Clinical trial results:
A Pivotal Phase II, Multicenter, Single-arm, Two-cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients With Advanced Basal Cell Carcinoma

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2008-004945-27
Trial protocol	BE DE GB
Global end of trial date	09 April 2014
Results information	
Result version number	v2 (current)
This version publication date	26 May 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set Quality check of data already entered before access for sponsors was blocked on 31 July 2015

Trial information

Trial identification	
Sponsor protocol code	SHH4476g
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00833417
WHO universal trial number (UTN)	-
Other trial identifiers	Other study ID: GO01541

Notes:

Sponsors	
Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	09 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a Phase II, single-arm, two-cohort multicenter clinical trial evaluating the efficacy and safety of vismodegib (GDC-0449) in subjects with advanced basal cell carcinoma (BCC). All subjects received vismodegib until evidence of progression, intolerable toxicities most probably attributable to vismodegib, or withdrawal from the study.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	United States: 72
Worldwide total number of subjects	104
EEA total number of subjects	30

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	41
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study population consisted of subjects >= 18 years old with a histologically confirmed diagnosis of advanced basal cell carcinoma (BCC), either metastatic or locally advanced BCC. Enrollment of subjects with locally advanced BCC was limited to 80 of a planned total of 100 subjects. Both cohorts received the same vismodegib 150 mg treatment.

Pre-assignment

Screening details:

Subjects with metastatic BCC were required to have histologic confirmation of a distant BCC metastasis. Subjects with locally advanced BCC were required to have disease that was considered inoperable or to have a medical contraindication to surgery.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Metastatic Basal-Cell Carcinoma

Arm description:

Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.

Arm type	Experimental
Investigational medicinal product name	vismodegib
Investigational medicinal product code	GDC-0449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study

Arm title	Locally Advanced Basal-Cell Carcinoma

Arm description:

Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.

Arm type	Experimental
Investigational medicinal product name	vismodegib
Investigational medicinal product code	GDC-0449
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study

Number of subjects in period 1	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma
Started	33	71
Completed	0	0
Not completed	33	71
Physician decision	3	7
Sponsor decision to terminate study	1	2
Disease progression	18	17
Adverse event, non-fatal	5	16
Death	1	3
Lost to follow-up	1	2
Patient decision to withdraw	4	23
Reason not specified	-	1

Baseline characteristics

Reporting groups

Reporting group title	Metastatic Basal-Cell Carcinoma
Reporting group description:	
Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.	
Reporting group title	Locally Advanced Basal-Cell Carcinoma
Reporting group description:	
Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.	

Reporting group values	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma	Total
Number of subjects	33	71	104
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	38	57
From 65-84 years	13	28	41
85 years and over	1	5	6
Age continuous Units: years			
arithmetic mean	61.6	61.2	
standard deviation	± 11.4	± 16.8	-
Gender categorical Units: Subjects			
Female	9	32	41
Male	24	39	63

Subject analysis sets

Subject analysis set title	Metastatic and Locally Advanced BCC Cohorts
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Efficacy-evaluable population: All treated patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with basal cell carcinoma.	

Reporting group values	Metastatic and Locally Advanced BCC Cohorts		
Number of subjects	104		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	57		
From 65-84 years	41		
85 years and over	6		
Age continuous			
Units: years			
arithmetic mean	61.4		
standard deviation	± 15.2		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Metastatic Basal-Cell Carcinoma

Reporting group description:

Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.

Reporting group title	Locally Advanced Basal-Cell Carcinoma

Reporting group description:

Subjects received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.

Subject analysis set title	Metastatic and Locally Advanced BCC Cohorts
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Efficacy-evaluable population: All treated patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with basal cell carcinoma.

Primary: Objective Response (OR) Determined by the Independent Review Facility

End point title	Objective Response (OR) Determined by the Independent Review Facility[1]

End point description:

OR=complete (CR) or partial response (PR). Metastatic-CR:Disappearance of all targets. PR:≥30% decreased sum of longest diameter (SLD) of targets compared to baseline (B). Locally advanced-Response=No progressive disease (PD) and ≥30% decreased SLD from baseline (radiography [R]) or ≥30% decreased SLD from B (externally visible dimension [EVD]) or completely resolved ulceration. CR:Response with no residual BCC on tumor biopsy (otherwise response was PR). PD:Any of ≥20% increased SLD from nadir (R or EVD), new ulceration, new lesions (R or physical exam) or non-target lesion progression by R.

End point type	Primary

End point timeframe:

From study initiation (enrollment of first subject) through 9 months following the first treatment of the last enrolled subject (clinical cutoff date of 26 November 2010)

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: Statistical analysis for clinical benefit was run against a pre-specified value for each cohort, not a comparison between groups, to exclude a response rate of <= 10% for Metastatic BCC cohort (n=33 in analysis) and <= 20% for the Locally Advanced BCC cohort (n=63 in analysis).

End point values	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63		
Units: Percentage of participants				
number (confidence interval 95%)	30.3 (15.6 to 48.2)	42.9 (30.5 to 56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (OR) Determined by the Independent Review Facility

End point title	Duration of Objective Response (OR) Determined by the Independent Review Facility

End point description:

Duration of OR was defined as the time from the initial CR or PR to the earliest documented disease progression (PD) or death. Metastatic BCC - PD: ≥ 20% increased sum of the longest diameter (SLD) of targets from nadir, or 1 or more new lesions. Locally advanced BCC - PD: any of: (1) ≥ 20% increased SLD from nadir (radiography or externally visible dimension); (2) new ulceration; (3) new lesions (radiography or physical exam); (4) progression of non-target lesions by radiography.

End point type	Secondary

End point timeframe:

From study initiation (enrollment of first subject) through 9 months following the first treatment of the last enrolled subject (clinical cutoff date of 26 November 2010)

End point values	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[2]	27		
Units: Months				
median (confidence interval 95%)	7.6 (5.62 to 999)	7.6 (5.65 to 9.66)		

Notes:

[2] - 999 = value not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Determined by the Independent Review Facility

End point title	Progression-free Survival (PFS) Determined by the Independent Review Facility

End point description:

PFS was defined as the time from start of treatment to the earliest documented disease progression (PD) or death. Metastatic BCC - PD: ≥ 20% increased sum of the longest diameter (SLD) of targets from nadir, or 1 or more new lesions. Locally advanced BCC - PD: any of: (1) ≥ 20% increased SLD from nadir (radiography or externally visible dimension); (2) new ulceration; (3) new lesions (radiography or physical exam); (4) progression of non-target lesions by radiography.

End point type	Secondary

End point timeframe:

From study initiation (enrollment of first subject) through 9 months following the first treatment of the last enrolled subject (clinical cutoff date of 26 November 2010)

End point values	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[3]	63		
Units: Months				
median (confidence interval 95%)	9.5 (7.36 to 999)	9.5 (7.39 to 11.93)		

Notes:

[3] - 999 = value not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the initial dose of vismodegib until death from any cause.

End point type	Secondary

End point timeframe:

From study initiation (enrollment of first subject) through 9 months following the first treatment of the last enrolled subject (clinical cutoff date of 26 November 2010)

End point values	Metastatic Basal-Cell Carcinoma	Locally Advanced Basal-Cell Carcinoma		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[4]	63		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Notes:

[4] - 999 = value not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 (SF-36) Health Survey Scores

End point title	Change From Baseline in Short Form 36 (SF-36) Health Survey Scores

End point description:

The SF-36 Health Survey (Version 2) uses patient-reported symptoms on 8 subscales to assess health-related quality of life (HRQoL). The Physical Component Summary (PCS) score summarizes the subscales Physical Functioning, Role−Physical, Bodily Pain, and General Health. The Mental Component Summary (MCS) score summarizes the subscales Vitality, Social Functioning, Role−Emotional, and Mental Health. Each score was scaled from 0 to 100. A positive change score indicates better HRQoL.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, and at the end of the study or early termination visit

End point values	Metastatic and Locally Advanced BCC Cohorts			
Subject group type	Subject analysis set			
Number of subjects analysed	93			
Units: Units on a scale				
arithmetic mean (confidence interval 95%)				
Change in MCS score at Week 12, n=82	2.2 (-0.22 to 4.62)			
Change in MCS score at Week 24, n=75	2.29 (0.05 to 4.53)			
Change in MCS score at end of study, n=20	-3.8 (-10.55 to 2.96)			
Change in PCS score at Week 12, n=82	-1.25 (-2.86 to 0.36)			
Change in PCS score at Week 24, n=75	-1.9 (-3.75 to -0.05)			
Change in PCS score at end of study, n=20	-2.86 (-7.39 to 1.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Absence of Residual Basal Cell Carcinoma BCC in Subjects With Locally Advanced BCC

End point title	Number of Subjects With Absence of Residual Basal Cell Carcinoma BCC in Subjects With Locally Advanced BCC[5]

End point description:

In subjects with locally advanced BCC, the histopathological effect of vismodegib was determined in tissue biopsies obtained at baseline and following vismodegib treatment. Reported is the number of subjects with pathology confirmed BCC in baseline biopsy, who had an absence of residual BCC post-baseline as assessed by an independent pathological review. This endpoint was measured in the efficacy-evaluable population: All treated subjects for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with basal cell carcinoma. Only locally advanced BCC subjects with available post-baseline biopsy assessed by an independent pathologist were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline through end of the study

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is specific to the arm labeled Locally Advanced BCC cohort. Therefore, data/statistics are not reported for the arm labeled Metastatic BCC cohort.

End point values	Locally Advanced Basal-Cell Carcinoma			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Number of participants				
number (not applicable)				
Absence of Residual BCC	34			
Prior to Week 24	6			
At Week 24	27			
After Week 24	1			

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 recorded from study initiation (enrollment of first subject) through the end of the study (09 Apr 2014).

Adverse event reporting additional description:

Adverse events were reported for the safety analysis population, which was defined as all enrolled subjects who received any amount of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	NA

Reporting groups

Reporting group title	Metastatic and Locally Advanced BCC Cohorts

Reporting group description:

Patients received vismodegib 150 mg orally once daily until disease progression; intolerable toxicity, most probably attributable to vismodegib; or withdrawal from the study.

Serious adverse events	Metastatic and Locally Advanced BCC Cohorts		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 104 (34.62%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastatic malignant melanoma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic squamous cell carcinoma			

subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal carcinoma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sarcoma			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Orthostatic hypotension			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Asthenia				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest discomfort				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	3 / 104 (2.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
General physical health deterioration				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumonia aspiration				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism				
subjects affected / exposed	2 / 104 (1.92%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	3 / 104 (2.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Spinal compression fracture				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina pectoris				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 104 (1.92%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac flutter				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				

subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Restrictive cardiomyopathy				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Convulsions local				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	4 / 104 (3.85%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 104 (0.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				

subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcerative keratitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Aphagia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 104 (0.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Metastatic and Locally Advanced BCC Cohorts		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 104 (99.04%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	12 / 104 (11.54%)		
occurrences (all)	27		
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Hypotension			

subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 104 (9.62%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	45 / 104 (43.27%)		
occurrences (all)	58		
Influenza like illness			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	7		
Local swelling			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	10 / 104 (9.62%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 104 (20.19%)		
occurrences (all)	23		
Dyspnoea			
subjects affected / exposed	8 / 104 (7.69%)		
occurrences (all)	13		
Epistaxis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	4		
Rhinorrhoea			

subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	7		
Upper-airway cough syndrome			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 104 (5.77%)		
occurrences (all)	9		
Depression			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	13		
Insomnia			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	7		
Investigations			
Weight decreased			
subjects affected / exposed	54 / 104 (51.92%)		
occurrences (all)	92		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	7		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	3		
Nervous system disorders			
Ageusia			
subjects affected / exposed	12 / 104 (11.54%)		
occurrences (all)	13		
Dizziness			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	12		
Dysgeusia			

subjects affected / exposed	58 / 104 (55.77%)		
occurrences (all)	90		
Headache			
subjects affected / exposed	16 / 104 (15.38%)		
occurrences (all)	24		
Hypoaesthesia			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	7		
Hypogeusia			
subjects affected / exposed	11 / 104 (10.58%)		
occurrences (all)	12		
Paraesthesia			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	9		
Tremor			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 104 (7.69%)		
occurrences (all)	10		
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	18		
Constipation			
subjects affected / exposed	20 / 104 (19.23%)		
occurrences (all)	25		
Diarrhoea			
subjects affected / exposed	28 / 104 (26.92%)		
occurrences (all)	71		
Dyspepsia			

subjects affected / exposed	11 / 104 (10.58%)		
occurrences (all)	14		
Flatulence			
subjects affected / exposed	6 / 104 (5.77%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	34 / 104 (32.69%)		
occurrences (all)	62		
Stomatitis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	19 / 104 (18.27%)		
occurrences (all)	38		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	5		
Actinic keratosis			
subjects affected / exposed	6 / 104 (5.77%)		
occurrences (all)	6		
Alopecia			
subjects affected / exposed	69 / 104 (66.35%)		
occurrences (all)	86		
Erythema			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	4		
Hair growth abnormal			
subjects affected / exposed	6 / 104 (5.77%)		
occurrences (all)	6		
Madarosis			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	5		

Night sweats			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	11 / 104 (10.58%)		
occurrences (all)	13		
Rash			
subjects affected / exposed	8 / 104 (7.69%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 104 (14.42%)		
occurrences (all)	18		
Arthritis			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	6 / 104 (5.77%)		
occurrences (all)	8		
Bone pain			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	75 / 104 (72.12%)		
occurrences (all)	179		
Muscular weakness			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	5		
Musculoskeletal chest pain			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	8		
Pain in extremity			

subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	9		
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	5 / 104 (4.81%)		
occurrences (all)	10		
Eye infection			
subjects affected / exposed	3 / 104 (2.88%)		
occurrences (all)	4		
Folliculitis			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	5		
Furuncle			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	4		
Infection			
subjects affected / exposed	4 / 104 (3.85%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	14 / 104 (13.46%)		
occurrences (all)	16		
Oral candidiasis			
subjects affected / exposed	2 / 104 (1.92%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	7 / 104 (6.73%)		
occurrences (all)	7		
Upper respiratory tract infection			
subjects affected / exposed	9 / 104 (8.65%)		
occurrences (all)	13		
Urinary tract infection			
subjects affected / exposed	10 / 104 (9.62%)		
occurrences (all)	13		

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 29 / 104 (27.88%) 47		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2008	In the safety plan intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 adverse events considered related to GDC-0449 that are likely to be life-threatening or irreversible, and when in the opinion of the investigator, the risk outweighs the benefit of continued treatment with GDC-0449. Added to Exclusion Criteria: Subjects with superficial multifocal BCC who may be considered unresectable due to breadth of involvement. Added to Tumor Assessments during Treatment, End of Study, or Early Termination: If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the subject is still deriving benefit from treatment, treatment with GDC-0449 should be continued, and the subject should be re-evaluated at the next tumor assessment time point.
15 January 2010	A requirement has been added for the investigator to consult the Medical Monitor before restarting GDC-0449 if a subject has experienced two treatment interruptions. In the eligibility criteria it has been clarified that for subjects with locally advanced BCC, the archival tissue submitted must be from a target lesion. It has been clarified that subjects with metastatic disease confined to bone are not considered eligible because of a lack of Response Evaluation Criteria In Solid Tumors (RECIST)-measurable disease, and that the Medical Monitor should be contacted if the investigator believes that a bone metastasis has an associated soft-tissue component that may be RECIST measurable. Inability or unwillingness to swallow capsules has been added as an exclusion criterion. Subjects who discontinue treatment with GDC-0449 but do not request withdrawal from the study will continue all study assessments. A requirement for a baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis has been added for subjects in the locally advanced cohort, to rule out occult metastatic disease or other preexisting radiographic abnormalities.
14 April 2011	The primary reason for the amendment is to provide safety updates. Specifically, the criteria for defining female subjects of childbearing and non-childbearing potential have been updated. The time period after which female subjects can become pregnant or plan to become pregnant following GDC-0449 treatment has been reduced from 12 months to 7 months. Sexually active male subjects must use a barrier form of contraception during GDC-0449 treatment and for 7 months after the last dose (previously 3 months) and should not donate sperm during this timeframe. In addition, the protocol now reflects the International Nonproprietary Name (INN) for GDC-0449: vismodegib. Language has been added to clarify that the study will continue after the completion of the planned analysis and that all subjects remaining on study will continue assessments and procedures according to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported