Clinical trial results:
A Phase II multi-center, open label, randomized study to assess safety and efficacy of two different schedules of oral LDE225 in adult patients with relapsed/refractory or untreated elderly patients with acute leukemia

Summary

EudraCT number	2012-004022-21
Trial protocol	AT ES GB IE SE NO BE DE FR NL HU IT
Global end of trial date	26 May 2015

Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

Trial information

Trial identification

Sponsor protocol code	CLDE225X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01826214
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	26 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the rate of complete remission (CR) and complete remission with incomplete blood count recovery (CRi) on two different dosing schedules of sonidegib in acute leukemia.

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	30 May 2013
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	Australia: 6
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	70
EEA total number of subjects	51

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)	19
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

35 patients were randomized but only 34 patients received at least one dose of study drug in the LDE225-800 (schedule B) arm.

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	LDE225-400

Arm description:

Patients who were randomized to Schedule A, and received 400 mg LDE225 twice daily for the first two weeks only and after two weeks, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sonidegib 400 mg 2x daily for 2 weeks, then 800mg once daily

Arm title	LDE225-800

Arm description:

Patients who were randomized to Schedule B, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.

Arm type	Experimental
Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sonidegib 800 mg taken orally one daily

Number of subjects in period 1	LDE225-400	LDE225-800
Started	35	35
Treated	35	34
Completed	0	0
Not completed	35	35
Adverse event, serious fatal	3	1
Physician decision	-	2
Study terminated by Sponsor	-	1
not treated	-	1
Adverse event, non-fatal	7	6
Lost to follow-up	1	-
Progressive disease	22	21
Subject/guardian decision	2	3

Baseline characteristics

Reporting groups	
Reporting group title	LDE225-400
Reporting group description:	
Patients who were randomized to Schedule A, and received 400 mg LDE225 twice daily for the first two weeks only and after two weeks, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.	
Reporting group title	LDE225-800
Reporting group description:	
Patients who were randomized to Schedule B, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.	

Reporting group values	LDE225-400	LDE225-800	Total
Number of subjects	35	35	70
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	8	19
From 65-84 years	24	26	50
85 years and over	0	1	1
Age Continuous Units: Years			
arithmetic mean	65.3	67.7	
standard deviation	± 12.31	± 11.65	-
Gender, Male/Female Units: Participants			
Female	18	13	31
Male	17	22	39

End points

End points reporting groups

Reporting group title	LDE225-400

Reporting group description:

Patients who were randomized to Schedule A, and received 400 mg LDE225 twice daily for the first two weeks only and after two weeks, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.

Reporting group title	LDE225-800

Reporting group description:

Patients who were randomized to Schedule B, received 800 mg LDE225 once daily until disease progression, toxicity, withdrawal of consent, death, discretion of the investigator or early termination of the study.

Primary: Rate of complete remission (CR)

End point title	Rate of complete remission (CR)[1]

End point description:

Complete Response (CR) was based on the International Working Group (IWG) criteria based on weekly peripheral blood count measurements and bone marrow biopsy/aspiration collection. Efficacy assessments were performed to determine CR. A treatment cycle was defined as 4 weeks. The outcome measure for the study is based on standardized response criteria as defined by the International Working Group (IWG) for AML. The IWG was established by a group of investigators interested in the design and conduct of clinical trials in acute myeloid leukemia (AML). The criteria established by this group (a set of recommendations for response assessment) are well established, endorsed by major institutions and Health Authorities, and are widely used in clinical trials. No statistical analysis was planned for this primary outcome.

End point type	Primary

End point timeframe:

at screening, every week up to Week 9, every 2 weeks thereafter until CR, every 4 weeks after CR up to 24 months

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: No statistical analysis was planned for this primary outcome.

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Complete remission with incomplete blood count recovery (CRi)

End point title	Complete remission with incomplete blood count recovery

End point description:

The other primary efficacy endpoint was CRi based on the International Working Group (IWG) criteria based on weekly peripheral blood count measurements and bone marrow biopsy/aspiration collection.

Efficacy assessments were performed to determine CRi. A treatment cycle was defined as 4 weeks. No statistical analysis was planned for this primary outcome.

End point type	Primary

End point timeframe:

within 3 days after clearance of blasts from peripheral blood (PB), monthly thereafter until CR or reappearance of blasts in the PB, after CR every other month until discontination up to 24 months

Notes:

[2] - 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: No statistical analysis was planned for this primary outcome.

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was the rate of complete remission (CR), complete remission with incomplete blood count recovery (CRi) or partial response (PR) according to IWG criteria. CR, CRi or PR will be assessed through bone marrow biopsy/aspirate and peripheral blood blasts counts.

End point type	Secondary

End point timeframe:

Every 8 weeks for the first 6 months and every 12 weeks until 53 weeks after the last patient is enrolled or until relapse up to 24 months

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Parmacokintics (PK) parameter: Cmax

End point title	Parmacokintics (PK) parameter: Cmax

End point description:

Cmax is the maximum observed plasma concentration after drug administration.The PK parameters

were determined in plasma using non-compartmental methods. A PK sample was excluded from analyses if the patient vomited within the first 4 hours following the last oral dose of study drug. Other PK samples were excluded as deemed appropriate by the pharmacokineticist. Cmax was derived from the PK concentrations collected at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose on W1D1 and W9D1. The PK concentration at each time point is not an endpoint in the protocol, but these concentrations are used to derive the PK parameters.

End point type	Secondary

End point timeframe:

Week 1 Day 1, Week 9 Day 1

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	33		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1	237 (± 158)	343 (± 275)		
Week 9 Day 1(n: 7, 7)	1640 (± 612)	1500 (± 874)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parmacokintics (PK) parameter: Tmax

End point title	Parmacokintics (PK) parameter: Tmax

End point description:

Tmax is the time to reach Cmax. The PK parameters were determined in plasma using non-compartmental methods. A PK sample was excluded from analyses if the patient vomited within the first 4 hours following the last oral dose of study drug. Other PK samples were excluded as deemed appropriate by the Pharmacokineticist. Tmax was derived from the PK concentrations collected at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose on W1D1 and W9D1. The PK concentration at each time point is not an endpoint in the protocol, but these concentrations are used to derive the PK parameters.

End point type	Secondary

End point timeframe:

Week 1 Day 1,Week 9 Day 1

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	33		
Units: hr				
median (inter-quartile range (Q1-Q3))				
Week 1 Day 1	2.13 (1 to 8.08)	2.12 (1 to 8)		
Week 9 Day 1 (n: 7, 7)	1.88 (1.12 to 8.13)	2.02 (0 to 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parmacokintics (PK) parameter: AUC0-8h

End point title	Parmacokintics (PK) parameter: AUC0-8h

End point description:

AUC0-8h is the area under the concentration-time curve from time zero to 8 hours. The PK parameters were determined in plasma using non-compartmental methods. A PK sample was excluded from analyses if the patient vomited within the first 4 hours following the last oral dose of study drug. Other PK samples were excluded as deemed appropriate by the Pharmacokineticist. AUC0-8h was derived from the PK concentrations collected at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose on W1D1 and W9D1. The PK concentration at each time point is not an endpoint in the protocol, but these concentrations are used to derive the PK parameters.

End point type	Secondary

End point timeframe:

Week 1 Day 1,Week 9 Day 1

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	33		
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Week 1 Day1	988 (± 542)	1560 (± 1230)		
Week 9 Day1 (n: 7, 7)	9750 (± 2830)	7910 (± 5090)		

Statistical analyses

No statistical analyses for this end point

Secondary: Parmacokintics (PK) parameter: AUC0-24h

End point title	Parmacokintics (PK) parameter: AUC0-24h

End point description:

AUC0-8h is the area under the concentration-time curve from time zero to 8 hours. The PK parameters were determined in plasma using non-compartmental methods. A PK sample was excluded from analyses if the patient vomited within the first 4 hours following the last oral dose of study drug. Other PK samples were excluded as deemed appropriate by the Pharmacokineticist. AUC0-8h was derived from the PK concentrations collected at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours post dose on W1D1 and W9D1. The PK concentration at each time point is not an endpoint in the protocol, but these concentrations are used to derive the PK parameters.

End point type	Secondary

End point timeframe:

Week 1 Day 1,Week 9 Day 1

End point values	LDE225-400	LDE225-800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	32		
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Week 1 Day 1	0 (± 0)	3110 (± 2620)		
Week 9 Day 1 (n: 7, 6)	26500 (± 6650)	24000 (± 11500)		

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 L:ast Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	LDE225 800 mg QD

Reporting group description:

LDE225 800 mg QD

Reporting group title	LDE225 400 mg BID in the first two weeks, then 800 QD

Reporting group description:

LDE225 400 mg BID in the first two weeks, then 800 QD

Serious adverse events	LDE225 800 mg QD	LDE225 400 mg BID in the first two weeks, then 800 QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 34 (73.53%)	25 / 35 (71.43%)	
number of deaths (all causes)	16	13	
number of deaths resulting from adverse events	0	0	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOGLOBIN BLOOD INCREASED			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			

subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKAEMIC INFILTRATION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
DYSGEUSIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

QUADRIPLEGIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	7 / 34 (20.59%)	9 / 35 (25.71%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 1	
LEUKOCYTOSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	1 / 34 (2.94%)	4 / 35 (11.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PYREXIA			
subjects affected / exposed	4 / 34 (11.76%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC HAEMORRHAGE			

subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GINGIVAL HYPERTROPHY			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL ULCER			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IDIOPATHIC PNEUMONIA SYNDROME			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL INFLAMMATION			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (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 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE SPASMS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOPATHY			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS INFECTIVE			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIAL INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPIGLOTTITIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	3 / 34 (8.82%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
SEPSIS			
subjects affected / exposed	4 / 34 (11.76%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID OVERLOAD			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LDE225 800 mg QD	LDE225 400 mg BID in the first two weeks, then 800 QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	35 / 35 (100.00%)	
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
HYPERTENSION			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
CHILLS			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	

FATIGUE			
subjects affected / exposed	10 / 34 (29.41%)	8 / 35 (22.86%)	
occurrences (all)	15	9	
FEELING COLD			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	3 / 34 (8.82%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
MALAISE			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
OEDEMA PERIPHERAL			
subjects affected / exposed	5 / 34 (14.71%)	4 / 35 (11.43%)	
occurrences (all)	5	4	
PAIN			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
PYREXIA			
subjects affected / exposed	10 / 34 (29.41%)	7 / 35 (20.00%)	
occurrences (all)	11	9	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 34 (11.76%)	3 / 35 (8.57%)	
occurrences (all)	6	3	
DYSPNOEA			
subjects affected / exposed	6 / 34 (17.65%)	7 / 35 (20.00%)	
occurrences (all)	8	9	
EPISTAXIS			
subjects affected / exposed	3 / 34 (8.82%)	4 / 35 (11.43%)	
occurrences (all)	3	4	
OROPHARYNGEAL PAIN			

subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
PRODUCTIVE COUGH			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 34 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	4	
CONFUSIONAL STATE			
subjects affected / exposed	0 / 34 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	4	
INSOMNIA			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	7 / 34 (20.59%)	8 / 35 (22.86%)	
occurrences (all)	9	9	
BLOOD CREATININE INCREASED			
subjects affected / exposed	5 / 34 (14.71%)	1 / 35 (2.86%)	
occurrences (all)	6	1	
BLOOD MAGNESIUM DECREASED			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
MYOGLOBIN BLOOD INCREASED			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
PLATELET COUNT DECREASED			

subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	5	3	
WEIGHT DECREASED			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 34 (14.71%)	2 / 35 (5.71%)	
occurrences (all)	7	2	
DYSGEUSIA			
subjects affected / exposed	5 / 34 (14.71%)	3 / 35 (8.57%)	
occurrences (all)	5	3	
HEADACHE			
subjects affected / exposed	5 / 34 (14.71%)	3 / 35 (8.57%)	
occurrences (all)	9	3	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 34 (17.65%)	5 / 35 (14.29%)	
occurrences (all)	8	6	
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 34 (5.88%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
LEUKOCYTOSIS			
subjects affected / exposed	4 / 34 (11.76%)	1 / 35 (2.86%)	
occurrences (all)	5	1	

LEUKOPENIA			
subjects affected / exposed	3 / 34 (8.82%)	2 / 35 (5.71%)	
occurrences (all)	4	4	
NEUTROPENIA			
subjects affected / exposed	2 / 34 (5.88%)	3 / 35 (8.57%)	
occurrences (all)	2	4	
THROMBOCYTOPENIA			
subjects affected / exposed	5 / 34 (14.71%)	7 / 35 (20.00%)	
occurrences (all)	7	7	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	3 / 34 (8.82%)	4 / 35 (11.43%)	
occurrences (all)	3	5	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
APHTHOUS STOMATITIS			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
CONSTIPATION			
subjects affected / exposed	8 / 34 (23.53%)	6 / 35 (17.14%)	
occurrences (all)	9	6	
DIARRHOEA			
subjects affected / exposed	8 / 34 (23.53%)	7 / 35 (20.00%)	
occurrences (all)	11	8	
DYSPEPSIA			
subjects affected / exposed	3 / 34 (8.82%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
DYSPHAGIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
GINGIVAL BLEEDING			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
HAEMORRHOIDS			

subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
MOUTH HAEMORRHAGE			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
MOUTH ULCERATION			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
NAUSEA			
subjects affected / exposed	10 / 34 (29.41%)	11 / 35 (31.43%)	
occurrences (all)	12	12	
ORAL DISORDER			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
ORAL PAIN			
subjects affected / exposed	3 / 34 (8.82%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
VOMITING			
subjects affected / exposed	12 / 34 (35.29%)	7 / 35 (20.00%)	
occurrences (all)	13	8	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
NIGHT SWEATS			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
PETECHIAE			
subjects affected / exposed	6 / 34 (17.65%)	1 / 35 (2.86%)	
occurrences (all)	8	1	
RASH			
subjects affected / exposed	2 / 34 (5.88%)	4 / 35 (11.43%)	
occurrences (all)	3	4	
SKIN LESION			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	

Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	2 / 34 (5.88%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
BONE PAIN			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
MUSCLE SPASMS			
subjects affected / exposed	5 / 34 (14.71%)	8 / 35 (22.86%)	
occurrences (all)	5	9	
MUSCULAR WEAKNESS			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
MYALGIA			
subjects affected / exposed	8 / 34 (23.53%)	4 / 35 (11.43%)	
occurrences (all)	9	5	
MYOPATHY			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
PAIN IN EXTREMITY			
subjects affected / exposed	4 / 34 (11.76%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Infections and infestations			
INFECTION			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
NASOPHARYNGITIS			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	1	

ORAL HERPES			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
SKIN INFECTION			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 34 (5.88%)	1 / 35 (2.86%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	5 / 34 (14.71%)	7 / 35 (20.00%)	
occurrences (all)	7	7	
HYPERKALAEMIA			
subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 34 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	4	
HYPOKALAEMIA			
subjects affected / exposed	6 / 34 (17.65%)	4 / 35 (11.43%)	
occurrences (all)	7	4	
HYPOMAGNESAEMIA			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2013	This amendment included the following changes in the protocol: Updated the eligibility criteria to add the exclusion of patients who are potentially eligible; for salvage allogenic stem cell transplant; a provision to stop recruitment in the study during the conduct of IA was added; a provision to keep the clinical trial team blinded was removed; PFS was replaced with event-free survival to be consistent with the International Working Group for AML.
07 July 2014	This amendment included the following changes in the protocol: Deletion of the post-treatment follow-up, and survival follow-up from the study design; addition that bone marrow assessment for patients, who remain in the study after IA, were performed every other month until the discontinuation of sonidegib; revision that the final analysis of the study will be performed after all patients who are on the study have either been placed in a roll-over protocol or discontinued treatment due to death, disease progression/treatment failure, withdrawal of consent or lost to follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 34 of the 35 patients in the LDE225 800 mg once daily arm received at least dose of study drug were analyzed for safety.

Notes: