Clinical trial results:
A Phase II, multi-center, open-label, single-arm study of the efficacy and safety of oral LDE225 in patients with Hh-pathway activated relapsed medulloblastoma

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

Summary

EudraCT number	2012-003066-40
Trial protocol	SE IT ES DE GB FR NL BE HU
Global end of trial date	05 October 2016

Results information

Result version number	v1 (current)
This version publication date	11 July 2018
First version publication date	11 July 2018

Trial information

Trial identification

Sponsor protocol code	CLDE225C2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01708174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000880-PIP02-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of sonidegib with respect to Overall Response Rate (ORR) according to the independent central review (ICR).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2013
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	France: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	22
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	1
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Analyses were performed by treatment and by age group.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sonidegib (LDE225) Children

Arm description:

500 mg/m2 orally

Arm type	Experimental
Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

500 mg/m2 orally

Arm title	Sonidegib (LDE225) Adults

Arm description:

600 mg orally

Arm type	Experimental
Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

600 mg orally

Arm title	Temozolomide (TMZ)

Arm description:

150 to 200 mg/m2 for 5 sequential days every 4 weeks according to prescribing information until the study was amended to a single arm study.

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 to 200 mg/m2 for 5 sequential days every 4 weeks according to prescribing information until the study was amended to a single arm study.

Number of subjects in period 1	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)
Started	2	16	4
Pharmacokinetic analysis set	2	13 [1]	0 [2]
Completed	1	14	3
Not completed	1	2	1
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	-
Progressive disease	-	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of patients in the follow-up period 2 was less than the number of patients who started Period 1
Not all patients who completed the trial were available for the follow period of the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This arm was not analyzed in the follow-up period.

Period 2

Period 2 title	Survival follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sonidegib (LDE225) Children

Arm description:
500 mg/m2 orally

Arm type	Experimental
Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:
500 mg/m2 orally

Arm title	Sonidegib (LDE225) Adults

Arm description:
600 mg orally

Arm type	Experimental

Investigational medicinal product name	Sonidegib
Investigational medicinal product code	LDE225
Other name	
Pharmaceutical forms	Concentrate for oral suspension
Routes of administration	Oral use

Dosage and administration details:

600 mg orally

Number of subjects in period 2[3]	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults
Started	1	10
Completed	1	10

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of patients in the follow-up period 2 was less than the number of patients who started Period 1.
Not all patients who completed the trial were available for the follow period of the trial

Baseline characteristics

Reporting groups	
Reporting group title	Sonidegib (LDE225) Children
Reporting group description:	
500 mg/m2 orally	
Reporting group title	Sonidegib (LDE225) Adults
Reporting group description:	
600 mg orally	
Reporting group title	Temozolomide (TMZ)
Reporting group description:	
150 to 200 mg/m2 for 5 sequential days every 4 weeks according to prescribing information until the study was amended to a single arm study.	

Reporting group values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)
Number of subjects	2	16	4
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)	1	0	0
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	0	16	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
median	8.5	37	35.5
full range (min-max)	4 to 13	24 to 51	31 to 38
Gender, Male/Female			
Units: Subjects			
Female	2	5	2
Male	0	11	2

Reporting group values	Total		
Number of subjects	22		
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)	1		
Adolescents (12-17 years)	1		

Adults (18-64 years)	20		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
median			
full range (min-max)	-		
Gender, Male/Female			
Units: Subjects			
Female	9		
Male	13		

End points

End points reporting groups

Reporting group title	Sonidegib (LDE225) Children
Reporting group description: 500 mg/m2 orally	
Reporting group title	Sonidegib (LDE225) Adults
Reporting group description: 600 mg orally	
Reporting group title	Temozolomide (TMZ)
Reporting group description: 150 to 200 mg/m2 for 5 sequential days every 4 weeks according to prescribing information until the study was amended to a single arm study.	
Reporting group title	Sonidegib (LDE225) Children
Reporting group description: 500 mg/m2 orally	
Reporting group title	Sonidegib (LDE225) Adults
Reporting group description: 600 mg orally	

Primary: Percentage of participants with Overall response rate (ORR) according to Independent Review Committee (IRC) from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	Percentage of participants with Overall response rate (ORR) according to Independent Review Committee (IRC) from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016[1]

End point description:

ORR was defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR) (as per tumor response guidelines and criteria for Medulloblastoma). The IRC evaluated all radiological images and applicable clinical data (i.e., neurological examination, steroid use and cerebrospinal fluid (CSF) results as applicable). Assessments after crossover were not included for TMZ participants.

End point type	Primary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

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 were not performed for this endpoint.

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: Percentage of participants				
number (not applicable)	0	18.8	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) according to IRC from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	Progression free survival (PFS) according to IRC from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point description:

PFS was defined as the time from date of randomization to the date of event defined as the first documented progression or death due to any cause (as per tumor response guidelines and criteria for Medulloblastoma). The IRC evaluated all radiological images and applicable clinical data (i.e., neurological examination, steroid use and cerebrospinal fluid (CSF) results as applicable). TMZ participants without event prior to crossover were censored.

End point type	Secondary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: months				
median (confidence interval 95%)	1.6 (-9999 to 9999)	3.3 (1.7 to 17.1)	2.9 (0.9 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	PFS according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point description:

PFS was defined as the time from date of randomization to the date of event defined as the first documented progression or death due to any cause. PFS was evaluated by local Investigator assessment per tumor response guidelines and criteria for Medulloblastoma.

End point type	Secondary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: months				
median (confidence interval 95%)	9999 (1.6 to 9999)	3.3 (1.6 to 13)	2.9 (0.9 to 4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with ORR according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	Percentage of participants with ORR according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point description:

ORR was defined as the percentage of participants with best overall response of complete response (CR) or partial response (PR). ORR was evaluated by local Investigator assessment per tumor response guidelines and criteria for Medulloblastoma. Assessments after crossover were not included for TMZ patients.

End point type	Secondary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: Percentage of participants				
number (not applicable)	0	25	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	Duration of response (DoR) according to local Investigator assessment from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point description:

DoR was defined as the time from the first documented onset of confirmed PR or CR to the date of

PD/relapse or death due to medulloblastoma. DoR was evaluated by local Investigator assessment per tumor response guidelines and criteria for Medulloblastoma. TMZ participants without an event prior to crossover were censored.

End point type	Secondary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: months				
median (confidence interval 95%)	9999 (-9999 to 9999)	8.5 (4.1 to 16.6)	9999 (-9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point title	Overall survival (OS) from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point description:

OS was defined as the time from date of randomization to date of death due to any cause. All deaths are considered, including deaths occurred after crossover for TMZ participants.

End point type	Secondary

End point timeframe:

from date first participant randomized, 13-Sep-2013 to date of data cut-off, 15-Nov-2016

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults	Temozolomide (TMZ)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	16	4	
Units: months				
median (confidence interval 95%)	9999 (4.5 to 9999)	9.5 (4.9 to 15.6)	9999 (1.2 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Summary of plasma trough concentrations for Sonidegib (LDE225)

End point title	Pharmacokinetics (PK): Summary of plasma trough concentrations for Sonidegib (LDE225)[2]

End point description:

Blood samples were collected for assessment. The children's group was analyzed up until week 25 only.

End point type	Secondary

End point timeframe:

Weeks 1, 3, 5, 7, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49 and 53

Notes:

[2] - 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: The Temozolomide arm was not analyzed at this milestone.

End point values	Sonidegib (LDE225) Children	Sonidegib (LDE225) Adults		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	13		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1 (n=2,11)	0 (± 0)	0 (± 0)		
Week 3 (n=2,10)	2890 (± 1240)	761 (± 519)		
Week 5 (n=2,8)	4930 (± 1380)	1090 (± 700)		
Week 7 (n=1,8)	2810 (± 9999)	1450 (± 842)		
Week 9 (n=1,8)	4670 (± 9999)	1530 (± 682)		
Week 13 (n=1,4)	3680 (± 9999)	2330 (± 1100)		
Week 17 (n=1,6)	3060 (± 9999)	1880 (± 730)		
Week 21 (n=1,5)	3770 (± 9999)	2270 (± 915)		
Week 25 (n=1,4)	1890 (± 9999)	2050 (± 625)		
Week 29 (n=NA,4)	9999 (± 9999)	2050 (± 906)		
Week 33 (n=NA,4)	9999 (± 9999)	2180 (± 512)		
Week 37 (n=NA,3)	9999 (± 9999)	2850 (± 306)		
Week 41 (n=NA,4)	9999 (± 9999)	2370 (± 916)		
Week 45 (n=NA,2)	9999 (± 9999)	2890 (± 290)		
Week 49 (n=NA,2)	9999 (± 9999)	2330 (± 990)		
Week 53 (n=NA,2)	9999 (± 9999)	2080 (± 764)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Sonidegib (Children)
Reporting group description: Sonidegib (Children)	
Reporting group title	Temozolomide
Reporting group description: Temozolomide	
Reporting group title	Sonidegib (Total)
Reporting group description: Sonidegib (Total)	
Reporting group title	Sonidegib (Adult)
Reporting group description: Sonidegib (Adult)	

Serious adverse events	Sonidegib (Children)	Temozolomide	Sonidegib (Total)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 4 (25.00%)	11 / 18 (61.11%)
number of deaths (all causes)	1	1	12
number of deaths resulting from adverse events	0	0	0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
EMBOLISM			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
SEIZURE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
COUGH			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG DEPENDENCE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HALLUCINATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CLOSTRIDIAL INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SEPSIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
THROMBOSIS IN DEVICE			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERNATRAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sonidegib (Adult)		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)		
number of deaths (all causes)	11		

number of deaths resulting from adverse events	0		
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
EMBOLISM			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
SEIZURE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PAIN			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
NAUSEA			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DYSPNOEA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DRUG DEPENDENCE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
HALLUCINATION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NECK PAIN			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
BACTERIAL SEPSIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CLOSTRIDIAL INFECTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LUNG INFECTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
SEPSIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
THROMBOSIS IN DEVICE			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

HYPERNATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sonidegib (Children)	Temozolomide	Sonidegib (Total)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	4 / 4 (100.00%)	18 / 18 (100.00%)
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPERTENSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPOTENSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
THROMBOSIS			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
FATIGUE			
subjects affected / exposed	0 / 2 (0.00%)	2 / 4 (50.00%)	7 / 18 (38.89%)
occurrences (all)	0	2	9
GAIT DISTURBANCE			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
PYREXIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Immune system disorders			
ALLERGY TO ARTHROPOD BITE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
APNOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
ATELECTASIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
COUGH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
DYSPNOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
EPISTAXIS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
PRODUCTIVE COUGH			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PNEUMONITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
CONFUSIONAL STATE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
DEPRESSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
INSOMNIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
IRRITABILITY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 2 (50.00%)	1 / 4 (25.00%)	8 / 18 (44.44%)
occurrences (all)	1	1	9
BLOOD CREATINE PHOSPHOKINASE MB INCREASED			
subjects affected / exposed	1 / 2 (50.00%)	1 / 4 (25.00%)	2 / 18 (11.11%)
occurrences (all)	1	1	2
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	4
BLOOD PHOSPHORUS INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
BODY TEMPERATURE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
GRANULOCYTE COUNT INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
CRYSTAL URINE PRESENT			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
OXYGEN SATURATION DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	5 / 18 (27.78%)
occurrences (all)	0	1	6
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
RED BLOOD CELL COUNT DECREASED			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PROTHROMBIN TIME PROLONGED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
RED BLOOD CELL SEDIMENTATION RATE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
WEIGHT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	2 / 18 (11.11%)
occurrences (all)	0	1	4
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cardiac disorders			
ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Nervous system disorders			
APHASIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
ATAXIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	1

DIZZINESS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	3 / 18 (16.67%)
occurrences (all)	0	1	3
DROOLING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
DYSARTHRIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
DYSGEUSIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	5 / 18 (27.78%)
occurrences (all)	0	0	6
FACIAL NERVE DISORDER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HEADACHE			
subjects affected / exposed	2 / 2 (100.00%)	1 / 4 (25.00%)	5 / 18 (27.78%)
occurrences (all)	2	1	6
HEMIPARESIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
IIIRD NERVE DISORDER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
LETHARGY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
MUSCLE SPASTICITY			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
MYOCLONUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2

NYSTAGMUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PARAESTHESIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PYRAMIDAL TRACT SYNDROME			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
SCIATICA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
SYNCOPE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
SOMNOLENCE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	4
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
EAR CONGESTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
VERTIGO			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye disorders			

DIPLOPIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PHOTOPHOBIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
VISION BLURRED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
ABDOMINAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	2 / 18 (11.11%)
occurrences (all)	0	2	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
AEROPHAGIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
ANAL INCONTINENCE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
CONSTIPATION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	6 / 18 (33.33%)
occurrences (all)	0	1	7
DYSPHAGIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
DIARRHOEA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	1	0	5
PARAESTHESIA ORAL			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
NAUSEA			
subjects affected / exposed	0 / 2 (0.00%)	3 / 4 (75.00%)	5 / 18 (27.78%)
occurrences (all)	0	4	9
HAEMATOCHEZIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
TOOTH LOSS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
TOOTH DISCOLOURATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
REGURGITATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
VOMITING			
subjects affected / exposed	2 / 2 (100.00%)	1 / 4 (25.00%)	9 / 18 (50.00%)
occurrences (all)	4	1	15
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
ALOPECIA			
subjects affected / exposed	2 / 2 (100.00%)	0 / 4 (0.00%)	8 / 18 (44.44%)
occurrences (all)	2	0	8
DRY SKIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPERHIDROSIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
ERYTHEMA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

PRURITUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
RASH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
MICTURITION URGENCY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
PROTEINURIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
URINARY RETENTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Endocrine disorders			
DIABETES INSIPIDUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
BACK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	4
MUSCLE SPASMS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	4

MYALGIA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	6 / 18 (33.33%)
occurrences (all)	1	0	8
NECK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	3 / 18 (16.67%)
occurrences (all)	0	1	3
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 2 (50.00%)	1 / 4 (25.00%)	3 / 18 (16.67%)
occurrences (all)	1	1	3
Infections and infestations			
ACINETOBACTER INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
FOLLICULITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
ORAL HERPES			
subjects affected / exposed	1 / 2 (50.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
RHINITIS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	5
FAILURE TO THRIVE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPERCALCAEMIA			

subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
HYPERURICAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
HYPOCALCAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
HYPONATRAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	5
HYPOKALAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	4 / 18 (22.22%)
occurrences (all)	0	0	4
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2

Non-serious adverse events	Sonidegib (Adult)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPERTENSION			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPOTENSION			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
THROMBOSIS			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
FATIGUE			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	9		
GAIT DISTURBANCE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
PAIN			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
PYREXIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Immune system disorders			
ALLERGY TO ARTHROPOD BITE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

APNOEA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
ATELECTASIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
COUGH			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
DYSPNOEA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
EPISTAXIS			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
PNEUMONITIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
CONFUSIONAL STATE			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
DEPRESSION			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
INSOMNIA			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
IRRITABILITY			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	8		
BLOOD CREATINE PHOSPHOKINASE MB INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
BLOOD CREATININE INCREASED			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
BLOOD PHOSPHORUS INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
BODY TEMPERATURE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
C-REACTIVE PROTEIN INCREASED			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
GRANULOCYTE COUNT INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
CRYSTAL URINE PRESENT			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
OXYGEN SATURATION DECREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	6		
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
RED BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
PROTHROMBIN TIME PROLONGED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
RED BLOOD CELL SEDIMENTATION RATE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
WEIGHT DECREASED			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	4		
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			

ATRIOVENTRICULAR BLOCK FIRST DEGREE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
SINUS TACHYCARDIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Nervous system disorders			
APHASIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
ATAXIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
DIZZINESS			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
DROOLING			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
DYSARTHRIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
DYSGEUSIA			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	6		
FACIAL NERVE DISORDER			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HEADACHE			

subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
HEMIPARESIS				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
IIIRD NERVE DISORDER				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
LETHARGY				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
MUSCLE SPASTICITY				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
MYOCLONUS				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
NEUROPATHY PERIPHERAL				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
NYSTAGMUS				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
PARAESTHESIA				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
PERIPHERAL MOTOR NEUROPATHY				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
PYRAMIDAL TRACT SYNDROME				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
SCIATICA				
subjects affected / exposed	0 / 16 (0.00%)			
occurrences (all)	0			
SYNCOPE				

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
SOMNOLENCE			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear and labyrinth disorders			
EAR CONGESTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
VERTIGO			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Eye disorders			
DIPLOPIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
PHOTOPHOBIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
VISION BLURRED			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
ABDOMINAL PAIN			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
ABDOMINAL PAIN UPPER			

subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
AEROPHAGIA				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
ANAL INCONTINENCE				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
CONSTIPATION				
subjects affected / exposed	6 / 16 (37.50%)			
occurrences (all)	7			
DYSPHAGIA				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
DIARRHOEA				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	4			
PARAESTHESIA ORAL				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
NAUSEA				
subjects affected / exposed	5 / 16 (31.25%)			
occurrences (all)	9			
HAEMATOCHEZIA				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
TOOTH LOSS				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
TOOTH DISCOLOURATION				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
REGURGITATION				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
VOMITING				

subjects affected / exposed occurrences (all)	7 / 16 (43.75%) 11		
Skin and subcutaneous tissue disorders DERMATITIS ACNEIFORM subjects affected / exposed occurrences (all) ALOPECIA subjects affected / exposed occurrences (all) DRY SKIN subjects affected / exposed occurrences (all) HYPERHIDROSIS subjects affected / exposed occurrences (all) ERYTHEMA subjects affected / exposed occurrences (all) PRURITUS subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all) RASH MACULO-PAPULAR subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 6 / 16 (37.50%) 6 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Renal and urinary disorders HAEMATURIA subjects affected / exposed occurrences (all) MICTURITION URGENCY subjects affected / exposed occurrences (all) PROTEINURIA	 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
URINARY RETENTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Endocrine disorders			
DIABETES INSIPIDUS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
BACK PAIN			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
MUSCLE SPASMS			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
MYALGIA			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	7		
NECK PAIN			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Infections and infestations			
ACINETOBACTER INFECTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
FOLLICULITIS			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
ORAL HERPES			

subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
RHINITIS			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
FAILURE TO THRIVE			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPERCALCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
HYPERURICAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
HYPOCALCAEMIA			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
HYPOMAGNESAEMIA			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
HYPONATRAEMIA			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		
HYPOKALAEMIA			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
HYPOPHOSPHATAEMIA			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2013	Protocol Version 1/Amendment 1 was issued before an eligible patient was identified. Key changes included: • Specifying a minimum number of pediatric patients • Addition of an exploratory objective to assess effects on bone and cartilage markers for pediatric patients • Collection of additional data (Tanner staging and age at menarche) to support interpretation of bone growth plate assessments in pediatric patients
17 April 2014	Protocol Version 2/Amendment 2 was issued after 11 patients (ten adults and one pediatric patient) had been enrolled and treated. Protocol Version 2 reduced the scope of the study to a single-arm Phase II study and decreased the total number of patients to be enrolled to 20. While the original estimation of Hh pathway mutation rate in patients with MB was approximately 20% – 30%, of 79 pediatric patients screened for Hh activation to date, approximately 5% were Hh-activated. In addition, many potential patients had a prior history of treatment with temozolomide, which led to an imbalance in patients eligible for the randomized arms. Other key changes included • All patients who had been assigned to the temozolomide arm were switched to sonidegib treatment • The time period for which women of child-bearing potential were required to use highly effective contraception after the final dose of study treatment was increased to 20 months • Guidance on management of suspected sonidegib-related toxicity was updated with respect to musculoskeletal toxicities.
22 June 2015	Protocol Version 3/Amendment 3 (22-Jun-2015) was issued when enrollment in the study was completed (total enrollment 22 patients) and five patients remained on study treatment. The purpose was to allow patients who were deriving clinical benefit according to the Investigator, to continue to receive sonidegib until discontinuation criteria were met or until other alternatives became available. The timing of the final analysis was changed to the point when all patients have discontinued the study treatment and completed the 30-day Safety Follow-up Period. Other key changes follow: • Several assessments that were collected and evaluated (tumor assessment, neurological assessment, lumbar puncture assessment, steroid use information, ECG) by ICR were to be reviewed locally after study Week 105 • The frequency of study visits and evaluations after Week 105 was changed to every 12 weeks • The schedule of assessments was modified for visits after Week 105 so that physical exam, weight, vital signs, ECG, and performance status assessments were performed per local standard of care • The dose modification table for CK was replaced with the program level updates (urine myoglobin and muscle biopsy were no longer applicable) These amendments affected the interpretation of study results per the initial design, as only four patients had been enrolled in the comparator arm (temozolomide) before the study was changed from a two-arm comparative study to a single-arm study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: