Sponsor

Novartis

Generic Drug Name

Sonidegib

Trial Indication(s)

Advanced solid tumor

Protocol Number

CLDE225X1101

Protocol Title

An East Asian phase I, multicenter, open-label, dose-escalation study of oral LDE225 in patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

Study Start/End Dates

27-Oct-2010 to 10-Oct-2013

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was a phase I dose-escalation study of LDE225 administered orally in a 28-day cycle to adult East Asian patients (i.e., Japanese patients in Japan and Chinese/Taiwanese patients in Hong Kong and Taiwan) with advanced solid tumors that had progressed despite standard therapy or for which no standard therapy exists. Patients with locally advanced, multifocal or metastatic basal cell carcinoma (BCC) were also eligible for this study, as were adult patients with recurrent medulloblastoma (MB).

Preceding a treatment period consisting of continuous oral treatment of LDE225 in a 28-day cycle, a 7-day pharmacokinetics (PK) run-in period was conducted in order to characterize the PK profile of LDE225 following a single oral dose.

Patients were separated into 2 groups to determine the maximum tolerated dose (MTD) and recommended phase II dose of each patient group.

- Group 1: Japanese patients who were enrolled in Japan
- Group 2: Chinese/Taiwanese patients who were enrolled in Hong Kong and/or Taiwan

A Bayesian logistic regression model (BLRM) using escalation with overdose control (EWOC) guided dose-escalation to determine the MTD, and the BLRM was applied separately in each patient group to assess the potential for ethnic differences. LDE225 400 mg quaque die (q.d.) was the initial dose of this study. Subsequent dose levels were decided at dose-escalation meetings.

Centers

Four centers in 3 countries: Hong Kong (1), Japan (2), and Taiwan (1).

Publication

None.

Objectives:

Primary objectives

- To determine the MTD and recommended phase II dose of single agent LDE225 when administered orally to adult Japanese patients with advanced solid tumors
- To determine the MTD and recommended phase II dose of single agent LDE225 when administered orally to adult Chinese/Taiwanese patients with advanced solid tumors

Secondary objectives

The following secondary objectives were assessed in both Japanese and Chinese/Taiwanese patients:

- To characterize the safety and tolerability of LDE225
- To characterize the PK of single and repeated doses of LDE225 and its metabolite(s), if possible
- To assess any preliminary anti-tumor activity (overall response rate) with LDE225 treatment
- To characterize the pharmacodynamics (PD) effects of LDE225 by measuring Gli1 expression in surrogate tissue (normal skin) and tumor samples (when available)

Test Product (s), Dose(s), and Mode(s) of Administration

Oral capsules of sonidegib 50 mg, 100 mg and 250 mg, once each morning after a light breakfast and a 2-hour fast.

Statistical Methods

The MTD was based upon the dose-determining set (DDS), which consisted of all patients from the safety set who either met the minimum exposure criterion and had sufficient safety evaluations, or discontinued earlier due to DLT in the 7-day PK run-in period or cycle 1. The minimum treatment and safety evaluation requirements had been met if, in cycle 1, the patient had been treated with LDE225 for $\geq$ 75% of the planned dose following the cycle 1 day 1 doses, and had completed all required safety evaluation for cycle 1, including assessments intended for cycle 2 day 1.

The statistical model for the dose-escalation within each group was based on a 2-parameter BLRM. Following the principle of dose EWOC, a recommended phase II dose or MTD was declared. The dose recommended by the adaptive BLRM was regarded as information to be integrated with a clinical assessment of the toxicity profiles, PK, PD, and other data observed thus far in determining the next dose to be investigated.

Objective response rate and the duration of overall response (Complete response or partial response), as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (local investigator's assessment), was listed by treatment group. Full analysis set (FAS) was used at the intended dose.

The assessment of safety was based on the type and frequency of adverse events, and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., Electrocardiogram [ECG], vital signs, and special tests) was considered as appropriate. Safety set were used.

Pharmacokinetic parameters in plasma were determined using non-compartmental method using Phoenix WinNonlin (Version 6.2 - Pharsight, Mountain View, CA). The single dose and multiple dose PK parameters such as AUClast, AUC0-24, AUCtau, Cmax and Tmax were estimated and reported.

