Clinical trial results:
A randomized pre-surgical pharmacodynamics study to assess the biological activity of LEE011 plus letrozole versus single agent letrozole in primary breast cancer (MONALEESA-1)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-002588-24
Trial protocol	NL ES FR
Global end of trial date	10 September 2014

Results information

Result version number	v2 (current)
This version publication date	13 August 2016
First version publication date	12 June 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLEE011A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01919229
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	10 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the difference in anti-proliferative activity of ribociclib 600 mg once daily and ribociclib 400 mg once daily in combination with letrozole 2.5 mg once daily vs. single agent letrozole 2.5 mg once daily as measured by changes in levels of the proliferative marker Ki67 from Baseline to time of surgery (Day 15).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 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	Spain: 6
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	14
EEA total number of subjects	6

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)	7
From 65 to 84 years	7

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

20 patients were screened, of those 14 patients completed the Screening phase and were randomized. 6 patients discontinued during the Screening phase; 3 patients were considered screen failure and 3 patients discontinued due to patient's decision.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Letrozole

Arm description:

Letrozole 2.5 mg alone once daily

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was supplied in 2.5mg tablets for oral use

Arm title	LEE011 400mg + letrozole

Arm description:

Letrozole 2.5 mg once daily and ribociclib 400 mg (2 capsules of 200 mg each) once daily.

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was supplied in 2.5mg tablets for oral use

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ribociclib was supplied in 200 mg hard gelatin capsules for oral use.

Arm title	LEE011 600mg + letrozole

Arm description:

Letrozole 2.5 mg once daily and ribociclib 600 mg (3 capsules of 200 mg each) once daily.

Arm type	Experimental

Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ribociclib was supplied in 200 mg hard gelatin capsules for oral use.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was supplied in 2.5mg tablets for oral use

Number of subjects in period 1	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole
Started	4	6	4
Completed	4	6	3
Not completed	0	0	1
Subject/guardian decision	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Letrozole
Reporting group description:	
Letrozole 2.5 mg alone once daily	
Reporting group title	LEE011 400mg + letrozole
Reporting group description:	
Letrozole 2.5 mg once daily and ribociclib 400 mg (2 capsules of 200 mg each) once daily.	
Reporting group title	LEE011 600mg + letrozole
Reporting group description:	
Letrozole 2.5 mg once daily and ribociclib 600 mg (3 capsules of 200 mg each) once daily.	

Reporting group values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole
Number of subjects	4	6	4
Age categorical Units: Subjects			
Adults (18-64 years)	4	3	0
From 65-84 years	0	3	4
Age Continuous | Units: years			
arithmetic mean	57	64.2	70
standard deviation	± 5.48	± 9.91	± 4.24
Gender, Male/Female Units: Participants			
Female	4	6	4
Male	0	0	0

Reporting group values	Total		
Number of subjects	14		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	7		
Age Continuous | Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Participants			
Female	14		
Male	0		

End points

End points reporting groups

Reporting group title	Letrozole
Reporting group description: Letrozole 2.5 mg alone once daily	
Reporting group title	LEE011 400mg + letrozole
Reporting group description: Letrozole 2.5 mg once daily and ribociclib 400 mg (2 capsules of 200 mg each) once daily.	
Reporting group title	LEE011 600mg + letrozole
Reporting group description: Letrozole 2.5 mg once daily and ribociclib 600 mg (3 capsules of 200 mg each) once daily.	

Primary: Cell cycle response rate per cell proliferation marker Ki67

End point title	Cell cycle response rate per cell proliferation marker Ki67[1]
End point description: Cell cycle response rate is defined by percentage of patients with natural logarithm of Ki-67 levels (expressed as percentage of baseline values) of less than 1 at the time of surgery. Since the trial was prematurely terminated, no statistical analysis was done.	
End point type	Primary
End point timeframe: Day 1, Day15	

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: Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Percentage of positive cells for Ki67				
number (not applicable)				

Notes:

[2] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[3] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[4] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability of the combination

End point title	Safety and tolerability of the combination
End point description: Occurrence, frequency and severity of adverse events (AEs), laboratory abnormalities	
End point type	Secondary

End point timeframe:
Up to 30 days after the last dose

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	4	
Units: patients				
Adverse Events	0	0	0	
Serious Adverse Events	0	0	0	
Death	0	0	0	
Other Adverse Events	2	5	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in electrocardiogram (ECG) parameters

End point title	Change from baseline in electrocardiogram (ECG) parameters

End point description:

End point type	Secondary

End point timeframe:
Baseline, Day 14

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: milliseconds				
least squares mean (standard error)	()	()	()	

Notes:
[5] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done
[6] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done
[7] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in expression of Retinoblastoma Protein (pRB)

End point title	Change from baseline in expression of Retinoblastoma Protein (pRB)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: unit on scale				
least squares mean (standard error)	()	()	()	

Notes:

[8] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[9] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[10] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: PK (pharmacokinetics) parameters, including but not limited to, Cmax, Tmax, AUClast for LEE011 (and any relevant metabolites) and letrozole.

End point title	PK (pharmacokinetics) parameters, including but not limited to, Cmax, Tmax, AUClast for LEE011 (and any relevant metabolites) and letrozole.

End point description:

End point type	Secondary

End point timeframe:

Days 1, 8, 14 and 15

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: ng/mL				

Notes:

[11] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[12] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[13] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ECG morphology

End point title	Change in ECG morphology

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 14

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: milliseconds				

Notes:

[14] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[15] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[16] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between PK concentrations and ECG changes

End point title	Correlation between PK concentrations and ECG changes

End point description:

Correlation between the QTc interval change from baseline and plasma concentrations of LEE011 and/or any relevant metabolites

End point type	Secondary

End point timeframe:

Day 14

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: ratio				

Notes:

[17] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[18] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[19] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in expression of Cyclin-Dependent Kinase 1 (CDK1)

End point title	Change from baseline in expression of Cyclin-Dependent Kinase 1 (CDK1)

End point description:

End point type	Secondary

End point timeframe:
Baseline, Day 15

End point values	Letrozole	LEE011 400mg + letrozole	LEE011 600mg + letrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[20]	0[21]	0[22]	
Units: percentage				

Notes:
[20] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done
[21] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done
[22] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Letrozole
Reporting group description: Letrozole 2.5 mg alone once daily	
Reporting group title	LEE 600mg
Reporting group description: Letrozole 2.5 mg once daily and ribociclib 600 mg (3 capsules of 200 mg each) once daily.	
Reporting group title	LEE 400mg
Reporting group description: Letrozole 2.5 mg once daily and ribociclib 400 mg (2 capsules of 200 mg each) once daily.	

Serious adverse events	Letrozole	LEE 600mg	LEE 400mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Letrozole	LEE 600mg	LEE 400mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	4 / 4 (100.00%)	5 / 6 (83.33%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
ASPARTATE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
LIPASE INCREASED			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
PROCEDURAL PAIN			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
SEROMA			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
FATIGUE			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
PYREXIA			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DIARRHOEA			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DYSPEPSIA			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
NAUSEA			
subjects affected / exposed	1 / 4 (25.00%)	3 / 4 (75.00%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
STOMATITIS			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
VOMITING			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
HERPES ZOSTER			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
POST PROCEDURAL INFECTION			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	The purpose of amendment 1 was to clarify some of the study assessments required in the protocol and to take into consideration differences in local practice at the study centers, based on consultation with the study steering committee and feedback received from participating centers' IRBs/IECs and Health Authorities. The amendment also included an update of nonclinical and clinical data for ribociclib alone and in combination with letrozole.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported