Sponsor

Novartis

Generic Drug Name

Sonidegib

Trial Indication(s)

Advanced solid tumors

Protocol Number

CLDE225X2101

Protocol Title

A 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

06-Apr-2009 to 18-Jul-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I dose-escalation study of sonidegib administered once daily (qd) and twice daily (bid) in a 28-day cycle to adult patients 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) and adult patients with recurrent medulloblastoma (MB) were also eligible for this study.

Once the maximum tolerated dose (MTD) was established in the dose-escalation phase, it was further evaluated in an expanded group of patients to better characterize the safety and tolerability of this dose. A two-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle was used during the dose-escalation phase for dose level selection and for determination of the MTD.

The primary data analysis was performed based on all patient data through the time when all patients had completed at least three cycles of treatment or discontinued the study. The results of these analyses were reported previously in the core clinical study report (CSR) (data cut-off date of 20-Feb-2012) dated 12-Oct-2012.

At the previous data cut-off date (20-Feb-2012) for the core CSR, six patients were still ongoing on the study. An additional CSR (extension report to the core CSR) presented cumulative data up to 18-Jul-2013 (data cut-off date) for a subset of the outputs presented in the core CSR (patient disposition, exposure, and key safety outputs).

Centers

Five centers in four countries. Two centers in United States of America, one center each in Spain, Switzerland, and United Kingdom.

Publication

None

Objectives:

Primary objective: The primary objective of this study was to determine the maximum-tolerated dose (MTD) of single agent sonidegib when administered orally once daily (qd) in a 28-day cycle to adult patients with advanced solid tumors that have progressed despite standard therapy or for which no standard therapy exists.

Secondary objectives:

- To characterize the safety and tolerability of sonidegib, including acute and chronic toxicities.
- To characterize the pharmacokinetic (PK) of single and repeated doses of sonidegib and its metabolite(s), when possible
- To assess any preliminary anti-tumor activity (overall response rate [ORR]) with sonidegib treatment
- To assess the pharmacodynamics (PD) of sonidegib pre- and post-treatment using the measurements outlined below:
    - To assess pre-treatment levels and post-treatment changes in the PD marker, glioma-associated oncogene homolog 1 (Gli1), as a measure of target inhibition in tumor, when available and accessible, and in surrogate tissues (i.e. skin, hair follicles, blood)

- To assess pre-treatment levels and post-treatment changes in targets linked to Hedgehog (Hh) pathway signaling e.g. 12-pass transmembrane protein patched (Ptch1), Ptch2, glioma-associated oncogene homolog 2 (Gli2), sonic hedgehog (Shh), smoothened (Smo), secreted frizzled-related protein 1 (sFRP1), pS6, pAKT, in tumor, when available and accessible, and in surrogate tissues (i.e. skin, hair follicles, blood)
- To assess pre-treatment levels and post-treatment changes in pathway effector molecules Cyclin D1, cleaved caspase 3 (CC3), and Ki-67, as measures of target response in tumor, when available and accessible, and in surrogate tissues (i.e. skin, hair follicles, blood)
- To assess pre-treatment levels and post-treatment changes in circulating markers of angiogenesis [e.g. vascular endothelial growth factor (VEGF), soluble VEGF receptor 2 (sVEGFR2), basic fibroblast growth factor (bFGF), placenta growth factor (PLGF), soluble VEGF receptor 1 (sVEGFR1), platelet derived growth factor alpha (PDGFa), insulin-like growth factor (IGF)] in plasma samples
- To assess pre-treatment levels and post-treatment changes in circulating markers of apoptosis (M30/M65) in serum samples
- To assess pre-treatment levels and post-treatment changes in bone markers [e.g., urine cross-linked N-telopeptide of type I collagen (NTx) and serum markers of cross-linked C-telopeptide of type I collagen (CTx), tartrate-resistant acid phosphatase isoform 5b (Trap5b), osteoprotegerin (OPG), osteocalcin, bone-specific alkaline phosphatase, and amino terminal propeptide of type I procollagen (PINP)] in serum and urine samples.

- To assess the potential anti-tumor activity of sonidegib by evaluating fluorine-18 labeled fluorodeoxyglucose positron emission tomography ([^{18}F]-FDG-PET) in tumors pre- and post-treatment.

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

Sonidegib capsules for oral administration were supplied to the Investigators at dose strength of 50, 100 and 250 mg.

Statistical Methods

Efficacy analysis was based upon the full analysis set (FAS), which included all patients who received at least one (full or partial) dose of sonidegib. The MTD and dose limiting toxicities (DLT) were based upon the dose-determining set (DDS), which consisted of all patients from the safety set (at least within the dose-escalation part) who either met the required minimum exposure criterion and had sufficient safety evaluations, or discontinued earlier due to DLT (including during the 7-day PK run-in period). All other safety tabulations were based on the safety set, which included those who received at least one dose of study drug and had at least one valid post-baseline safety assessment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. Histologically or cytologically confirmed diagnosis of an advanced solid tumor (including locally advanced, multifocal or metastatic BCC, and MB) that had progressed despite standard therapy or for which no standard therapy exists. Inclusion was irrespective of stage of disease or extent of prior therapy.
2. Patients with recurrent MB who were taking corticosteroids were to be on a non-increasing dose of steroids for at least 14 days prior to starting study drug.
3. Age 18 years or older
4. WHO performance status ≤ 2
5. Patients who had measurable or evaluable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) for solid tumors or by the Neuro-Oncology Criteria of Tumor Response for MB.
6. Life expectancy of at least three months
7. Patients who had the following laboratory values:
   - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
   - Hemoglobin (Hgb) ≥ 9 g/dL
   - Platelets ≥ 100 x 10^9/L
   - Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal)
   - AST and ALT ≤ 2.5 x ULN or ≤ 5.0 x ULN if liver metastases are present
   - Serum creatinine ≤ 1.5 x ULN or 24-hour creatinine clearance of ≥ 50 mL/minute
8. For participation in the [18F]-FDG-PET studies, patients were to had at least one lesion ≥ 2 cm in size on computerized tomography (CT) and a tumor: background signal ratio of ≥ 2 on baseline [18F]-FDG-PET scanning. The patient's glucose value was to be <200 mg/dL at the time of scanning and the patient had to tolerate lying supine for a positron emission tomography (PET) examination for at least 40 minutes. Patients with recurrent MB did not undergo [18F]-FDG-PET scanning since this examination was of limited value in the evaluation central nervous system tumors.
9. A negative serum pregnancy test ≤ 72 hours before starting study treatment for pre-menopausal women and for women <1 year after the completion of menopause.

Exclusion criteria:

1. Patients with a history of primary central nervous system tumors or brain metastases (except for recurrent MB) or who had signs/symptoms attributable to brain metastases and had not been assessed with radiologic imaging to rule out the presence of brain metastases.
   2. History of a positive human immunodeficiency virus (HIV) test (HIV testing was not mandatory).
3. History of a positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result (Hepatitis B or C testing was not mandatory).
4. Impairment of gastrointestinal (GI) function or GI disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

5. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. uncontrolled diabetes, uncontrolled diarrhea).
6. Peripheral vascular disease requiring active therapy or having had surgery <12 months prior to starting study drug.
7. Impaired cardiac function or clinically significant heart disease, including any one of the following:
   - Angina pectoris within three months
   - Acute myocardial infarction within three months
   - QTcF >450 msec for males and >470 msec for females on the screening electrocardiogram (ECG)
   - A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
   - 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)
8. Patients who were receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that cannot be discontinued prior to study entry and for the duration of the study. Medications that are strong CYP3A4/5 inhibitors were to be discontinued for at least 2 days, and strong CYP3A4/5 inducers for at least 1 week prior to initiating sonidegib dosing.
9. Patients who had received chemotherapy within a period of time that is less than 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
10. Patients who had received biologic therapy (e.g. antibodies) ≤ 4 weeks prior to starting study drug or who have not recovered from the side effects of such therapy.
11. Patients who had been treated with a small molecule therapeutic ≤ 5 t1/2 or ≤ 4 weeks (whichever was shorter) prior to starting study drug or who have not recovered from the side effects of such therapy.
12. Patients who had received any other investigational agents ≤ 5 t1/2 or ≤ 4 weeks (whichever was shorter) prior to starting study drug or who have not recovered from the side effects of such therapy.
13. Patients who had 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.
14. Patients who were receiving treatment with therapeutic doses of warfarin sodium (Coumadin) who could not discontinue this treatment at least 5 days prior to starting study drug.
15. Patients who were receiving immunosuppressive treatment and in whom the treatment could not be discontinued prior to starting study drug, except in the case of Patients with BCC. Immunosuppressive treatment was to be discontinued for at least 1 week prior to initiating sonidegib dosing.

16. Patients receiving medications that were recognized to cause rhabdomyolysis, such as HMG CoA reductase inhibitors (statins) clofibrate, gemfibrozil, and that cannot be stopped at least 2 weeks prior to the initiation of sonidegib treatment.
17. Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from such therapy.
18. Women of childbearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners had been sterilized by vasectomy or other means, UNLESS they were using two forms of highly effective contraception, throughout the study and for three months after the last treatment.
19. Fertile males not willing to use condoms throughout the study and for three months after the last treatment.

Participant Flow Table

Patient disposition by treatment (Full analysis set)

Disposition Reason	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Patients treated											
Treatment discontinued	6 (100.0)	6 (100.0)	5 (100)	26 (100.0)	11 (100.0)	9 (100)	10 (100)	14 (100.0)	8 (100.0)	8 (100.0)	103 (100.0)
Primary reason for treatment discontinuation											
Adverse event(s)	0	0	0	4 (15.4)	2 (18.2)	4 (44.4)	3 (30.0)	2 (14.3)	1 (12.5)	6 (75.0)	22 (21.4)
Patient withdrew consent	0	0	2(40.0)	2 (7.7)	2 (18.2)	0	1(10.0)	1 (7.1)	0	0	8 (7.8)
Administrative problem(s)	0	1(16.7)	1(20.0)	0	0	0	0	0	0	0	2 (1.9)
Death	0	0	0	2 (7.7)	0	0	0	0	0	0	2 (1.9)
Disease progression	6(100.0)	5(83.3)	2(40.0)	18(69.2)	7(63.6)	5(55.6)	6(60.0)	11(78.6)	7(87.5)	2(25.0)	69 (67.0)
Primary reason for study evaluation completion											
Patient withdrew consent	0	0	2(40.0)	2 (7.7)	1 (9.1)	0	0	0	0	0	5 (4.9)
Lost to follow-up	0	1(16.7)	0	3(11.5)	0 (0.0)	2(22.2)	1(10.0)	2 (14.3)	0	0	9 (8.7)
Death	1(16.7)	0	1(20.0)	4(15.4)	3(27.3)	2(22.2)	1(10.0)	3(21.4)	2(25.0)	1(12.5)	18 (17.5)
Disease progression	1(16.7)	1(16.7)	0	1 (3.8)	1 (9.1)	0	1(10.0)	5(35.7)	0	0	10 (9.7)
Follow-up phase completed	4 (66.7)	4(66.7)	2(40.0)	16 (61.5)	6 (54.5)	5(55.6)	7(70.0)	4(28.6)	6(75.0)	7(87.5)	61 (59.2)

Baseline Characteristics

Demographic summary at baseline by treatment (Full analysis set)

Demographic variable	100 mg qd N=6	200 mg qd N=6	400 mg qd N=5	800 mg qd N=26	1000 mg qd N=11	1500 mg qd N=9	3000 mg qd N=10	250 mg bid. N=14	400 mg bid N=8	750 mg bid N=8	All N=103
Age (Years)											
n	6	6	5	26	11	9	10	14	8	8	103
Mean	43.17	52.17	54.20	57.73	58.27	51.67	61.70	61.57	54.88	63.75	57.07
SD	17.702	13.136	14.325	15.896	13.785	18.378	7.196	16.759	14.999	10.082	15.050
Median	40.50	54.50	56.00	60.00	59.00	57.00	59.50	66.50	57.00	63.00	59.00
Minimum	23.0	35.0	32.0	29.0	37.0	22.0	54.0	28.0	26.0	49.0	22.0
Maximum	75.0	70.0	72.0	87.0	75.0	74.0	75.0	80.0	76.0	80.0	87.0
Age category- n (%)											
<65 years	5 (83.3)	5 (83.3)	4 (80.0)	16 (61.5)	7 (63.6)	6 (66.7)	7 (70.0)	6 (42.9)	6 (75.0)	4 (50.0)	66 (64.1)
≥ 65 years	1 (16.7)	1 (16.7)	1 (20.0)	10 (38.5)	4 (36.4)	3 (33.3)	3 (30.0)	8 (57.1)	2 (25.0)	4 (50.0)	37 (35.9)
Sex- n (%)											
Male	2 (33.3)	3 (50.0)	3 (60.0)	18 (69.2)	8 (72.7)	2 (22.2)	8 (80.0)	7 (50.0)	7 (87.5)	5 (62.5)	63 (61.2)
Female	4 (66.7)	3 (50.0)	2 (40.0)	8 (30.8)	3 (27.3)	7 (77.8)	2 (20.0)	7 (50.0)	1 (12.5)	3 (37.5)	40 (38.8)
Race- n (%)											
Caucasian	5 (83.3)	6(100.0)	5(100.0)	24 (92.3)	11 (100.0)	7 (77.8)	8 (80.0)	13 (92.9)	8 (100.0)	7 (87.5)	94 (91.3)
Black	1 (16.7)	0	0	0	0	2 (22.2)	1 (10.0)	0	0	0	4 (3.9)
Native American	0	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.0)
Other	0	0	0	2 (7.7)	0	0	1 (10.0)	1 (7.1)	0	0	4 (3.9)
Ethnicity- n (%)											
Hispanic/Latino	2 (33.3)	2 (33.3)	2 (40.0)	10 (38.5)	5 (45.5)	3 (33.3)	3 (30.0)	6 (42.9)	4 (50.0)	2 (25.0)	39 (37.9)
Indian (Indian subcontinent)	0	0	0	1 (3.8)	0	0	1 (10.0)	0	0	0	2 (1.9)
Other	4 (66.7)	4 (66.7)	3 (60.0)	15 (57.7)	6 (54.5)	6 (66.7)	6 (60.0)	8 (57.1)	4 (50.0)	6 (75.0)	62 (60.2)
Weight (kg) at baseline											
n	6	6	5	26	11	9	10	14	8	8	103
Mean	75.10	88.35	67.96	73.15	75.35	66.44	82.18	73.33	88.95	71.83	75.57
SD	11.751	15.256	16.891	15.970	15.590	11.778	13.911	14.348	20.070	10.663	15.709
Median	75.20	84.40	58.00	71.30	76.20	64.00	79.40	71.95	88.50	71.20	73.00
Minimum	59.0	75.0	53.0	44.1	45.0	50.0	63.5	52.9	65.0	54.0	44.1
Maximum	90.5	118.2	89.3	110.0	100.2	87.0	112.0	97.4	120.0	88.0	120.0
Body surface area (m^2) at screening[a]											

Demographic variable	100 mg qd N=6	200 mg qd N=6	400 mg qd N=5	800 mg qd N=26	1000 mg qd N=11	1500 mg qd N=9	3000 mg qd N=10	250 mg bid. N=14	400 mg bid N=8	750 mg bid N=8	All N=103
n	6	6	5	26	11	9	10	14	8	8	103
Mean	1.87	2.07	1.78	1.86	1.89	1.75	1.98	1.84	2.07	1.86	1.89
SD	0.205	0.210	0.258	0.244	0.242	0.178	0.191	0.209	0.266	0.165	0.231
Median	1.83	2.00	1.66	1.87	1.94	1.69	1.98	1.86	2.01	1.87	1.88
Minimum	1.6	1.9	1.5	1.4	1.4	1.5	1.7	1.5	1.8	1.6	1.4
Maximum	2.2	2.5	2.1	2.4	2.3	2.0	2.3	2.2	2.5	2.1	2.5
ECOG performance status-n (%)											
0	3 (50.0)	2 (33.3)	1 (20.0)	10 (38.5)	4 (36.4)	4 (44.4)	4 (40.0)	5 (35.7)	4 (50.0)	4 (50.0)	41 (39.8)
1	2 (33.3)	4 (66.7)	4 (80.0)	14 (53.8)	7 (63.6)	4 (44.4)	5 (50.0)	9 (64.3)	3 (37.5)	3 (37.5)	55 (53.4)
2	1 (16.7)	0	0	2 (7.7)	0	1 (11.1)	1 (10.0)	0	1 (12.5)	1 (12.5)	7 (6.8)

[a]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 results section for primary outcome result.

Secondary Outcome Result(s)

Summary of best overall response by treatment (Full analysis set)

	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
CR	0	0	0	0	0	0	0	0	1 (12.5)	0	1 (1.0)
PR	1 (16.7)	1 (16.7)	0	3 (11.5)	1 (9.1)	0	0	1 (7.1)	0	0	7 (6.8)
SD	1 (16.7)	2 (33.3)	2 (40.0)	6 (23.1)	1 (9.1)	3 (33.3)	2 (20.0)	4 (28.6)	2 (25.0)	1 (12.5)	24 (23.3)
PD	3 (50.0)	3 (50.0)	3 (60.0)	11 (42.3)	6 (54.5)	3 (33.3)	3 (30.0)	6 (42.9)	4 (50.0)	2 (25.0)	44 (42.7)
Unknown	1 (16.7)	0	0	6 (23.1)	3 (27.3)	3 (33.3)	5 (50.0)	3 (21.4)	1 (12.5)	5 (62.5)	27 (26.2)

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Best overall response is based on investigator's assessment of disease status using RECIST for patients with solid tumors or neuro-oncology criteria for medulloblastoma.

Summary of pharmacokinetic parameters of sonidegib by treatment

	Parameter	Statistics	100 mg qd	200 mg qd	400 mg qd	800 mg qd	1000 mg qd	1500 mg qd	3000 mg qd	250 mg bid	400 mg bid	750 mg bid
PK	Cmax	n	6	6	5	25	11	9	10	14	8	8
run-in	(ng/mL)	Mean (SD)	85.75 (52.345)	160.22 (114.770)	266.90 (239.023)	429.76 (381.214)	321.54 (258.279)	376.33 (198.766)	429.46 (236.656)	149.67 (111.304)	333.85 (299.862)	226.00 (179.673)
		CV% mean	61.0	71.6	89.6	88.7	80.3	52.8	55.1	74.4	89.8	79.5
	Tmax (hr)	n	6	6	5	25	11	9	10	14	8	8
		Median	2.00	2.09	4.00	3.98	2.00	4.00	2.09	2.11	4.00	3.00
		[Min; Max]	[1.00; 24.13]	[2.00; 47.50]	[4.00; 4.33]	[1.00; 27.17]	[1.00; 4.00]	[2.00; 24.33]	[1.00; 8.00]	[1.00; 4.03]	[1.87; 4.00]	[1.00; 22.92]
	C24h	n	6	6	5	24	11	9	10	14	8	8
	(ng/mL)	Mean (SD)	13.87 (12.583)	17.60 (8.540)	66.12 (79.460)	54.01 (51.590)	46.16 (32.792)	159.20 (184.064)	101.89 (129.988)	23.16 (16.917)	68.93 (80.566)	67.02 (86.081)
		CV% mean	90.8	48.5	120.2	95.5	71.0	115.6	127.6	73.0	116.9	128.4
	AUC0-168h	n	6	6	5	25	11	9	10	14	8	8
	(ng*hr/mL)	Mean (SD)	1882.71 (1150.049)	3673.26 (2132.907)	7447.54 (8533.919)	7866.78 (6950.344)	7395.61 (6343.245)	12633.28 (7112.644)	11756.64 (11208.69)	3224.40 (2322.672)	7527.29 (7023.841)	6918.86 (7110.512)
		CV% mean	61.1	58.1	114.6	88.4	85.8	56.3	95.3	72.0	93.3	102.8
C1D15	Cmax	n	3	5	4	20	8	8	6	13	7	8
	(ng/mL)	Mean (SD)	155.07 (63.438)	269.00 (162.989)	557.75 (286.293)	839.70 (457.392)	1231.75 (1395.457)	1323.00 (656.971)	1673.00 (1045.343)	806.69 (353.189)	864.29 (333.427)	1570.63 (1024.865)
		CV% mean	40.9	60.6	51.3	54.5	113.3	49.7	62.5	43.8	38.6	65.3
	Tmax (hr)	n	3	5	4	20	8	8	6	13	7	8
		Median	4.00	4.00	13.00	2.00	4.00	5.00	2.96	2.00	2.00	4.00
		[Min; Max]	[2.00; 6.00]	[0.00; 6.00]	[1.00; 24.00]	[1.00; 6.00]	[1.52; 6.00]	[1.83; 23.67]	[0.00; 21.00]	[0.00; 6.20]	[0.00; 8.00]	[0.00; 7.92]
	AUC0-24h	n	3	3	4	16	6	3	4	12	5	6
	(ng*hr/mL)	Mean (SD)	2691.25 (1337.054)	5915.71 (3886.224)	10177.69 (5880.069)	12781.32 (6351.414)	15168.12 (18470.95)	27420.16 (14290.62)	24583.02 (8768.006)	14495.33 (4780.563)	13779.83 (6388.688)	26942.07 (17313.54)
		CV% mean	49.7	65.7	57.8	49.7	121.8	52.1	35.7	33.0	46.4	64.3

	Parameter	Statistics	100 mg qd	200 mg qd	400 mg qd	800 mg qd	1000 mg qd	1500 mg qd	3000 mg qd	250 mg bid	400 mg bid	750 mg bid
Steady	Cmin,ss	n			1	11	3	4		8	5	2
state	(ng/mL)	Mean (SD)			518.75	1049.65 (788.460)	1357.62 (751.510)	1323.58 (454.840)		1158.76 (567.358)	1516.30 (202.255)	1641.67
		CV% mean				75.1	55.4	34.4		49.0	13.3	25.7
	Racc (fold)	n				11	3	3				
		Mean (SD)				27.28 (25.514)	34.60 (17.776)	13.14 (6.707)				
		CV% mean				93.5	51.4	51.1				
	T1/2,acc	n				11	3	3				
	(hr)	Mean (SD)				445.31 (424.499)	567.16 (295.751)	210.07 (111.625)				
		CV% mean				95.3	52.1	53.1				

Change from Baseline FDG-PET sSUVmax by treatment (Full analysis set)

	Statistics	100 mg qd N=6	200 mg qd N=6	400 mg qd N=5	800 mg qd N=26	1000 mg qd N=11	1500 mg qd N=9	3000 mg qd N=10	250 mg bid N=14	400 mg bid N=8	750 mg bid N=8	All patients N=103
Baseline	n	4	4	3	16	8	6	4	9	4	3	61
	Mean	29.962	47.261	26.989	30.238	41.701	33.465	36.550	31.319	43.681	24.808	34.185
	SD	12.8890	37.4317	16.5196	27.6838	22.1302	14.9331	21.6563	24.1381	29.9708	11.4581	23.3266
	Median	29.315	46.531	19.827	23.699	42.365	34.722	29.965	24.360	37.224	18.828	31.588
	Min	16.90	3.31	15.26	5.13	15.56	8.12	19.71	2.39	14.64	17.58	2.39
	Max	44.32	92.67	45.88	102.01	76.21	50.59	66.56	64.02	85.63	38.02	102.01
C1D28	n	4	4	3	11	5	4	2	5	2	3	43
	Mean	41.943	47.502	29.864	28.970	25.531	29.008	23.344	24.405	42.317	28.915	31.391
	SD	25.9276	40.5438	11.7287	28.3052	15.6941	11.1102	9.8281	20.4096	16.7344	10.5181	22.4854
	Median	39.089	43.615	32.796	19.065	21.359	25.937	23.344	18.556	42.317	25.254	26.940

	Statistics	100 mg qd N=6	200 mg qd N=6	400 mg qd N=5	800 mg qd N=26	1000 mg qd N=11	1500 mg qd N=9	3000 mg qd N=10	250 mg bid N=14	400 mg bid N=8	750 mg bid N=8	All patients N=103
	Min	15.74	4.00	16.95	4.90	10.58	20.38	16.39	3.98	30.48	20.72	3.98
	Max	73.86	98.78	39.85	95.33	50.19	43.78	30.29	57.22	54.15	40.77	98.78
Change from baseline	n	4	4	3	11	5	4	2	5	2	3	43
	Mean	30.750	2.675	21.133	6.464	-17.420	-23.875	11.350	22.400	-25.050	19.733	5.335
	SD	30.5280	15.9753	40.2003	30.4406	22.2053	7.9826	39.8101	35.8167	16.6170	13.5434	30.4553
	Median	31.600	3.850	11.100	5.200	-7.700	-25.850	11.350	18.200	-25.050	17.900	3.300
	Min	-6.90	-17.80	-13.10	-46.10	-42.70	-30.30	-16.80	-13.40	-36.80	7.20	-46.10
	Max	66.70	20.80	65.40	56.40	6.40	-13.50	39.50	66.50	-13.30	34.10	66.70
C2D28	n	1	2	2	7	3	1	1	4	1	0	22
	Mean	15.870	50.937	25.729	33.165	28.866	15.570	21.193	13.304	31.130		27.685
	SD		66.4143	13.6111	23.6681	17.8901			9.5394			23.2392
	Median	15.870	50.937	25.729	24.630	20.498	15.570	21.193	11.651	31.130		20.846
	Min	15.87	3.98	16.10	10.74	16.69	15.57	21.19	3.75	31.13		3.75
	Max	15.87	97.90	35.35	72.78	49.41	15.57	21.19	26.16	31.13		97.90
Change from baseline	n	1	2	2	7	3	1	1	4	1	0	22
	Mean	-6.100	12.850	-8.700	24.414	17.900	-46.500	7.500	13.100	-11.500		10.395
	SD		10.2530	20.0818	52.9598	23.8158			34.1464			36.6979
	Median	-6.100	12.850	-8.700	18.300	31.600	-46.500	7.500	10.650	-11.500	6.500	
	Min	-6.10	5.60	-22.90	-28.60	-9.60	-46.50	7.50	-26.00	-11.50	-46.50	
	Max	-6.10	20.10	5.50	109.20	31.70	-46.50	7.50	57.10	-11.50	109.20	

Gli-1 fold change and percent inhibition by treatment (Full analysis set)

Dose Group	Group Size	Log2 Fold Change and 95% CI	Fold Change and 95% CI	Percent Inhibition
100 mg qd	5	-0.50 (-2.38, 1.39)	-1.41 (-5.21, 2.62)	29.12
200 mg qd	4	-1.66 (-3.51, 0.19)	-3.17 (-11.42, 1.14)	68.42
400 mg qd	3	-3.03 (-5.71, -0.34)	-8.15 (-52.49,-1.26)	87.73
800 mg qd	20	-1.92 (-2.72, -1.11)	-3.78 (-6.61, -2.16)	73.53
1000 mg qd	6	-2.51 (-4.40, -0.63)	-5.71 (-21.14, -1.54)	82.49
1500 mg qd	5	-3.98 (-4.93, -3.03)	-15.79 (-30.43, -8.19)	93.67
3000 mg qd	4	-3.68 (-4.76, -2.60)	-12.78 (-27.03, -6.05)	92.18
250 mg bid	10	-2.95 (-3.51, -2.39)	-7.74 (-11.40, -5.26)	87.08
400 mg bid	7	-2.66 (-3.48, -1.84)	-6.32 (-11.13, -3.59)	84.18
750 mg bid	5	-4.46 (-5.03, -3.89)	-21.98 (-32.60, -14.81)	95.45

Summary of Safety

Safety Results

Number and percent of patients with dose limiting toxicities during Cycle 1 by treatment (Dose determining set)

	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Number of Patients evaluable for MTD	5	6	4	21	7	8	4	12	6	5	78
Number of Patient with DLT	0	0	0	1 (4.8)	1 (14.3)	0	0	0	0	3 (60.0)	5 (6.4)

A patient with multiple occurrences of dose limiting toxicity under one treatment is counted only once.

Dose limiting toxicities by patient (Dose determining set)

Patient	Age/sex/race	Initial dose	Study day	Adverse event (preferred term)	CTCAE Grade
X2101-0020-00111	35/M/Ca	800 mg qd	30	Aspartate aminotransferase elevated	3
			30	Blood creatine phosphokinase increased	4
			30	Blood creatine phosphokinase MB increased	2
			30	Myoglobin blood increased	4
X2101-0502-00122	71/M/Ca	1000 mg qd	24	Blood creatine phosphokinase increased	4
X2101-0001-00123	56/F/Ca	750 mg bid	28	Blood creatine phosphokinase increased	4

X2101-0502-00117	59/M/Ca	750 mg bid	29	Blood creatine phosphokinase increased	4
X2101-0502-00118	80/M/Ca	750 mg bid	29	Blood creatine phosphokinase increased	4

Ca= Caucasian; F=female; M = Male

Adverse events (greater than or equal to 5 percent), regardless of study drug relationship, by primary system organ class and treatment (Safety set) (Primary analysis)

Primary System Organ Class	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Any primary system organ class	6 (100)	6 (100)	5 (100)	26 (100)	10 (90.9)	9 (100)	10 (100)	14 (100)	8 (100)	8 (100)	102 (99.0)
Gastrointestinal disorders	4 (66.7)	5 (83.3)	0	16 (61.5)	7 (63.6)	9 (100)	6 (60.0)	10 (71.4)	7 (87.5)	8 (100)	72 (69.9)
General disorders and administration site conditions	6 (100)	3 (50.0)	2 (40.0)	15 (57.7)	4 (36.4)	9 (100)	6 (60.0)	10 (71.4)	6 (75.0)	5 (62.5)	66 (64.1)
Investigations	2 (33.3)	1 (16.7)	0	16 (61.5)	7 (63.6)	6 (66.7)	9 (90.0)	6 (42.9)	6 (75.0)	8 (100)	61 (59.2)
Musculoskeletal and connective tissue disorders	3 (50.0)	3 (50.0)	2 (40.0)	14 (53.8)	6 (54.5)	5 (55.6)	5 (50.0)	10 (71.4)	6 (75.0)	7 (87.5)	61 (59.2)
Nervous system disorders	3 (50.0)	3 (50.0)	1 (20.0)	18 (69.2)	7 (63.6)	4 (44.4)	6 (60.0)	10 (71.4)	4 (50.0)	4 (50.0)	60 (58.3)
Metabolism and nutrition disorders	3 (50.0)	2 (33.3)	3 (60.0)	10 (38.5)	6 (54.5)	3 (33.3)	6 (60.0)	4 (28.6)	5 (62.5)	4 (50.0)	46 (44.7)
Respiratory, thoracic and mediastinal disorders	4 (66.7)	1 (16.7)	2 (40.0)	9 (34.6)	4 (36.4)	4 (44.4)	5 (50.0)	5 (35.7)	4 (50.0)	2 (25.0)	40 (38.8)
Infections and infestations	3 (50.0)	2 (33.3)	1 (20.0)	10 (38.5)	4 (36.4)	2 (22.2)	5 (50.0)	5 (35.7)	3 (37.5)	2 (25.0)	37 (35.9)
Skin and subcutaneous tissue disorders	2 (33.3)	1 (16.7)	0	10 (38.5)	4 (36.4)	3 (33.3)	1 (10.0)	3 (21.4)	3 (37.5)	1 (12.5)	28 (27.2)
Blood and lymphatic system disorders	2 (33.3)	1 (16.7)	2 (40.0)	4 (15.4)	3 (27.3)	1 (11.1)	2 (20.0)	4 (28.6)	1 (12.5)	1 (12.5)	21 (20.4)
Psychiatric disorders	3 (50.0)	0	1 (20.0)	6 (23.1)	1 (9.1)	2 (22.2)	4 (40.0)	2 (14.3)	1 (12.5)	2 (25.0)	22 (21.4)
Hepatobiliary disorders	0	2 (33.3)	2 (40.0)	2 (7.7)	1 (9.1)	4 (44.4)	1 (10.0)	1 (7.1)	0	0	13 (12.6)
Eye disorders	2 (33.3)	1 (16.7)	0	4 (15.4)	0	1 (11.1)	0	1 (7.1)	0	2 (25.0)	11 (10.7)
Injury, poisoning and procedural complications	0	1 (16.7)	0	2 (7.7)	1 (9.1)	2 (22.2)	1 (10.0)	3 (21.4)	0	1 (12.5)	11 (10.7)
Renal and urinary disorders	2 (33.3)	1 (16.7)	0	1 (3.8)	2 (18.2)	1 (11.1)	2 (20.0)	0	0	1 (12.5)	10 (9.7)

Primary System Organ Class	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Vascular disorders	1 (16.7)	1 (16.7)	1 (20.0)	1 (3.8)	1 (9.1)	2 (22.2)	0	1 (7.1)	2 (25.0)	0	10 (9.7)
Cardiac disorders	1 (16.7)	0	0	3 (11.5)	0	0	1 (10.0)	0	1 (12.5)	0	6 (5.8)

5% is based on 'All' Column.

Primary system organ classes are sorted in descending frequency, as reported in the "All" group.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Adverse events (greater than or equal to 5 percent), regardless of study drug relationship, by preferred term and treatment (Safety set) (Final analysis)

Primary System Organ Class Preferred Term	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Nausea	3 (50.0)	2 (33.3)	0	10 (38.5)	5 (45.5)	7 (77.8)	4 (40.0)	6 (42.9)	4 (50.0)	6 (75.0)	47 (45.6)
Blood creatine phosphokinase increased	1 (16.7)	1 (16.7)	0	8 (30.8)	5 (45.5)	3 (33.3)	4 (40.0)	3 (21.4)	4 (50.0)	6 (75.0)	35 (34.0)
Muscle spasms	2 (33.3)	2 (33.3)	0	9 (34.6)	3 (27.3)	5 (55.6)	1 (10.0)	5 (35.7)	4 (50.0)	4 (50.0)	35 (34.0)
Vomiting	1 (16.7)	3 (50.0)	0	10 (38.5)	3 (27.3)	3 (33.3)	3 (30.0)	4 (28.6)	3 (37.5)	3 (37.5)	33 (32.0)
Decreased appetite	2 (33.3)	2 (33.3)	2 (40.0)	5 (19.2)	5 (45.5)	3 (33.3)	3 (30.0)	3 (21.4)	4 (50.0)	2 (25.0)	31 (30.1)
Dysgeusia	1 (16.7)	1 (16.7)	0	5 (19.2)	4 (36.4)	3 (33.3)	5 (50.0)	6 (42.9)	3 (37.5)	3 (37.5)	31 (30.1)
Fatigue	4 (66.7)	2 (33.3)	1 (20.0)	6 (23.1)	3 (27.3)	5 (55.6)	0	2 (14.3)	3 (37.5)	3 (37.5)	29 (28.2)
Asthenia	2 (33.3)	1 (16.7)	0	7 (26.9)	2 (18.2)	3 (33.3)	1 (10.0)	4 (28.6)	3 (37.5)	1 (12.5)	24 (23.3)
Myalgia	1 (16.7)	1 (16.7)	0	5 (19.2)	4 (36.4)	2 (22.2)	2 (20.0)	5 (35.7)	1 (12.5)	3 (37.5)	24 (23.3)
Anaemia	2 (33.3)	1 (16.7)	2 (40.0)	4 (15.4)	2 (18.2)	1 (11.1)	2 (20.0)	4 (28.6)	1 (12.5)	1 (12.5)	20 (19.4)
Constipation	2 (33.3)	1 (16.7)	0	3 (11.5)	2 (18.2)	2 (22.2)	2 (20.0)	2 (14.3)	1 (12.5)	3 (37.5)	18 (17.5)
Weight decreased	1 (16.7)	1 (16.7)	0	5 (19.2)	1 (9.1)	1 (11.1)	3 (30.0)	2 (14.3)	2 (25.0)	2 (25.0)	18 (17.5)
Diarrhoea	1 (16.7)	2 (33.3)	0	3 (11.5)	1 (9.1)	0	2 (20.0)	2 (14.3)	4 (50.0)	2 (25.0)	17 (16.5)

Primary System Organ Class Preferred Term	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Pyrexia	3 (50.0)	0	2 (40.0)	3 (11.5)	0	1 (11.1)	1 (10.0)	2 (14.3)	2 (25.0)	1 (12.5)	15 (14.6)
Alopecia	1 (16.7)	1 (16.7)	0	4 (15.4)	1 (9.1)	2 (22.2)	1 (10.0)	2 (14.3)	2 (25.0)	0	14 (13.6)
Aspartate aminotransferase increased	0	0	0	3 (11.5)	1 (9.1)	2 (22.2)	2 (20.0)	3 (21.4)	2 (25.0)	1 (12.5)	14 (13.6)
Abdominal pain	1 (16.7)	1 (16.7)	0	2 (7.7)	2 (18.2)	2 (22.2)	4 (40.0)	0	1 (12.5)	0	13 (12.6)
Dyspnoea	0	0	1 (20.0)	5 (19.2)	0	1 (11.1)	3 (30.0)	1 (7.1)	2 (25.0)	0	13 (12.6)
Insomnia	3 (50.0)	0	1 (20.0)	2 (7.7)	1 (9.1)	0	1 (10.0)	2 (14.3)	1 (12.5)	2 (25.0)	13 (12.6)
Cough	2 (33.3)	0	2 (40.0)	1 (3.8)	2 (18.2)	1 (11.1)	1 (10.0)	2 (14.3)	1 (12.5)	0	12 (11.7)
Dizziness	0	1 (16.7)	0	4 (15.4)	1 (9.1)	2 (22.2)	0	1 (7.1)	2 (25.0)	1 (12.5)	12 (11.7)
Abdominal pain upper	1 (16.7)	2 (33.3)	0	4 (15.4)	1 (9.1)	0	0	1 (7.1)	1 (12.5)	1 (12.5)	11 (10.7)
Back pain	1 (16.7)	0	1 (20.0)	2 (7.7)	0	1 (11.1)	2 (20.0)	1 (7.1)	1 (12.5)	2 (25.0)	11 (10.7)
Headache	2 (33.3)	0	1 (20.0)	3 (11.5)	2 (18.2)	1 (11.1)	1 (10.0)	1 (7.1)	0	0	11 (10.7)
Alanine aminotransferase increased	0	0	0	2 (7.7)	0	2 (22.2)	2 (20.0)	3 (21.4)	1 (12.5)	0	10 (9.7)
Oedema peripheral	1 (16.7)	1 (16.7)	0	1 (3.8)	1 (9.1)	2 (22.2)	2 (20.0)	2 (14.3)	0	0	10 (9.7)
Blood bilirubin increased	0	0	0	1 (3.8)	3 (27.3)	2 (22.2)	0	2 (14.3)	0	1 (12.5)	9 (8.7)
Hypoalbuminaemia	0	0	2 (40.0)	2 (7.7)	1 (9.1)	1 (11.1)	2 (20.0)	0	1 (12.5)	0	9 (8.7)
Dyspnoea exertional	1 (16.7)	1 (16.7)	0	3 (11.5)	0	0	1 (10.0)	1 (7.1)	1 (12.5)	0	8 (7.8)
Pain in extremity	1 (16.7)	0	0	1 (3.8)	1 (9.1)	3 (33.3)	0	1 (7.1)	1 (12.5)	0	8 (7.8)
Arthralgia	0	0	2 (40.0)	0	1 (9.1)	0	1 (10.0)	2 (14.3)	0	1 (12.5)	7 (6.8)
Lethargy	0	0	0	3 (11.5)	1 (9.1)	0	1 (10.0)	1 (7.1)	0	1 (12.5)	7 (6.8)
Musculoskeletal pain	1 (16.7)	2 (33.3)	0	0	1 (9.1)	0	1 (10.0)	0	1 (12.5)	1 (12.5)	7 (6.8)
Urinary tract infection	0	1 (16.7)	0	1 (3.8)	1 (9.1)	1 (11.1)	1 (10.0)	0	1 (12.5)	1 (12.5)	7 (6.8)
Hyperbilirubinaemia	0	2 (33.3)	0	2 (7.7)	0	0	1 (10.0)	1 (7.1)	0	0	6 (5.8)

Primary System Organ Class Preferred Term	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Muscular weakness	0	0	0	2 (7.7)	1 (9.1)	1 (11.1)	1 (10.0)	0	0	1 (12.5)	6 (5.8)
Pruritus	1 (16.7)	0	0	2 (7.7)	0	1 (11.1)	0	0	1 (12.5)	1 (12.5)	6 (5.8)
Somnolence	0	0	0	1 (3.8)	1 (9.1)	2 (22.2)	1 (10.0)	0	1 (12.5)	0	6 (5.8)

5% is based on 'All' Column.

Preferred terms are sorted in descending frequency, as reported in the 'All' column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Serious adverse events, and deaths

	100 mg qd N=6 n (%)	200 mg qd N=6 n (%)	400 mg qd N=5 n (%)	800 mg qd N=26 n (%)	1000 mg qd N=11 n (%)	1500 mg qd N=9 n (%)	3000 mg qd N=10 n (%)	250 mg bid N=14 n (%)	400 mg bid N=8 n (%)	750 mg bid N=8 n (%)	All N=103 n (%)
Any AE	6 (100)	6 (100)	5 (100)	26 (100)	10 (90.9)	9 (100)	10 (100)	14 (100)	8 (100)	8 (100)	102 (99.0)
Any SAE	1 (16.7)	2 (33.3)	4 (80.0)	10 (38.5)	6 (54.5)	7 (77.8)	6 (60.0)	6 (42.9)	4 (50.0)	6 (75.0)	52 (50.5)
Death	1 (16.7)	0	1 (20.0)	4 (15.4)	3 (27.3)	1 (11.1)	0	2 (14.3)	1 (12.5)	1 (12.5)	14 (13.6)

Other Relevant Findings

No meaningful analysis could be conducted for all the biomarkers.

Conclusion:

- The MTD of sonidegib is 800 mg qd and 250 mg bid. The most common DLT was increased creatine phosphokinase.
- Mean plasma exposure to sonidegib appeared to increase approximately dose-proportionally up to 400 mg, but less than proportionally above 400 mg. The median Tmax of sonidegib occurred at 2-13 hours after single or repeated oral dosing of 100 to 3000 mg/day.
- Gli-1 inhibition in biopsies of normal skin was a good surrogate marker for the pharmacodynamic effect of sonidegib.
- Sonidegib was well tolerated. Increased creatine kinase was the most common SAE, grade 3/4 AE, and DLT. There was no indication of cardiac muscle injury.
- Sonidegib demonstrated clinically important antitumor activity in patients with metastatic and locally advanced, unresectable BCC and medulloblastoma.

- The additional data collected from the six patients who were ongoing since the data cut-off used for the core CSR, regarding efficacy, safety, PK, and biomarkers does not affect conclusions drawn in the core CSR.

Date of Clinical Trial Report

Core CSR: 07 Dec 2012

Final CSR: 23 June 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

9 Jul 2014

Date of Latest Update

Not applicable

Reason for Update

Not applicable