Biomarker summary statistics (including changes from baseline and/or percentage change from baseline) by dose level were provided. Individual data, time-course of marker levels, descriptive and exploratory statistics were displayed in tables, figures or listings, as appropriate.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients eligible for inclusion in this study had to meet **all** of the following criteria:

1. Histologically or cytologically confirmed diagnosis of an advanced solid tumor (including locally advanced, multifocal or metastatic BCC, and recurrent MB) that have progressed despite standard therapy or for which no standard therapy exists. Inclusion is irrespective of stage of disease or extent of prior therapy

2. **(For patients with MB only)** Patients with recurrent MB who are taking corticosteroids should be on a non-increasing dose of steroids for at least 14 days prior to starting study drug
3. Patients with age: ≥ 18 years in Hong Kong and Taiwan, ≥ 20 years in Japan
4. World Health Organization (WHO) performance status ≤ 2
5. Patients must have measurable or evaluable disease as measured by RECIST version 1.0
6. Life expectancy of at least 3 months
7. Patients must have the following laboratory values:
   - Absolute neutrophil count ≥ 1,500/mm^3
   - Hemoglobin ≥ 9 g/dL
   - Platelets ≥ 100,000/mm^3
   - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN)
   - AST and ALT ≤ 2.5 x ULN or ≤ 5.0 x ULN if liver metastases are present
   - Serum creatinine ≤ 1.5 x ULN
8. Patients must give written informed consent prior to any screening procedure. Computed tomography (CT)/ magnetic resonance imaging (MRI) and echocardiogram (Echo) / multiple uptake gated acquisition (MUGA) scan performed prior to obtaining consent from the patient and within 21 days prior to starting study drug can be used as screening assessments, if available.

Exclusion criteria

Patients eligible for this study had not to meet **any** of the following criteria:

< History/current medical conditions >

1. **(For all patients, excluding patients with MB)** Patients with symptomatic brain metastases or a history of primary central nervous system tumors. However, patients with resected brain metastasis with no radiological evidence of disease or patients with stable brain metastasis with no evidence of progression (as shown by 2 CT or MRI scans spaced at least 3 months apart) are eligible. Such patients must have no need for treatment with steroids or anti-epileptic medications
2. History of a positive human immunodeficiency virus (HIV) test (HIV testing is not mandatory)
3. A positive hepatitis B surface antigen (HBsAg)
4. A positive hepatitis C virus antibody (HCV-Ab) and HCV RNA-PCR
5. Impairment of gastro-intestinal (GI) function or GI disease (e.g., ulcerative disease, uncontrolled nausea, vomiting or diarrhea, malabsorption syndrome or small bowel resection, gastrectomy)
6. Patients who have not recovered from fractures (patients with pathological bone fractures that are not expected to heal/recover [e.g. fractures due to bone metastases] may be

enrolled onto the study at the discretion of the investigator and with agreement from the sponsor)

7. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. uncontrolled diabetes)
8. Peripheral vascular disease requiring active therapy or having had surgery < 12 months prior to starting study drug
9. Impaired cardiac function or clinically significant heart disease, including any one of the following:
    - Angina pectoris within 3 months prior to study treatment
    - Acute myocardial infarction within 3 months prior to study treatment
    - QTcF > 450 msec for males and > 470 msec for females on the screening ECG
    - A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
    - Left ventricular ejection fraction < 45% on the screening MUGA/Echo
    - Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

< Prior therapies >

10. Patients who have received cytotoxic agents or multi-agent chemotherapy within a period of time that is < the cycle length used for that treatment (e.g. < 6 weeks for nitrosoureas, mitomycin-C) prior to starting study drug or who have not recovered from the side effects of such therapy
11. Patients who have received biologic anti-cancer therapy (e.g. antibodies) ≤ 4 weeks prior to starting study drug or who have not recovered from the side effects of such therapy
12. Patients who have been treated with a molecularly targeted therapy for cancer ≤ 5 T1/2 or ≤ 4 weeks (whichever is shorter) prior to starting study drug or who have not recovered from the side effects of such therapy
13. Patients who have received any other investigational agents ≤ 5 T1/2 or ≤ 4 weeks (whichever is shorter) prior to starting study drug or who have not recovered from the side effects of such therapy
14. Patients who have received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
15. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from such therapy

Note: Patients who experience adverse effects that have a prolonged recovery or are not expected to resolve (e.g. alopecia, pigmentation, skin rash) as a result of previous therapy may be enrolled at the discretion of the investigator and agreement of the sponsor, provided that the adverse event has resolved to Grade 1 or stabilization of the event can be confirmed.

< Concomitant medications/therapies >

16. Patients who are receiving treatment with medications that are known to be strong inhibitors or inducers of Cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 with low therapeutic index that cannot be discontinued prior to study entry and for the duration of the study. Medications that are strong CYP3A4/5 inhibitors should be discontinued for at least 2 days and strong CYP3A4/5 inducers for at least 1 week prior to starting study drug.
17. Patients on treatments that are linked with increases CK and/or rhabdomyolysis, such as statins. Such medication should be discontinued at least 2 weeks prior to initiating LDE225 dosing and for the duration of the study.
18. Patients who are currently receiving treatment with therapeutic doses of warfarin who cannot discontinue this treatment at least 5 days prior to starting study drug
19. Patients who are currently receiving immunosuppressive treatment and in whom the treatment cannot be discontinued prior to starting study drug, except in the case of patients with BCC. Immunosuppressive treatment should be discontinued for at least 1 week prior to starting study drug.

< Others >

20. Pregnant or nursing (lactating) women, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using two forms of highly effective contraception (see Appendix 16.1.1-Protocol Amendment 3-Section 4.2) throughout the study and for 6 months after the last treatment.
    In case of use of oral contraception, women should have been stabile for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, is she considered not of child bearing potential.
22. Sexually active male, UNLESS they use a condom during intercourse while taking study drug and for 6 months after stopping LDE225 treatment, and should not father a child in a period. A condom is required to be used also by vasectomized men in order to prevent delivery of the study drug via seminal fluid.
23. Patients unwilling or unable to comply with the protocol

Participant Flow Table

Patient disposition by treatment- Group 1(FAS)

Disposition Reason	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Treatment ongoing	0	0	0
End of treatment	12 (100.0)	9 (100.0)	21 (100.0)
Primary reason for treatment discontinuation			
Adverse Event(s)	2 (16.7)	3 (33.3)	5 (23.8)
Subject withdrew consent	1 (8.3)	0	1 (4.8)
Disease progression	9 (75.0)	6 (66.7)	15 (71.4)
Primary reason for study evaluation completion			
Disease progression	1 (8.3)	1 (11.1)	2 (9.5)
Follow-up phase completed as per protocol	11 (91.7)	8 (88.9)	19 (90.5)

Patient disposition by treatment- Group 2 (FAS)

Disposition Reason	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=8 n (%)	LDE225 800 mg QD N=4 n (%)	All patients N=24 n (%)
Treatment ongoing	0	0	0	0
End of treatment	12 (100.0)	8 (100.0)	4 (100.0)	24 (100.0)
Primary reason for treatment discontinuation				
Adverse Event(s)	1 (8.3)	1 (12.5)	2 (50.0)	4 (16.7)
Subject withdrew consent	1 (8.3)	2 (25.0)	1 (25.0)	4 (16.7)
Disease progression	10 (83.3)	5 (62.5)	1 (25.0)	16 (66.7)
Primary reason for study evaluation completion				
Subject withdrew consent	1 (8.3)	0	0	1 (4.2)
New cancer therapy	2 (16.7)	1 (12.5)	0	3 (12.5)
Disease progression	0	1 (12.5)	0	1 (4.2)
Follow-up phase completed as per protocol	9 (75.0)	6 (75.0)	4 (100.0)	19 (79.2)

Baseline Characteristics

Demographics by treatment- Group 1 (FAS)

	Demographic Variable	LDE225 400 mg QD N=12	LDE225 600 mg QD N=9	All patients N=21
Age (Years)	n	12	9	21
	Mean (SD)	55.2 (14.85)	51.2 (19.85)	53.5 (16.82)

	Demographic Variable	LDE225 400 mg QD N=12	LDE225 600 mg QD N=9	All patients N=21
	Median	62.0	60.0	62.0
	Range (Min-Max)	20.0-67.0	22.0-71.0	20.0-71.0
Age Category (Years)	<65	8 (66.7%)	7 (77.8%)	15 (71.4%)
	≥65	4 (33.3%)	2 (22.2%)	6 (28.6%)
Sex	Male	4 (33.3%)	4 (44.4%)	8 (38.1%)
	Female	8 (66.7%)	5 (55.6%)	13 (61.9%)
Race	Asian	12 (100.0%)	9 (100.0%)	21 (100.0%)
Ethnicity	Japanese	12 (100.0%)	9 (100.0%)	21 (100.0%)
Weight (kg)	n	12	9	21
	Mean (SD)	57.4 (10.34)	56.6 (9.22)	57.1 (9.64)
	Median	55.7	57.2	56.3
	Range (Min-Max)	41.9-72.2	45.5-77.0	41.9-77.0
Height (cm)	n	12	9	21
	Mean (SD)	159.5 (7.74)	159.4 (6.24)	159.5 (6.97)
	Median	158.9	160.9	160.1
	Range (Min-Max)	148.0-171.7	150.4-168.6	148.0-171.7
Body surface area (m^2)*	n	12	9	21
	Mean (SD)	1.6 (0.17)	1.6 (0.15)	1.6 (0.16)
	Median	1.6	1.6	1.6
	Range (Min-Max)	1.3-1.8	1.4-1.9	1.3-1.9
WHO performance status	0	4 (33.3%)	3 (33.3%)	7 (33.3%)
	1	8 (66.7%)	6 (66.7%)	14 (66.7%)

* Body surface area (Gehan and George): BSA (m^2) = 234.94*(height [cm] $^{0.422}$)*(weight [kg] $^{0.515}$)/10000

Demographics by treatment- Group 2 (FAS)

	Demographic Variable	LDE225 400 mg QD N=12	LDE225 600 mg QD N=8	LDE225 800 mg QD N=4	All patients N=24
Age (Years)	n	12	8	4	24
	Mean (SD)	53.2 (12.28)	55.3 (6.67)	47.8 (9.18)	53.0 (10.16)
	Median	55.5	55.5	46.5	53.0
	Range (Min-Max)	31.0-69.0	45.0-63.0	38.0-60.0	31.0-69.0
Age Categoly (Years)	<65	9 (75.0%)	8 (100.0%)	4 (100.0%)	21 (87.5%)
	≥65	3 (25.0%)	0	0	3 (12.5%)
Sex	Male	6 (50.0%)	4 (50.0%)	3 (75.0%)	13 (54.2%)
	Female	6 (50.0%)	4 (50.0%)	1(25.0%)	11 (45.8%)
Race	Asian	12(100.0%)	8 (100.0%)	4 (100.0%)	24 (100.0%)

	Demographic Variable	LDE225 400 mg QD N=12	LDE225 600 mg QD N=8	LDE225 800 mg QD N=4	All patients N=24
Ethnicity	Chinese	12 (100.0%)	8 (100.0%)	4 (100.0%)	24 (100.0%)
Weight (kg)	n	12	8	4	24
	Mean (SD)	58.6 (14.84)	53.6 (14.45)	62.6 (11.86)	57.6 (14.06)
	Median	54.1	51.2	65.2	53.6
	Range (Min-Max)	36.0-79.2	32.9-83.2	46.0-74.0	32.9-83.2
Height (cm)	n	12	8	4	24
	Mean (SD)	163.2 (8.36)	160.5 (9.69)	168.0 (7.07)	163.1 (8.66)
	Median	163.9	156.5	167.9	161.5
	Range (Min-Max)	152.3-177.0	152.7-182.0	161.0-175.0	152.3-182.0
Body surface area (m^2)*	n	12	8	4	24
	Mean (SD)	1.6 (0.25)	1.6 (0.27)	1.7 (0.22)	1.6 (0.24)
	Median	1.6	1.5	1.8	1.6
	Range (Min-Max)	1.2-2.0	1.2-2.1	1.4-1.9	1.2-2.1
WHO performance status	0	7 (58.3%)	6 (75.0%)	1 (25.0%)	14 (58.3%)
	1	4 (33.3%)	1 (12.5%)	3 (75.0%)	8 (33.3%)
	2	1 (8.3%)	1 (12.5%)	0	2 (8.3%)

* Body surface area (Gehan and George): BSA (m^2) = 234.94*(height [cm] $^{0.422}$)*(weight [kg] $^{0.515}$)/10000

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of best overall response by treatment- Group 1 (FAS)

	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Best overall response			
Stable disease	4 (33.3)	1 (11.1)	5 (23.8)
Progressive disease	8 (66.7)	7 (77.8)	15 (71.4)
Unknown	0	1 (11.1)	1 (4.8)

Summary of best overall response by treatment- Group 2 (FAS)

	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=8 n (%)	LDE225 800 mg QD N=4 n (%)	All patients N=24 n (%)
Best overall response				
Stable disease	6 (50.0)	3 (37.5)	1 (25.0)	10 (41.7)
Progressive disease	4 (33.3)	4 (50.0)	1 (25.0)	9 (37.5)
Unknown	2 (16.7)	1 (12.5)	2 (50.0)	5 (20.8)

Summary of pharmacokinetic parameters of LDE225 by treatment- Group 1 (PAS)

Period	PK parameter	Statistic	LDE225 400 mg QD N=12	LDE225 600 mg QD N=9
PK run-in	Cmax (ng/mL)	n	12	9
		mean (SD)	304.99 (269.54)	658.56 (783.63)
		CV%	88.4	119.0
		median	210.00	517.00
		range	83.60-984.00	83.00-2620.00
		geometric mean	226.83	399.70
		geometric CV%	91.3	142.3
	Tmax (hr)	n	12	9
		mean (SD)	3.70 (2.35)	2.64 (1.91)
		CV%	63.4	72.4
		median	2.97	2.00
		range	1.00-8.00	1.95-7.73
		geometric mean	3.07	2.33
		geometric CV%	71.7	47.5
	AUClast (hr*ng/mL)	n	12	9
		mean (SD)	6307.57 (3852.69)	10781.92 (8528.22)
		CV%	61.1	79.1
		median	6214.68	6772.28
		range	1417.93-12034.91	2651.32-26948.62
		geometric mean	5070.18	7905.31
		geometric CV%	85.3	104.2
	AUC0-24 (hr*ng/mL)	n	12	9
		mean (SD)	2559.25 (1681.59)	4845.70 (4077.17)
		CV%	65.7	84.1
		median	1960.46	2724.18
		range	535.12-4936.38	819.92-12218.24
		geometric mean	2006.39	3333.25

Period	PK parameter	Statistic	LDE225 400 mg QD N=12	LDE225 600 mg QD N=9
		geometric CV%	90.2	122.9
Cycle 1 Day 15	Cmax (ng/mL)	n	12	8
		mean (SD)	813.25 (567.08)	1140.50 (596.11)
		CV%	69.7	52.3
		median	611.00	1125.00
		range	217.00-1890.00	404.00-2300.00
		geometric mean	645.46	1006.90
		geometric CV%	83.2	59.3
	Tmax (hr)	n	12	8
		mean (SD)	2.99 (2.12)	3.49 (2.74)
		CV%	71.0	78.6
		median	2.00	2.02
		range	1.00-8.00	1.98-8.02
		geometric mean	2.45	2.83
		geometric CV%	71.3	70.5
	AUClast (hr*ng/mL)*	n	12	8
		mean (SD)	12526.32 (7974.51)	17869.84 (10041.90)
		CV%	63.7	56.2
		median	11037.00	18220.36
		range	3029.26-24085.78	6378.75-36307.78
		geometric mean	9903.42	15380.00
		geometric CV%	88.3	66.3
	AUC0-24 (hr*ng/mL)	n	6	4
		mean (SD)	7808.36 (6912.55)	15489.89 (8979.57)
		CV%	88.5	58.0
		median	4852.75	15163.48
		range	3029.26-21240.72	6378.75-25253.87
		geometric mean	6106.81	13368.30
		geometric CV%	81.6	72.3

*: The last PK sampling point was set as 24hr in the protocol. Therefore, AUClast on Day 15 approximately corresponds to AUC0-24 on Day 15 (the smaller n for AUC0-24 is because actual 24hr samplings in some patients occurred slightly before 24hr and curve stripping for extrapolation for concentrations at 24hr was disabled).

Summary of pharmacokinetic parameters of LDE225 by treatment- Group 2 (PAS)

Period PK parameter	Statistic	LDE225 400 mg QD N=12	LDE225 600 mg QD N=8	LDE225 800 mg QD N=4
PK run-in				
Cmax (ng/mL)	n	12	8	4

Period PK parameter	Statistic	LDE225 400 mg QD N=12	LDE225 600 mg QD N=8	LDE225 800 mg QD N=4
	mean (SD)	420.78 (248.65)	466.40 (309.66)	589.50 (474.25)
	CV%	59.1	66.4	80.4
	median	368.00	415.50	600.50
	range	87.40-840.00	92.20-1060.00	147.00-1010.00
	geometric mean	348.50	376.71	420.04
	geometric CV%	77.0	86.1	133.6
Tmax (hr)	n	12	8	4
	mean (SD)	2.96 (1.43)	3.50 (1.98)	2.39 (0.91)
	CV%	48.2	56.8	38.0
	median	2.99	2.96	2.00
	range	1.13-5.83	1.98-7.67	1.82-3.75
	geometric mean	2.63	3.09	2.28
	geometric CV%	56.4	54.7	34.3
AUClast (hr*ng/mL)	n	12	8	4
	mean (SD)	9230.97 (5850.59)	10104.27 (5010.16)	14187.05 (10986.62)
	CV%	63.4	49.6	77.4
	median	9624.96	10650.37	15381.07
	range	1701.40-19298.61	2587.80-17432.31	2136.61-23849.44
	geometric mean	7395.31	8741.23	9734.69
	geometric CV%	86.0	69.9	163.9
AUC0-24 (hr*ng/mL)	n	12	8	4
	mean (SD)	3430.90 (1878.58)	4108.79 (2575.05)	5245.96 (4048.84)
	CV%	54.8	62.7	77.2
	median	3330.18	3142.45	5413.37
	range	722.69-6262.52	1180.38-7877.55	842.71-9314.41
	geometric mean	2889.19	3423.18	3654.08
	geometric CV%	73.6	74.2	156.0
Cycle 1 Day 15				
Cmax (ng/mL)	n	9	5	2
	mean (SD)	853.44 (396.34)	860.20 (481.34)	1245.00 (275.77)
	CV%	46.4	56.0	22.2
	median	709.00	651.00	1245.00
	range	429.00-1550.00	511.00-1690.00	1050.00-1440.00
	geometric mean	777.29	778.02	1229.63
	geometric CV%	48.3	50.1	22.6
Tmax (hr)	n	9	5	2
	mean (SD)	3.01 (2.41)	6.92 (9.60)	1.87 (0.00)

Period PK parameter	Statistic	LDE225 400 mg QD N=12	LDE225 600 mg QD N=8	LDE225 800 mg QD N=4
	CV%	80.0	138.7	0.0
	median	2.00	4.00	1.87
	range	0.00-7.75	0.50-23.88	1.87-1.87
	geometric mean	2.87	3.33	1.87
	geometric CV%	63.9	245.1	0.0
AUClast (hr*ng/mL)*	n	9	5	2
	mean (SD)	14407.92 (8498.27)	15904.08 (8433.05)	22335.80 (6398.59)
	CV%	59.0	53.0	28.6
	median	12728.90	12548.25	22335.80
	range	5782.13-30159.14	9537.42-29551.52	17811.32-26860.29
	geometric mean	12323.98	14398.99	21872.75
	geometric CV%	65.4	51.3	29.7
AUC0-24 (hr*ng/mL)	n	4	2	1
	mean (SD)	12254.50 (7900.23)	20664.38 (12203.72)	17749.38
	CV%	64.5	59.1	-
	median	9731.82	20664.38	17749.38
	range	6195.59-23358.79	12035.05-29293.72	-
	geometric mean	10606.82	18776.35	17749.38
	geometric CV%	66.7	69.7	-

*: The last PK sampling point was set as 24hr in the protocol. Therefore, AUClast on Day 15 approximately corresponds to AUC0-24 on Day 15 (the smaller n for AUC0-24 is because actual 24hr samplings in some patients occurred slightly before 24hr and curve stripping for extrapolation for concentrations at 24hr was disabled).

Summary of Safety

Safety Results

Dose limiting toxicities occurring during the first cycle by treatment- Group 1 (DDS)

DLT count	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Number of patients evaluated	12 (100.0)	9 (100.0)	21 (100.0)
Number of patients had DLT	1 (8.3)	1 (11.1)	2 (9.5)
CK ELEVATION*	0	1 (11.1)	1 (4.8)
CPK INCREASE*	1 (8.3)	0	1 (4.8)

*Reported term

Dose limiting toxicities occurring during the first cycle by treatment- Group 2 (DDS)

DLT count	LDE225 400 mg QD N=10 n (%)	LDE225 600 mg QD N=6 n (%)	LDE225 800 mg QD N=3 n (%)	All patients N=19 n (%)
Number of patients evaluated	10 (100.0)	6 (100.0)	3 (100.0)	19 (100.0)
Number of patients had DLT	0	0	1 (33.3)	1 (5.3)
CPK ELEVATION*	0	0	1 (33.3)	1 (5.3)

* Reported term

Adverse events, regardless of study drug relationship, by primary system organ class and treatment- Group 1 (Safety set)

Primary System Organ Class	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Any primary system organ class	12 (100.0)	9 (100.0)	21 (100.0)
Gastrointestinal disorders	11 (91.7)	6 (66.7)	17 (81.0)
Investigations	8 (66.7)	5 (55.6)	13 (61.9)
Musculoskeletal and connective tissue disorders	5 (41.7)	7 (77.8)	12 (57.1)
General disorders and administration site conditions	5 (41.7)	5 (55.6)	10 (47.6)
Metabolism and nutrition disorders	5 (41.7)	5 (55.6)	10 (47.6)
Skin and subcutaneous tissue disorders	7 (58.3)	3 (33.3)	10 (47.6)
Nevous system disorders	4 (33.3)	5 (55.6)	9 (42.9)
Infections and infestations	3 (25.0)	1 (11.1)	4 (19.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (16.7)	2 (22.2)	4 (19.0)
Blood and lymphatic system disorders	1 (8.3)	2 (22.2)	3 (14.3)
Hepatobiliary disorders	1 (8.3)	2 (22.2)	3 (14.3)
Psychiatric disorders	1 (8.3)	2 (22.2)	3 (14.3)
Renal and urinary disorders	1 (8.3)	2 (22.2)	3 (14.3)
Reproductive system and breast disorders	3 (25.0)	0	3 (14.3)
Respiratory, thoracic and mediastinal disorders	1 (8.3)	1 (11.1)	2 (9.5)
Vascular disorders	0	2 (22.2)	2 (9.5)
Cardiac disorders	1 (8.3)	0	1 (4.8)

Adverse events, regardless of study drug relationship, by primary system organ class and treatment- Group 2 (Safety set)

Primary system organ class	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=8 n (%)	LDE225 800 mg QD N=4 n (%)	All patients N=24 n (%)
Any primary system organ class	12 (100.0)	8 (100.0)	4 (100.0)	24 (100.0)
General disorders and administration site conditions	7 (58.3)	3 (37.5)	3 (75.0)	13 (54.2)
Investigations	6 (50.0)	4 (50.0)	3 (75.0)	13 (54.2)
Gastrointestinal disorders	4 (33.3)	6 (75.0)	2 (50.0)	12 (50.0)
Metabolism and nutrition disorders	3 (25.0)	5 (62.5)	2 (50.0)	10 (41.7)
Musculoskeletal and connective tissue disorders	3 (25.0)	3 (37.5)	3 (75.0)	9 (37.5)
Nervous system disorders	3 (25.0)	3 (37.5)	3 (75.0)	9 (37.5)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	5 (62.5)	0	7 (29.2)
Infections and infestations	2 (16.7)	0	1 (25.0)	3 (12.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (8.3)	1 (12.5)	1 (25.0)	3 (12.5)
Psychiatric disorders	2 (16.7)	0	1 (25.0)	3 (12.5)
Cardiac disorders	1 (8.3)	1 (12.5)	0	2 (8.3)
Renal and urinary disorders	0	1 (12.5)	1 (25.0)	2 (8.3)
Injury, poisoning and procedural complications	0	1 (12.5)	0	1 (4.2)
Reproductive system and breast disorders	1 (8.3)	0	0	1 (4.2)
Skin and subcutaneous tissue disorders	1 (8.3)	0	0	1 (4.2)
Vascular disorders	0	0	1 (25.0)	1 (4.2)

Adverse events (more than or equal to 10%), regardless of study drug relationship, by preferred term and treatment- Group 1 (Safety set)

Preferred term	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Blood creatine phosphokinase increased	3 (25.0)	5 (55.6)	8 (38.1)
Constipation	3 (25.0)	4 (44.4)	7 (33.3)
Fatigue	2 (16.7)	5 (55.6)	7 (33.3)
Myalgia	2 (16.7)	5 (55.6)	7 (33.3)
Vomiting	3 (25.0)	4 (44.4)	7 (33.3)
Alanine aminotransferase increased	3 (25.0)	3 (33.3)	6 (28.6)
Decreased appetite	3 (25.0)	3 (33.3)	6 (28.6)

Preferred term	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Nausea	2 (16.7)	4 (44.4)	6 (28.6)
Aspartate aminotransferase increased	3 (25.0)	2 (22.2)	5 (23.8)
Rash	3 (25.0)	2 (22.2)	5 (23.8)
Alopecia	2 (16.7)	2 (22.2)	4 (19.0)
Back pain	3 (25.0)	1 (11.1)	4 (19.0)
Cancer pain	2 (16.7)	2 (22.2)	4 (19.0)
Dysgeusia	2 (16.7)	2 (22.2)	4 (19.0)
Pruritus	2 (16.7)	2 (22.2)	4 (19.0)
Abdominal pain	3 (25.0)	0	3 (14.3)
Diarrhoea	3 (25.0)	0	3 (14.3)
Pyrexia	2 (16.7)	1 (11.1)	3 (14.3)
Weight decreased	2 (16.7)	1 (11.1)	3 (14.3)

Adverse events (more than or equal to 10%), regardless of study drug relationship, by preferred term and treatment- Group 2 (Safety set)

Preferred term	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=8 n (%)	LDE225 800 mg QD N=4 n (%)	All patients N=24 n (%)
Blood creatine phosphokinase increased	6 (50.0)	3 (37.5)	3 (75.0)	12 (50.0)
Fatigue	5 (41.7)	2 (25.0)	3 (75.0)	10 (41.7)
Aspartate aminotransferase increased	2 (16.7)	3 (37.5)	3 (75.0)	8 (33.3)
Myalgia	2 (16.7)	3 (37.5)	3 (75.0)	8 (33.3)
Alanine aminotransferase increased	1 (8.3)	3 (37.5)	3 (75.0)	7 (29.2)
Decreased appetite	0	4 (50.0)	2 (50.0)	6 (25.0)
Dysgeusia	2 (16.7)	3 (37.5)	1 (25.0)	6 (25.0)
Nausea	0	3 (37.5)	2 (50.0)	5 (20.8)
Pyrexia	2 (16.7)	2 (25.0)	1 (25.0)	5 (20.8)
Muscular weakness	0	1 (12.5)	3 (75.0)	4 (16.7)
Vomiting	1 (8.3)	2 (25.0)	1 (25.0)	4 (16.7)
Abdominal pain upper	1 (8.3)	2 (25.0)	0	3 (12.5)
Diarrhoea	1 (8.3)	1 (12.5)	1 (25.0)	3 (12.5)
Dizziness	0	1 (12.5)	2 (50.0)	3 (12.5)
Insomnia	2 (16.7)	0	1 (25.0)	3 (12.5)
Tumour pain	1 (8.3)	1 (12.5)	1 (25.0)	3 (12.5)

Serious adverse events and deaths-Group 1 (Safety set)

	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=9 n (%)	All patients N=21 n (%)
Death	0	0	0
Any SAE	4 (33.3)	4 (44.4)	8 (38.1)
Discontinued due to SAE(s)	1 (8.3)	3 (33.3)	4 (19.0)

Serious adverse events and deaths-Group 2 (Safety set)

	LDE225 400 mg QD N=12 n (%)	LDE225 600 mg QD N=8 n (%)	LDE225 800 mg QD N=4 n (%)	All patients N=24 n (%)
Death	0	0	0	0
Any SAE	4 (33.3)	1 (12.5)	3 (75.0)	8 (33.3)
Discontinued due to SAE(s)	1 (8.3)	0	2 (50.0)	3 (12.5)

Other Relevant Findings

Not applicable.

Conclusion:

- The recommended dose was LDE225 400 mg q.d.
- Maximum tolerated dose for Chinese/Taiwanese patients was declared as LDE225 600 mg q.d., whereas Maximum tolerated dose for Japanese patients was not statistically established.
- Exposure of LDE225 increased as the dose escalated from LDE225 400 mg to LDE225 800 mg in an under-proportional manner. Accumulation of exposure was observed after repeated doses. It was suggested that the steady state is not achieved within Cycle 1.
- Gli1 inhibition in normal skin after LDE225 treatment was confirmed. However no clear conclusion was obtained from biomarker assessment due to the small number of samples and large individual variability.
- The most common adverse event was blood creatine phosphokinase increased. Blood creatine phosphokinase increased and creatine phosphokinase elevation were reported most frequently at the 800 mg q.d. dose level of LDE225.
- Majority of clinically significant events were muscle-related events. A depressed level of consciousness, pyrexia, dysgeusia were reported as a treatment related serious adverse event in one patient each.
- Other than creatine phosphokinase elevation, grade 3/4 aspartate aminotransferase elevation and grade 3 alanine aminotransferase elevation coincided with grade 4 creatine

phosphokinase elevation, there were no clinically significant changes in laboratory values and electrocardiogram parameters.

- Clinically significant events first occurred during cycles 1 and 2. Therefore at least two cycles of safety monitoring is recommended.
- The long half-life may result in continued worsening of some adverse events after interruption of LDE225, and a prolonged recovery. Adverse event monitoring after discontinuation of LDE225 is important.

Date of Clinical Trial Report

26 June 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

28 July 2014

Date of Latest Update

Reason for Update