion phase was initiated with a newly recruited group of patients.
Binimetinib 45 mg BID + ribociclib 200 mg QD on 28-day schedule

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) includes all patients who received at least one dose of LEE011 (QD) or MEK162 (BID). Patients will be analyzed according to the planned treatment combination.

Primary: Phase 1b -Incidence of DLTs in Cycle 1

End point title	Phase 1b -Incidence of DLTs in Cycle 1

End point description:

Objective is to estimate the MTD(s) and/or to identify the RP2D and schedule of ribociclib and binimetinib in combination.

End point type	Primary

End point timeframe:

Time from the first dose taken until end of the trial.

End point values	28-day schedule	21-day schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: incidence	6	4		

Statistical analyses

Statistical analysis title	Statistical Analysis Plan v 1.0 dated 16 May 18
Comparison groups	28-day schedule v 21-day schedule

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.6
upper limit	31.8
Variability estimate	Standard deviation

Primary: Phase 2 - Objective Response Rate (ORR)

End point title	Phase 2 - Objective Response Rate (ORR)

End point description:

ORR (CR and PR) according to RECIST 1.1. Objective response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR). The primary analysis of the ORR was based on the Investigator's assessment of overall lesion responses per RECIST 1.1.

End point type	Primary

End point timeframe:

Time from taking first dose of study drug until end of the trial.

End point values	28-day schedule	21-day schedule	Binimetinib plus Ribociclib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	32	41	
Units: percent				
number (confidence interval 95%)	20.7 (8.0 to 39.7)	18.8 (7.2 to 36.4)	19.5 (8.8 to 34.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis version 1.0 dated 16 May 2018

Statistical analysis description:

Best overall response is based on investigator's assessment using RECIST v1.1 (Response Evaluation Criteria for Solid Tumors).

Comparison groups	21-day schedule v 28-day schedule v Binimetinib plus Ribociclib
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	19.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	34.9
Variability estimate	Standard deviation

Notes:

[1] - The ORR (overall response rate) is the proportion of patients with a BOR (best overall response of CR (complete response) or PR (partial response). Patients were summarized in terms of percentage rate with a 95% CI. An exact binomial CI (implemented using the SAS procedure FREQ with the EXACT statement for one-way tables) was calculated (Clopper and Pearson).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After signing of the informed consent until 30 days after study treatment discontinuation.

Adverse event reporting additional description:

An AE was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Phase 1b - Dose Escalation Phase

Reporting group description: -

Reporting group title	Phase 2 - Dose Expansion Phase

Reporting group description: -

Serious adverse events	Phase 1b - Dose Escalation Phase	Phase 2 - Dose Expansion Phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 61 (49.18%)	22 / 41 (53.66%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 61 (8.20%)	5 / 41 (12.20%)	
occurrences causally related to treatment / all	4 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 61 (1.64%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 61 (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	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme			
subjects affected / exposed	0 / 61 (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	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 61 (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	
Myocardial infarction			
subjects affected / exposed	0 / 61 (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	
Acute myocardial infarction			
subjects affected / exposed	0 / 61 (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 / 1	
Nervous system disorders			
Slow speech			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 61 (8.20%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 61 (8.20%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	4 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 61 (1.64%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal obstruction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 61 (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 / 1	
Chills			
subjects affected / exposed	0 / 61 (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	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 61 (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	
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 61 (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	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Micturition frequency			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 61 (1.64%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Muscular weakness			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 61 (3.28%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 61 (6.56%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	3 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Staphylococcal bacteraemia			
subjects affected / exposed	0 / 61 (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	
Erysipelas			
subjects affected / exposed	0 / 61 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 61 (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	
Herpes zoster			
subjects affected / exposed	0 / 61 (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	
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid intake reduced			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 61 (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	
Hypokalaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase 1b - Dose Escalation Phase	Phase 2 - Dose Expansion Phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)	41 / 41 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 61 (9.84%)	4 / 41 (9.76%)	
occurrences (all)	6	4	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	21 / 61 (34.43%)	18 / 41 (43.90%)	
occurrences (all)	21	18	
Fatigue			
subjects affected / exposed	26 / 61 (42.62%)	15 / 41 (36.59%)	
occurrences (all)	26	15	
Pyrexia			
subjects affected / exposed	10 / 61 (16.39%)	11 / 41 (26.83%)	
occurrences (all)	10	11	
Chills			
subjects affected / exposed	6 / 61 (9.84%)	6 / 41 (14.63%)	
occurrences (all)	6	6	
Asthenia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	5 / 61 (8.20%)	5 / 41 (12.20%)	
occurrences (all)	5	5	
Epistaxis			
subjects affected / exposed	1 / 61 (1.64%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	33 / 61 (54.10%)	24 / 41 (58.54%)	
occurrences (all)	33	24	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 61 (34.43%)	20 / 41 (48.78%)	
occurrences (all)	21	20	
Alanine aminotransferase increased			
subjects affected / exposed	16 / 61 (26.23%)	18 / 41 (43.90%)	
occurrences (all)	16	18	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 61 (9.84%)	8 / 41 (19.51%)	
occurrences (all)	6	8	
Blood creatinine increased			
subjects affected / exposed	12 / 61 (19.67%)	5 / 41 (12.20%)	
occurrences (all)	12	5	
Troponin T increased			
subjects affected / exposed	0 / 61 (0.00%)	5 / 41 (12.20%)	
occurrences (all)	0	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	8 / 61 (13.11%)	4 / 41 (9.76%)	
occurrences (all)	8	4	
Ejection fraction decreased			
subjects affected / exposed	0 / 61 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Lipase increased			
subjects affected / exposed	1 / 61 (1.64%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Neutrophil count decreased			

subjects affected / exposed	2 / 61 (3.28%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 61 (16.39%)	5 / 41 (12.20%)	
occurrences (all)	10	5	
Visual field defect			
subjects affected / exposed	0 / 61 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Dysgeusia			
subjects affected / exposed	6 / 61 (9.84%)	3 / 41 (7.32%)	
occurrences (all)	6	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 61 (34.43%)	10 / 41 (24.39%)	
occurrences (all)	21	10	
Neutropenia			
subjects affected / exposed	15 / 61 (24.59%)	5 / 41 (12.20%)	
occurrences (all)	15	5	
Thrombocytopenia			
subjects affected / exposed	9 / 61 (14.75%)	4 / 41 (9.76%)	
occurrences (all)	9	4	
Eye disorders			
Retinal detachment			
subjects affected / exposed	7 / 61 (11.48%)	8 / 41 (19.51%)	
occurrences (all)	7	8	
Chorioretinopathy			
subjects affected / exposed	7 / 61 (11.48%)	6 / 41 (14.63%)	
occurrences (all)	7	6	
Macular oedema			
subjects affected / exposed	5 / 61 (8.20%)	5 / 41 (12.20%)	
occurrences (all)	5	5	
Periorbital oedema			
subjects affected / exposed	2 / 61 (3.28%)	5 / 41 (12.20%)	
occurrences (all)	2	5	
Subretinal fluid			

subjects affected / exposed	5 / 61 (8.20%)	5 / 41 (12.20%)	
occurrences (all)	5	5	
Detachment of retinal pigment			
subjects affected / exposed	2 / 61 (3.28%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	27 / 61 (44.26%)	22 / 41 (53.66%)	
occurrences (all)	27	22	
Diarrhoea			
subjects affected / exposed	33 / 61 (54.10%)	21 / 41 (51.22%)	
occurrences (all)	33	21	
Vomiting			
subjects affected / exposed	25 / 61 (40.98%)	14 / 41 (34.15%)	
occurrences (all)	25	14	
Constipation			
subjects affected / exposed	14 / 61 (22.95%)	8 / 41 (19.51%)	
occurrences (all)	14	8	
Abdominal pain			
subjects affected / exposed	8 / 61 (13.11%)	5 / 41 (12.20%)	
occurrences (all)	8	5	
Dry mouth			
subjects affected / exposed	10 / 61 (16.39%)	4 / 41 (9.76%)	
occurrences (all)	10	4	
Stomatitis			
subjects affected / exposed	9 / 61 (14.75%)	4 / 41 (9.76%)	
occurrences (all)	9	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 61 (4.92%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	17 / 61 (27.87%)	18 / 41 (43.90%)	
occurrences (all)	17	18	
Rash			

subjects affected / exposed	20 / 61 (32.79%)	6 / 41 (14.63%)	
occurrences (all)	20	6	
Dry skin			
subjects affected / exposed	7 / 61 (11.48%)	5 / 41 (12.20%)	
occurrences (all)	7	5	
Pruritus			
subjects affected / exposed	6 / 61 (9.84%)	5 / 41 (12.20%)	
occurrences (all)	6	5	
Rash maculo-papular			
subjects affected / exposed	5 / 61 (8.20%)	5 / 41 (12.20%)	
occurrences (all)	5	5	
Pruritus generalised			
subjects affected / exposed	3 / 61 (4.92%)	4 / 41 (9.76%)	
occurrences (all)	3	4	
Alopecia			
subjects affected / exposed	5 / 61 (8.20%)	3 / 41 (7.32%)	
occurrences (all)	5	3	
Rash generalised			
subjects affected / exposed	7 / 61 (11.48%)	3 / 41 (7.32%)	
occurrences (all)	7	3	
Skin fissures			
subjects affected / exposed	5 / 61 (8.20%)	3 / 41 (7.32%)	
occurrences (all)	5	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 61 (1.64%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 61 (9.84%)	6 / 41 (14.63%)	
occurrences (all)	6	6	
Myalgia			
subjects affected / exposed	2 / 61 (3.28%)	4 / 41 (9.76%)	
occurrences (all)	2	4	
Infections and infestations			

Erysipelas			
subjects affected / exposed	0 / 61 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Rash pustular			
subjects affected / exposed	1 / 61 (1.64%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	4 / 61 (6.56%)	3 / 41 (7.32%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	7 / 61 (11.48%)	9 / 41 (21.95%)	
occurrences (all)	7	9	
Hypophosphataemia			
subjects affected / exposed	5 / 61 (8.20%)	7 / 41 (17.07%)	
occurrences (all)	5	7	
Decreased appetite			
subjects affected / exposed	3 / 61 (4.92%)	6 / 41 (14.63%)	
occurrences (all)	3	6	
Hypoalbuminaemia			
subjects affected / exposed	14 / 61 (22.95%)	6 / 41 (14.63%)	
occurrences (all)	14	6	
Hyperphosphataemia			
subjects affected / exposed	12 / 61 (19.67%)	4 / 41 (9.76%)	
occurrences (all)	12	4	
Hypocalcaemia			
subjects affected / exposed	0 / 61 (0.00%)	4 / 41 (9.76%)	
occurrences (all)	0	4	
Hypomagnesaemia			
subjects affected / exposed	0 / 61 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2013	The purpose of this amendment is to implement health authority mandated changes. In addition, editorial changes have been made to sections where previous language was deemed inaccurate or ambiguous by site staff and study investigators, to ensure better protocol compliance. - The statement, there was no evidence of cardio vascular toxicity in the 4 week toxicology studies, and rare and isolated have been removed from Section 1.2.1.3 to be consistent with language that will be included in an updated [LEE011 Investigator's Brochure]. - Section 1.2.2.4.1 has been updated to include information on cardiac toxicity that has been observed in patients who have received MEK162 post the release of the version 8 [Investigator's Brochure]. - Section 6.2.3.2 has been updated to include if two or more patients experience CTCAE grade 2 or greater treatment-related toxicities at a dose level in any cohort, all future dose escalations of LEE011 will be 50%. Only toxicities that occur during the first cycle will necessarily be considered for decisions. - Hepato-biliary related DLT criterion (Table 6-2) has been updated to CTCAE grade 2 total bilirubin concurrent with grade 2 ALT is a DLT except for patients with known liver metastatic disease. The corresponding changes to the dose modification table have been made. Table 6-3 has been updated to in the event of this DLT hold LEE011 and MEK162 until the toxicity resolves to Grade 1 and restart at one dose level below for both agents. If toxicity recurs at the lower dose, then discontinue from study. - Blood chemistry panel (Table 7-2) has been updated to include brain natriuretic peptide (BNP) and troponin measurements at each cycle of treatment for additional cardiac monitoring in patients.
05 March 2014	Emerging safety data from this and other studies with LEE011 and MEK162 warrant the following changes to the protocol: - Preliminary evaluation of LEE011 and MEK162 indicates it is an active combination but associated with frequent adverse events necessitating dosing interruptions and reductions. In order to determine the most tolerable and efficacious dosing schedule for the combination, evaluation of alternate dosing schedules are incorporated. - Evaluation of the 28 day continuous dosing schedule was performed in the phase 1 single agent LEE011 study [CLEE011X2101]. Due to hematological toxicity, this schedule will not be pursued any longer. Therefore all references to continuous dosing schedule will be removed from this protocol. In addition, the eligibility criterion is modified to include only patients with ECOG performance score of 0 and 1. - The phase II section has been updated to include information regarding the RSTANCE2101 companion protocol. The statement has been added to inform the Investigator that patients may elect to participate in a companion protocol to study the mechanisms of resistance to the study drugs. - Results from the MEK162 food effect study and preliminary results from the LEE011 food effect study indicate that MEK162 and LEE011 can be administered with or without food. As of this amendment, MEK162 and LEE011 may be administered irrespective of food. - The objectives and endpoints and PK sections were updated to include exploratory analysis of the possible relationship between exposures of LEE011 and/or LEQ803 and QT prolongation. Finally, changes to correct typographical errors and harmonize protocol text where applicable have been made.

11 August 2015	The main purpose of this amendment is to address recently observed safety findings from patients treated with LEE0l 1 (Ribociclib) in other clinical trials. 1. Recent data suggests a potential risk of hepatic toxicity (drug induced liver injury [DILi] indicated by an increase of transaminases, in isolation or with bilirubin increase, in patients treated with LEE01. 2. Updates to monitoring and dose adjustment guidelines for QTcF prolongation in order to improve patient safety based on program standard language recommendations have been implemented. 3. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. • The Protocol Summary is updated to reflect the changes to the inclusion and exclusion criteria • Section 5.2 Inclusion criteria has been updated with the following: • Clarification of inclusion criteria for serum total bilirubin for patients with Gilbert syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN • Update of AST and ALT <2.5 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT< 5 x ULN. • Section 5.3 Exclusion criteria has been updated with the following: • Clarification of QTcF interval criteria on the ECG (ie: unreadable or not interpretable) or QTcF >450 ms (using Frederica's correction). All as determined by screening ECG (mean of triplicate ECGs). • Addition of symptomatic pericarditis within 12 months prior to starting study drug • Increase in exclusion window from 3 months to 12 months prior to starting study drug for angina pectoris • Increase in exclusion window from 3 months to 12 months prior to starting study drug for acute myocardial infarction

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported