Clinical trial results:
A Phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma

EMA directed use of 999999 as the EU results system will not accept “not estimable”.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2010-022629-14
Trial protocol	DE BE GR GB ES NL HU IT
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	CLDE225A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01327053
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of sonidegib as measured by the objective response rate (ORR).

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	20 July 2011
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: 12
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	230
EEA total number of subjects	122

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)	105
From 65 to 84 years	125
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomization was stratified across the two treatment arms according to the stage of disease (laBCC or mBCC), histological subtype (non-aggressive or aggressive for laBCC patients) and the regions (Australia, Europe, and North America).

Pre-assignment

Screening details:

All eligible, enrolled patients were randomized in 1:2 ratio to sonidegib treatment with either 200 mg or 800 mg once-daily dose. In total, 230 patients were evaluated as FAS population: 79 and 151 patients randomized to 200mg and 800 mg sonidegib respectively. However, 1 patient randomized to 800 mg sonidegib did not receive study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LDE225 (sonidegib) 200 mg

Arm description:

The study is double blinded and will enroll at least 50 evaluable patients in the 200 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

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 was administered orally, on a continuous once-daily schedule, at a dose of 200 mg. The 200-mg arm received 1 sonidegib capsule+3 placebo capsules.

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

Dosage and administration details:

Sonidegib placebo was administered orally, on a continuous once-daily schedule, at a dose of 200 mg. The 200-mg arm received 1 sonidegib capsule+3 placebo capsules. Placebo was formulated to be indistinguishable from the sonidegib capsules.

Arm title	LDE225 (sonidegib) 800 mg

Arm description:

The study is double blinded and will enroll at least 100 evaluable patients in the 800 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

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 was administered orally, on a continuous once-daily schedule, at a dose of 800 mg. The 800-mg arm received 4 capsules of sonidegib.

Number of subjects in period 1	LDE225 (sonidegib) 200 mg	LDE225 (sonidegib) 800 mg
Started	79	151
Untreated	0	1
Patients cont. to next phase of trial	52	89
Survival follow-up	33	49
Post-tretment follow-up	19	40
Completed	0	0
Not completed	79	151
Adverse event, serious fatal	1	5
Physician decision	10	14
Study terminated by Sponsor	1	3
Adverse event, non-fatal	23	57
Non-compliance with study treatment	-	5
Untreated	-	1
Patient/guardian decision	11	35
Lost to follow-up	2	4
Progressive disease	31	26
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LDE225 (sonidegib) 200 mg

Reporting group description:

The study is double blinded and will enroll at least 50 evaluable patients in the 200 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Reporting group title	LDE225 (sonidegib) 800 mg

Reporting group description:

The study is double blinded and will enroll at least 100 evaluable patients in the 800 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Reporting group values	LDE225 (sonidegib) 200 mg	LDE225 (sonidegib) 800 mg	Total
Number of subjects	79	151	230
Age categorical Units: Subjects			
Adults (18-64 years)	32	73	105
From 65-84 years	38	67	105
85 years and over	9	11	20
Age Continuous Units: Years			
arithmetic mean	65.6	63.6	
standard deviation	± 15.67	± 14.59	-
Sex: Female, Male Units: Subjects			
Female	31	55	86
Male	48	96	144
Race/Ethnicity, Customized Units: Subjects			
Black	0	1	1
Caucasian	71	145	216
Other	8	5	13

End points

End points reporting groups

Reporting group title	LDE225 (sonidegib) 200 mg

Reporting group description:

The study is double blinded and will enroll at least 50 evaluable patients in the 200 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Reporting group title	LDE225 (sonidegib) 800 mg

Reporting group description:

The study is double blinded and will enroll at least 100 evaluable patients in the 800 mg LDE225 arm. The efficacy and safety of LDE225 will be analyzed separately in each group. Patients who meet all the inclusion and none of the exclusion criteria will be treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 200mg laBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 200mg laBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 800mg laBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 800mg laBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 200mg mBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 200mg mBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 800mg mBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 800mg mBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 200mg laBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 200mg laBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 800mg laBCC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The efficacy and safety of LDE225 800mg laBCC cohort were analyzed separately in each group. Patients who met all the inclusion and none of the exclusion criteria were treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or

withdrawal of consent.

Subject analysis set title	LDE225 200 mg qd
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who met all the inclusion and none of the exclusion criteria were treated with 200 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Subject analysis set title	LDE225 800 mg qd
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who met all the inclusion and none of the exclusion criteria were treated with 800 mg LDE225 daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawal of consent.

Primary: Objective response rate (ORR) based on Central Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (for metastatic basal cell carcinoma (mBCC)) per Primary efficacy analysis set (pEAS)

End point title	Objective response rate (ORR) based on Central Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (for metastatic basal cell carcinoma (mBCC)) per Primary efficacy analysis set (pEAS)[1]

End point description:

ORR is the percentage of patient's objective response (ORR) by 6 months after starting LDE225 treatment. A responder was defined as a subject with confirmed partial response (PR) or confirmed complete response (CR) 6 months after starting LDE225 treatment.Treatment with sonidegib was considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study was 30% or higher. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Primary

End point timeframe:

6 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 endpoint.

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
number (confidence interval 95%)	42.9 (27.7 to 59.0)	37.6 (27.8 to 48.3)	15.4 (1.9 to 45.4)	17.4 (5.0 to 38.8)

Statistical analyses

No statistical analyses for this end point

Primary: Objective response rate (ORR) based on Central Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (metastatic basal cell carcinoma (mBCC)) per Full Analysis Set (FAS)

End point title	Objective response rate (ORR) based on Central Review according to mRECIST (for locally advanced basal cell

	carcinoma (laBCC)) and RECIST 1.1 (metastatic basal cell carcinoma (mBCC)) per Full Analysis Set (FAS)[2]

End point description:

ORR is the percentage of patient's objective response (ORR) by 6 months after starting LDE225 treatment. A responder was defined as a subject with confirmed partial response (PR) or confirmed complete response (CR) 6 months after starting LDE225 treatment.Treatment with sonidegib was to be considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study was 30% or higher. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Primary

End point timeframe:

6 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 endpoint.

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Percentage of participants				
number (confidence interval 95%)	15.4 (1.9 to 45.4)	17.4 (5.0 to 38.8)	47.0 (34.6 to 59.7)	35.2 (26.9 to 44.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per Central Review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Duration of response (DoR) per Central Review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Duration of response is the time from the first observed confirmed response (CR or PR) to disease progression or death due to any reason. Duration of response was for participants with ORR. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. Progressive disease (PD): At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm2.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Months				
median (confidence interval 95%)	12.9 (9.99 to 999)	23.7 (10.8 to 29.6)	24.0 (9.99 to 999)	999 (9.99 to 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per Central Review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point title	Duration of response (DoR) per Central Review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point description:

Duration of response is the time from the first observed confirmed response (CR or PR) to disease progression or death due to any reason. Median DoR for patients with laBCC was non-estimable for both treatment arms. Median DoR was non-estimable for patients with mBCC receiving treatment with sonidegib 200 mg. Duration of response was for participants with ORR. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Months				
median (confidence interval 95%)	24.0 (9.9 to 999)	999 (999 to 999)	26.1 (9.9 to 999)	23.3 (12.2 to 29.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response rate (CRR) per Central Review (pEAS)

End point title	Complete response rate (CRR) per Central Review (pEAS)

End point description:

Rate of complete response is the percentage of patients with best overall response of complete response (CR) after starting LDE225 treatment. The rate of CR was determined according to mRECIST for laBCC and RECIST 1.1 for mBCC. Patients with best overall response of 'Unknown" were treated as non responders. Complete Response (CR): Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
number (confidence interval 95%)	4.8 (0.6 to 16.2)	2.2 (0.3 to 7.6)	0.0 (0.0 to 24.7)	0.0 (0.0 to 14.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response rate (CRR) per Central Review (FAS)

End point title	Complete response rate (CRR) per Central Review (FAS)

End point description:

Rate of complete response is the proportion of patients with best overall response of complete response (CR) after starting LDE225 treatment. The rate of CR will be determined according to mRECIST for laBCC and RECIST 1.1 for mBCC. Patients with best overall response of 'Unknown" will be treated as non responders

End point type	Secondary

End point timeframe:

6 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 24.7)	0.0 (0.0 to 14.8)	3.0 (0.4 to 10.5)	0.0 (0.0 to 2.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Progression-free survival (PFS) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
median (confidence interval 95%)	19.0 (9.9 to 999)	19.4 (13.8 to 30.5)	13.1 (5.6 to 33.1)	11.1 (7.3 to 16.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point title	Progression-free survival (PFS) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point description:

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Percentage of participants				
median (confidence interval 95%)	13.1 (5.6 to 33.1)	11.1 (7.3 to 16.6)	22.1 (9.9 to 999)	24.9 (19.2 to 33.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Time to tumor response (TTR) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Time to tumor response (TTR) is defined as the time from date of enrollment to the date of first documented tumor response (CR or PR). PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
median (confidence interval 95%)	4.0 (3.7 to 5.6)	3.7 (2.0 to 5.5)	9.2 (9 to 999)	1.0 (1.0 to 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point title	Time to tumor response (TTR) per Central review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point description:

Time to tumor response (TTR) is defined as the time from date of enrollment to the date of first documented tumor response (CR or PR). PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
median (confidence interval 95%)	4.0 (3.7 to 5.6)	3.7 (2.0 to 5.5)	9.2 (9 to 999)	1.0 (1.0 to 2.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) based on Site Investigator Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (for metastatic basal cell carcinoma (mBCC)) per Primary efficacy analysis set (pEAS)

End point title	Objective response rate (ORR) based on Site Investigator Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (for metastatic basal cell carcinoma (mBCC)) per Primary efficacy analysis set (pEAS)

End point description:

ORR is the percentage of patient's objective response (ORR) by 42 months after starting LDE225 treatment. A responder was defined as a subject with confirmed partial response (PR) or confirmed complete response (CR) 42 months after starting LDE225 treatment. Treatment with sonidegib was considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study was 30% or higher. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
number (confidence interval 95%)	71.4 (55.4 to 84.3)	61.3 (50.6 to 71.2)	23.1 (5.0 to 53.8)	34.8 (16.4 to 57.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) based on Site Investigator Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (metastatic basal cell carcinoma (mBCC)) per Full Analysis Set (FAS)

End point title	Objective response rate (ORR) based on Site Investigator Review according to mRECIST (for locally advanced basal cell carcinoma (laBCC)) and RECIST 1.1 (metastatic basal cell carcinoma (mBCC)) per Full Analysis Set (FAS)

End point description:

ORR is the percentage of patient's objective response (ORR) by 6 months after starting LDE225 treatment. A responder was defined as a subject with confirmed partial response (PR) or confirmed complete response (CR) 42 months after starting LDE225 treatment.Treatment with sonidegib was to be considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study was 30% or higher. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Percentage of participants				
number (confidence interval 95%)	23.1 (5.0 to 53.8)	34.8 (16.4 to 57.3)	71.2 (58.7 to 81.7)	58.6 (49.6 to 67.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per Site Investigator Review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Duration of response (DoR) per Site Investigator Review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Duration of response is the time from the first observed confirmed response (CR or PR) to disease progression or death due to any reason. Duration of response was for participants with ORR. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. Progressive disease (PD): At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm2.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Months				
median (confidence interval 95%)	18.2 (12.9 to 23.0)	26.0 (15.7 to 47.3)	18.1 (17.7 to 18.4)	10.2 (9.9 to 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) per Site Investigatorl Review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point title	Duration of response (DoR) per Site Investigatorl Review using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS)

End point description:

Duration of response is the time from the first observed confirmed response (CR or PR) to disease progression or death due to any reason. Median DoR for patients with laBCC was non-estimable for both treatment arms. Median DoR was non-estimable for patients with mBCC receiving treatment with sonidegib 200 mg. Duration of response was for participants with ORR. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Months				
median (confidence interval 95%)	18.1 (17.7 to 18.4)	10.2 (9.9 to 999)	15.7 (12.0 to 20.2)	26.0 (18.3 to 47.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) per Site Investigator review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Progression-free survival (PFS) per Site Investigator review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
median (confidence interval 95%)	20.1 (14.8 to 23.8)	28.0 (19.4 to 49.8)	13.1 (9.2 to 19.4)	14.3 (11.1 to 17.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tumor response (TTR) per Site Investigator review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point title	Time to tumor response (TTR) per Site Investigator review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

End point description:

Time to tumor response (TTR) is defined as the time from date of enrollment to the date of first documented tumor response (CR or PR). PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg laBCC	LDE225 800mg laBCC	LDE225 200mg mBCC	LDE225 800mg mBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	93	13	23
Units: Percentage of participants				
median (confidence interval 95%)	1.9 (1.8 to 3.9)	1.8 (1.1 to 2.0)	1.0 (0.9 to 3.7)	2.7 (1.0 to 5.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of sonidegib (LDE225)

End point title	Plasma Concentration of sonidegib (LDE225)

End point description:

Blood PK samples were collected either by direct venipuncture or an indwelling cannula inserted in a forearm vein for the determination of trough (Cmin) plasma concentrations of sonidegib and its main circulating metabolite, LGE899, from all patients who enrolled in the study. Blood was collected in

Weeks 1, 3, 5, 9 (pre-dose), and subsequently pre-dose every 4 weeks up to Week 21, and every 12 weeks thereafter up to week 69.

End point type	Secondary

End point timeframe:

Weeks 1, 3, 5, 9, 13, 17, 21, 33, 45, 57, 69

End point values	LDE225 200 mg qd	LDE225 800 mg qd		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	139		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 1 (n = 0, 0)	0 (± 0)	0 (± 0)		
Week 3 (n = 66, 128)	209.91 (± 78.24)	586.76 (± 97.13)		
Week 5 (n = 71, 120)	374.24 (± 68.50)	1012.63 (± 70.42)		
Week 9 (n = 68, 101)	559.29 (± 67.30)	1353.06 (± 63.43)		
Week 13 (n = 63, 85)	714.01 (± 60.79)	1443.84 (± 61.57)		
Week 17 (n = 66, 81)	688.93 (± 64.43)	1594.28 (± 60.77)		
Week 21 (n = 59, 68)	713.13 (± 63.35)	1564.10 (± 64.08)		
Week 33 (n = 43, 43)	663.48 (± 96.19)	1562.73 (± 79.20)		
Week 45 (n = 22, 27)	711.32 (± 46.54)	1433.13 (± 76.91)		
Week 57 (n = 13, 17)	525.53 (± 86.24)	1328.04 (± 69.47)		
Wek 69 (n = 6, 11)	459.10 (± 188.64)	1185.95 (± 118.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from date of randomization t date of death due to any cause or the last date that a patient was known to be alive (censored observation) as of the data cut-off.

End point type	Secondary

End point timeframe:

42 months

End point values	LDE225 200mg mBCC	LDE225 800mg mBCC	LDE225 200mg laBCC	LDE225 800mg laBCC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	23	66	128
Units: Participants	1	2	1	7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 76.2 months.

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	19.1

Reporting groups

Reporting group title	LDE225 200 mg qd
Reporting group description:	
LDE225 200 mg qd	
Reporting group title	LDE225 800 mg qd
Reporting group description:	
LDE225 800 mg qd	

Serious adverse events	LDE225 200 mg qd	LDE225 800 mg qd	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 79 (20.25%)	58 / 150 (38.67%)	
number of deaths (all causes)	1	7	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			

subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive papillary breast carcinoma			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial pain			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Uterine prolapse			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 79 (1.27%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinorrhoea			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sputum discoloured			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 79 (1.27%)	6 / 150 (4.00%)	
occurrences causally related to treatment / all	1 / 1	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoglobin blood increased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgeusia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 79 (1.27%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 79 (0.00%)	5 / 150 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Chronic gastritis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			

subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 79 (0.00%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer perforation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 79 (0.00%)	4 / 150 (2.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle contracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 79 (1.27%)	5 / 150 (3.33%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 79 (2.53%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonas infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			

subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Superinfection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
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	1 / 79 (1.27%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 79 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 79 (1.27%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 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 200 mg qd	LDE225 800 mg qd	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 79 (96.20%)	145 / 150 (96.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	4 / 79 (5.06%)	5 / 150 (3.33%)	
occurrences (all)	4	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 79 (10.13%)	16 / 150 (10.67%)	
occurrences (all)	11	18	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 79 (12.66%)	9 / 150 (6.00%)	
occurrences (all)	14	12	
Fatigue			
subjects affected / exposed	26 / 79 (32.91%)	55 / 150 (36.67%)	
occurrences (all)	31	70	
Pyrexia			
subjects affected / exposed	4 / 79 (5.06%)	5 / 150 (3.33%)	
occurrences (all)	5	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 79 (8.86%)	11 / 150 (7.33%)	
occurrences (all)	8	14	
Oropharyngeal pain			
subjects affected / exposed	4 / 79 (5.06%)	6 / 150 (4.00%)	
occurrences (all)	6	6	
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 79 (6.33%)	9 / 150 (6.00%)	
occurrences (all)	6	9	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	23 / 79 (29.11%)	54 / 150 (36.00%)	
occurrences (all)	29	74	

Lipase increased			
subjects affected / exposed	6 / 79 (7.59%)	13 / 150 (8.67%)	
occurrences (all)	12	19	
Weight decreased			
subjects affected / exposed	24 / 79 (30.38%)	64 / 150 (42.67%)	
occurrences (all)	25	70	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 79 (6.33%)	5 / 150 (3.33%)	
occurrences (all)	6	6	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 79 (1.27%)	15 / 150 (10.00%)	
occurrences (all)	1	15	
Dizziness			
subjects affected / exposed	7 / 79 (8.86%)	15 / 150 (10.00%)	
occurrences (all)	7	21	
Dysgeusia			
subjects affected / exposed	35 / 79 (44.30%)	89 / 150 (59.33%)	
occurrences (all)	38	99	
Headache			
subjects affected / exposed	12 / 79 (15.19%)	20 / 150 (13.33%)	
occurrences (all)	15	51	
Hypogeusia			
subjects affected / exposed	0 / 79 (0.00%)	9 / 150 (6.00%)	
occurrences (all)	0	9	
Paraesthesia			
subjects affected / exposed	4 / 79 (5.06%)	6 / 150 (4.00%)	
occurrences (all)	4	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 79 (5.06%)	13 / 150 (8.67%)	
occurrences (all)	4	20	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 79 (0.00%)	11 / 150 (7.33%)	
occurrences (all)	0	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 79 (10.13%)	9 / 150 (6.00%)	
occurrences (all)	8	12	
Abdominal pain upper			
subjects affected / exposed	7 / 79 (8.86%)	12 / 150 (8.00%)	
occurrences (all)	9	15	
Constipation			
subjects affected / exposed	6 / 79 (7.59%)	24 / 150 (16.00%)	
occurrences (all)	7	27	
Diarrhoea			
subjects affected / exposed	25 / 79 (31.65%)	34 / 150 (22.67%)	
occurrences (all)	43	46	
Dry mouth			
subjects affected / exposed	4 / 79 (5.06%)	8 / 150 (5.33%)	
occurrences (all)	4	8	
Nausea			
subjects affected / exposed	31 / 79 (39.24%)	71 / 150 (47.33%)	
occurrences (all)	45	106	
Vomiting			
subjects affected / exposed	9 / 79 (11.39%)	41 / 150 (27.33%)	
occurrences (all)	14	63	
Dyspepsia			
subjects affected / exposed	7 / 79 (8.86%)	10 / 150 (6.67%)	
occurrences (all)	9	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	39 / 79 (49.37%)	87 / 150 (58.00%)	
occurrences (all)	41	91	
Pruritus			
subjects affected / exposed	6 / 79 (7.59%)	12 / 150 (8.00%)	
occurrences (all)	7	12	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 79 (16.46%)	17 / 150 (11.33%)	
occurrences (all)	16	20	
Back pain			
subjects affected / exposed	6 / 79 (7.59%)	16 / 150 (10.67%)	
occurrences (all)	6	18	
Muscle spasms			
subjects affected / exposed	43 / 79 (54.43%)	104 / 150 (69.33%)	
occurrences (all)	66	189	
Muscular weakness			
subjects affected / exposed	4 / 79 (5.06%)	8 / 150 (5.33%)	
occurrences (all)	4	10	
Musculoskeletal pain			
subjects affected / exposed	4 / 79 (5.06%)	7 / 150 (4.67%)	
occurrences (all)	4	7	
Myalgia			
subjects affected / exposed	15 / 79 (18.99%)	42 / 150 (28.00%)	
occurrences (all)	18	53	
Pain in extremity			
subjects affected / exposed	5 / 79 (6.33%)	8 / 150 (5.33%)	
occurrences (all)	6	8	
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 79 (5.06%)	8 / 150 (5.33%)	
occurrences (all)	4	8	
Nasopharyngitis			
subjects affected / exposed	8 / 79 (10.13%)	17 / 150 (11.33%)	
occurrences (all)	13	25	
Pneumonia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 150 (2.00%)	
occurrences (all)	4	3	
Upper respiratory tract infection			
subjects affected / exposed	5 / 79 (6.33%)	11 / 150 (7.33%)	
occurrences (all)	5	12	
Urinary tract infection			

subjects affected / exposed occurrences (all)	7 / 79 (8.86%) 19	7 / 150 (4.67%) 15	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 18 / 79 (22.78%) 24	 52 / 150 (34.67%) 57	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2011	Wording on contraceptive precautions updated: Wording on contraceptive precautions updated To ensure compliance with the UK Guideline of Prevention of Pregnancies in Participants in Clinical Trials
17 November 2011	- Inclusion criteria modified to clarify eligible patient population: Reasons for ineligibility for local therapies or curative surgery to be collected. - Central histopathological analysis implemented: Initiated for confirmation of diagnosis and eligibility (NB: as a result, a majority of laBCC patients enrolled prior to this ineligible for analysis of ORR per mRECIST) - Central histopathological analysis implemented: Initiated for confirmation of diagnosis and eligibility (NB: as a result, a majority of laBCC patients enrolled prior to this ineligible for analysis of ORR per mRECIST) - Sample size increased from 80 to 100 in 800-mg arm and from 40 to 50 in the 200-mg arm: To collect additional safety and efficacy data - Criteria for assessing ORR amended from RECIST 1.1 to mRECIST for patients with laBCC: Tumor response assessment in patients with laBCC when associated with ulceration, cysts, and scarring/fibrosis are not adequately covered by RECIST 1.1 - Implementation of central reading for determination of primary endpoint: To obtain more robust conclusions
23 November 2011	Patients experiencing asymptomatic treatment-emergent grade 1 CK elevation to undergo weekly monitoring until resolution: To satisfy local regulatory requirements in France
28 June 2012	- Introduction of primary efficacy analysis set (pEAS): mRECIST implemented in Amendment 2; consequently, a majority of patients with laBCC enrolled prior to this may not have been eligible for analysis of ORR per mRECIST. The pEAS defined a subset of the full analysis set (FAS) and excluded laBCC patients who were not eligible for tumor assessment per mRECIST. - Sample size further expanded to approximately 210 patients: To ensure a sufficient number of patients in the pEAS (i.e. 50 patients on 200 mg and 100 patients on 800 mg)
03 June 2013	Statistical analysis for secondary endpoints updated: Allowed ORR according to RECIST 1.1 to be derived for central review data by MRI and photography independently without lesion matching between MRI/photograph and lesions
14 November 2013	Institution of Independent Review Committee to integrate MRI, photography, and histology data to assess composite overall response: To provide clarification on how the 3 methods of assessment per mRECIST (MRI, color photography, and histology) were to be integrated to determine the composite overall response for patients with laBCC
04 April 2014	Extension of study duration by further 104 weeks to enable collection of long-term efficacy and safety data: Results of the primary analysis (obtained in Feb-2014) showed both the 200-mg and 800-mg doses to be efficacious and to provide clinical benefit. Data also indicated that both doses were associated with acceptable safety profiles. The IDMC and SSC recommended that the study should continue without change.
24 February 2015	Updated language regarding the Independent Data Monitoring Committee: To provide clarification regarding the composition of the IDMC.

16 March 2016	Extension of study treatment for patients receiving clinical benefit post final efficacy analysis: Extension of study treatment for patients receiving clinical benefit post final efficacy analysis: Allowed patients on treatment (post Week 182 following last patient first treatment [LPFT]) who are deriving clinical benefit to continue to receive LDE225 until disease progression, intolerable toxicity, death, or withdrawal of consent. As a result, the visit evaluation schedule and study assessments were modified to be performed according to standard clinical practices post Week 182 following LPFT.

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.

230 patients evaluated in the study in the Full Analysis Set: 79 randomized to LDE225 (Sonidegib) 200mg group and 151 randomized to LDE225 800mg group. 1 patient randomized to the 800mg group did not receive study treatment.

Notes: