Clinical trial results:
A phase I/II multicenter, open-label study of CLR457 administered orally in adult patients with advanced solid malignancies

Summary

EudraCT number	2014-000316-34
Trial protocol	FR IT
Global end of trial date	12 November 2015

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	CCLR457X2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02189174
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)	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	12 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To determine the maximum tolerated dose (MTD) or recommended dose (RP2D) of CLR457 (dose escalation phase I)
2. To investigate the anti-tumor activity of CLR457 (Phase II)

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	07 August 2014
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	Canada: 4
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	31
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a Phase 1/2, multi-center open-label study. Phase 1 was the dose escalation part to determine the maximum tolerated dose (MTD) or recommended dose for phase 2 (RP2D). Due to poor tolerability and lack of efficacy, the study was terminated and phase 2 was not conducted.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CLR457 5 mg

Arm description:

Patients received CLR457 5 mg orally once daily until they met the criteria for study discontinuation.

Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5mg CLR457 orally once daily

Arm title	CLR457 10 mg

Arm description:

Patients received CLR457 10 mg orally once daily until they met the criteria for study discontinuation.

Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10mg CLR457 orally once daily

Arm title	CLR457 20 mg

Arm description:

Patients received CLR457 20 mg orally once daily until they met the criteria for study discontinuation.

Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20mg CLR457 orally once daily

Arm title	CLR457 40 mg
Arm description:	
Patients received CLR457 40 mg orally once daily until they met the criteria for study discontinuation.	
Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
40mg CLR457 orally once daily	
Arm title	CLR457 70 mg
Arm description:	
Patients received CLR457 70 mg orally once daily until they met the criteria for study discontinuation.	
Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
70mg CLR457 orally once daily	
Arm title	CLR457 100 mg
Arm description:	
Patients received CLR457 100 mg orally once daily until they met the criteria for study discontinuation.	
Arm type	Experimental
Investigational medicinal product name	CLR457
Investigational medicinal product code	CLR457
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
100mg CLR457 orally once daily	

Number of subjects in period 1	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg
Started	2	3	4
Completed	0	0	0
Not completed	2	3	4
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Progressive disease	2	3	4

Number of subjects in period 1	CLR457 40 mg	CLR457 70 mg	CLR457 100 mg
Started	5	6	11

Completed	0	0	0
Not completed	5	6	11
Consent withdrawn by subject	1	-	2
Physician decision	-	-	2
Adverse event, non-fatal	1	-	4
Progressive disease	3	6	3

Baseline characteristics

Reporting groups	
Reporting group title	CLR457 5 mg
Reporting group description:	
Patients received CLR457 5 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 10 mg
Reporting group description:	
Patients received CLR457 10 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 20 mg
Reporting group description:	
Patients received CLR457 20 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 40 mg
Reporting group description:	
Patients received CLR457 40 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 70 mg
Reporting group description:	
Patients received CLR457 70 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 100 mg
Reporting group description:	
Patients received CLR457 100 mg orally once daily until they met the criteria for study discontinuation.	

Reporting group values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg
Number of subjects	2	3	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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	1
From 65-84 years	1	2	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	57	62.7	68.5
standard deviation	± 14.14	± 8.5	± 10.12
Gender categorical Units: Subjects			
Female	1	2	2
Male	1	1	2

Reporting group values	CLR457 40 mg	CLR457 70 mg	CLR457 100 mg
Number of subjects	5	6	11

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)	4	5	7
From 65-84 years	1	1	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60	59.8	59.9
standard deviation	± 8.09	± 10.42	± 9.65
Gender categorical Units: Subjects			
Female	5	5	8
Male	0	1	3

Reporting group values	Total		
Number of subjects	31		
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)	19		
From 65-84 years	12		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	23		
Male	8		

End points

End points reporting groups

Reporting group title	CLR457 5 mg
Reporting group description:	
Patients received CLR457 5 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 10 mg
Reporting group description:	
Patients received CLR457 10 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 20 mg
Reporting group description:	
Patients received CLR457 20 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 40 mg
Reporting group description:	
Patients received CLR457 40 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 70 mg
Reporting group description:	
Patients received CLR457 70 mg orally once daily until they met the criteria for study discontinuation.	
Reporting group title	CLR457 100 mg
Reporting group description:	
Patients received CLR457 100 mg orally once daily until they met the criteria for study discontinuation.	

Primary: Best Overall Response - Phase 1

End point title	Best Overall Response - Phase 1[1]
End point description:	
Tumor response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Categories assessed were complete response (CR), partial response (PR), non-CR/non-progressive disease, stable disease (SD1), progressive disease, unknown, overall response rate (ORR: CR+PR) and disease control rate (DCR: CR+PR+SD1+Non-CR/non-progressive disease).	
End point type	Primary
End point timeframe:	
28 days	

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 does not apply to this end point.

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: Patients				
CR	0	0	0	0
PR	0	0	0	0
Non-CR/non-progressive disease	0	0	0	1
SD1	0	0	0	2
Progressive disease	2	3	4	2
Unknown	0	0	0	0
ORR	0	0	0	0
DCR	0	0	0	3

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Patients				
CR	0	0		
PR	0	0		
Non-CR/non-progressive disease	0	1		
SD1	2	4		
Progressive disease	3	3		
Unknown	1	3		
ORR	0	0		
DCR	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: area under the plasma concentration-time curve from time 0 to 24 hours (AUC0_24h)

End point title	Pharmacokinetic (PK) parameter: area under the plasma concentration-time curve from time 0 to 24 hours (AUC0_24h)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 1: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1182 (± 40.8)	2241 (± 7.5)	6718 (± 41.6)	9567 (± 34.9)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	10537 (± 47.6)	18390 (± 25.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: observed maximum plasma concentration following administration (Cmax)

End point title	PK parameter: observed maximum plasma concentration following administration (Cmax)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 1: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)	100 (± 0.4)	230 (± 24.5)	475 (± 24.2)	687 (± 47.2)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	732 (± 44.8)	1449 (± 28.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: time to reach the maximum concentration after drug administration (Tmax)

End point title	PK parameter: time to reach the maximum concentration after drug administration (Tmax)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 1: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: hour				
median (full range (min-max))	2.5 (1 to 4)	1 (0.917 to 2)	2.51 (2.05 to 3.95)	2.07 (0.983 to 6)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: hour				
median (full range (min-max))	3.5 (0.717 to 24.1)	2.93 (0.5 to 7.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: area under the plasma concentration-time curve from time zero to the end of dosing interval tau at steady state (AUCtau)

End point title	PK parameter: area under the plasma concentration-time curve from time zero to the end of dosing interval tau at steady state (AUCtau)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1665 (± 81.7)	2846 (± 25.5)	7662 (± 45.3)	11727 (± 39)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	14762 (± 37.1)	23754 (± 40.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: lowest plasma concentration observed during a dosing interval at steady state (Cmin)

End point title	PK parameter: lowest plasma concentration observed during a dosing interval at steady state (Cmin)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: ng/mL				
geometric mean (geometric coefficient of variation)	18 (± 291.6)	48 (± 48.2)	148 (± 56.3)	270 (± 84.8)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	257 (± 31.4)	148 (± 726)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: apparent systemic clearance from plasma following extravascular administration (CL/F)

End point title	PK parameter: apparent systemic clearance from plasma following extravascular administration (CL/F)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: mL/h				
geometric mean (geometric coefficient of variation)	3003 (± 81.7)	3514 (± 25.5)	2610 (± 45.3)	3411 (± 39)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: mL/h				
geometric mean (geometric coefficient of variation)	4742 (± 37.1)	4210 (± 40.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: apparent volume of distribution using the terminal elimination phase following extravascular administration (V/F)

End point title	PK parameter: apparent volume of distribution using the terminal elimination phase following extravascular administration (V/F)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: mL				
geometric mean (geometric coefficient of variation)	43139 (± 6.6)	66520 (± 11.5)	55193 (± 32.1)	115503 (± 109.2)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: mL				
geometric mean (geometric coefficient of variation)	72822 (± 49.9)	67311 (± 38.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: accumulation ration (Racc)

End point title	PK parameter: accumulation ration (Racc)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: ratio				
geometric mean (geometric coefficient of variation)	1.4 (± 33.4)	1.3 (± 24.3)	1.1 (± 28.4)	1.3 (± 38.4)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ratio				
geometric mean (geometric coefficient of variation)	1.4 (± 29.5)	1.3 (± 37)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: effective half-life based on drug accumulation at steady state (T1/2, acc)

End point title	PK parameter: effective half-life based on drug accumulation at steady state (T1/2, acc)

End point description:

Plasma samples were collected and analyzed.

End point type	Secondary

End point timeframe:

Day 15: pre-dose at 0 hour (h), post dose at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h

End point values	CLR457 5 mg	CLR457 10 mg	CLR457 20 mg	CLR457 40 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	4
Units: hour				
median (full range (min-max))	13.9 (7.58 to 20.2)	7.92 (6.53 to 18.4)	11.8 (5.71 to 15.3)	11 (4.13 to 27.9)

End point values	CLR457 70 mg	CLR457 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: hour				
median (full range (min-max))	16.8 (11.9 to 23.7)	12.1 (5.04 to 27)		

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	18.1

Reporting groups

Reporting group title	CLR457 5 mg
Reporting group description:	
CLR457 5 mg	
Reporting group title	CLR457 10 mg
Reporting group description:	
CLR457 10 mg	
Reporting group title	CLR457 100 mg
Reporting group description:	
CLR457 100 mg	
Reporting group title	CLR457 40 mg
Reporting group description:	
CLR457 40 mg	
Reporting group title	CLR457 70 mg
Reporting group description:	
CLR457 70 mg	
Reporting group title	CLR457 20 mg
Reporting group description:	
CLR457 20 mg	

Serious adverse events	CLR457 5 mg	CLR457 10 mg	CLR457 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	7 / 11 (63.64%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
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 CREATININE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
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			
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
ABDOMINAL PAIN LOWER			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PNEUMONITIS			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
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 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CLR457 40 mg	CLR457 70 mg	CLR457 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	5 / 6 (83.33%)	2 / 4 (50.00%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	0	0
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PNEUMONITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CLR457 5 mg	CLR457 10 mg	CLR457 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
EMBOLISM			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPERTENSION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	2
FACE OEDEMA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
CHILLS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
FATIGUE			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	6 / 11 (54.55%)
occurrences (all)	1	1	6
FEELING ABNORMAL			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
LOCALISED OEDEMA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
MALAISE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	8 / 11 (72.73%)
occurrences (all)	0	0	13
THIRST			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
VAGINAL DISCHARGE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PELVIC PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	4 / 11 (36.36%)
occurrences (all)	0	0	4
DYSPHONIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DYSPNOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
EPISTAXIS			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
HICCUPS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPOXIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NASAL INFLAMMATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
RHINORRHOEA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
UPPER-AIRWAY COUGH SYNDROME			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Psychiatric disorders			
AGITATION			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DELIRIUM			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
ANXIETY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
DEPRESSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DISORIENTATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INSOMNIA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
AMYLASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
BLOOD BILIRUBIN INCREASED			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	3
LIPASE INCREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	5
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

CONTUSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
FALL			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DYSKINESIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DYSGEUSIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
HEADACHE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
SYNCOPE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
SCIATICA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPERSOMNIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			

LYMPHOPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
NEUTROPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ANAEMIA			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Eye disorders			
VISION BLURRED			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
VITREOUS FLOATERS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ABDOMINAL PAIN			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
CHEILITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DRY MOUTH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
DIARRHOEA			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	5 / 11 (45.45%)
occurrences (all)	0	0	9
CONSTIPATION			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
DYSPEPSIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DYSPHAGIA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
GASTRIC ULCER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
GLOSSITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HAEMATEMESIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
LIP SWELLING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
NAUSEA			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	4 / 11 (36.36%)
occurrences (all)	1	1	4
OBSTRUCTION GASTRIC			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	10 / 11 (90.91%)
occurrences (all)	0	0	12

RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
VOMITING			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
DECUBITUS ULCER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DRY SKIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
ERYTHEMA			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
NAIL DISORDER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ONYCHALGIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
PRURITUS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
RASH			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
RASH MACULAR			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	7 / 11 (63.64%)
occurrences (all)	0	0	8
RASH PRURITIC			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
SWELLING FACE			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
POLLAKIURIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
PROTEINURIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
BACK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
MUSCLE SPASMS			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MUSCULAR WEAKNESS			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MUSCULOSKELETAL DISORDER			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
MYALGIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
NECK PAIN			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
CANDIDA INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
KLEBSIELLA BACTERAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
MUCOSAL INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
LUNG INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
PNEUMONIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2

SKIN INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
WOUND INFECTION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	4 / 11 (36.36%)
occurrences (all)	1	0	4
DEHYDRATION			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
HYPOCALCAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	5 / 11 (45.45%)
occurrences (all)	0	0	7
HYPERCALCAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
GOUT			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
HYPOKALAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	3
HYPONATRAEMIA			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2

Non-serious adverse events	CLR457 40 mg	CLR457 70 mg	CLR457 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 6 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
EMBOLISM			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HYPERTENSION			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	2
FACE OEDEMA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
CHILLS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
FATIGUE			
subjects affected / exposed	3 / 5 (60.00%)	5 / 6 (83.33%)	2 / 4 (50.00%)
occurrences (all)	3	6	2

FEELING ABNORMAL			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
LOCALISED OEDEMA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MALAISE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
PYREXIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
THIRST			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
SEASONAL ALLERGY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
VAGINAL DISCHARGE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
PELVIC PAIN			

subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 5 (80.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	4	1	0
DYSPHONIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
DYSPNOEA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
EPISTAXIS			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HICCUPS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPOXIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
NASAL INFLAMMATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
RHINORRHOEA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
UPPER-AIRWAY COUGH SYNDROME			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
DELIRIUM			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ANXIETY			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
DEPRESSION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
DISORIENTATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
INSOMNIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
AMYLASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ASPARTATE AMINOTRANSFERASE			

INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
LIPASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	4	0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
WEIGHT DECREASED			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
FALL			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
DYSKINESIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DYSGEUSIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
HEADACHE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
SYNCOPE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SCIATICA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
HYPERSOMNIA			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
NEUTROPENIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
ANAEMIA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	3	1
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
VISION BLURRED			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
VITREOUS FLOATERS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
ABDOMINAL PAIN			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	1	2	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
CHEILITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			

subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
DIARRHOEA			
subjects affected / exposed	4 / 5 (80.00%)	4 / 6 (66.67%)	0 / 4 (0.00%)
occurrences (all)	4	8	0
CONSTIPATION			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	3	2	1
DYSPEPSIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
DYSPHAGIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
GASTRIC ULCER			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
GLOSSITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HAEMATEMESIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
LIP SWELLING			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NAUSEA			
subjects affected / exposed	3 / 5 (60.00%)	4 / 6 (66.67%)	1 / 4 (25.00%)
occurrences (all)	3	6	1
OBSTRUCTION GASTRIC			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

STOMATITIS			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	2	0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
VOMITING			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	4	2
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
DECUBITUS ULCER			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
DRY SKIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
ERYTHEMA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
NAIL DISORDER			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
ONYCHALGIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
RASH			

subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	5	1
RASH MACULAR			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
RASH MACULO-PAPULAR			
subjects affected / exposed	2 / 5 (40.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	3	0
RASH PRURITIC			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
SWELLING FACE			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
POLLAKIURIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
PROTEINURIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
BACK PAIN			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	2	2
MUSCLE SPASMS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
MUSCULOSKELETAL DISORDER			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
MYALGIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
NECK PAIN			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
CANDIDA INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
KLEBSIELLA BACTERAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
MUCOSAL INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
LUNG INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
PNEUMONIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0

URINARY TRACT INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
SKIN INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
WOUND INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	2 / 4 (50.00%)
occurrences (all)	3	3	3
DEHYDRATION			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPOCALCAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
HYPERCALCAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
GOUT			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
HYPOKALAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
HYPOMAGNESAEMIA			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	3	2	3
HYPONATRAEMIA			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2014	This amendment addressed the following revisions requested by Heath Authorities. The main objective was to increase patient safety mainly based on potential toxicities related to CLR457 and patient medical history: Change in dose limiting toxicity criteria for hematologic and hepatic toxicities and corresponding dose modification criteria; change in exclusion criteria; and clarification that Japanese patients are required to be hospitalized during Cycle 1 of Phase I.
13 November 2014	The rational for this amendment was to comply with Health Authority request to include the following: change in exclusion criteria to exclude patient with current or past history of interstitial lung disease/pneumonitis; clarification regarding dose limiting toxicity criteria for hematologic toxicity in case of use of hematopoietic colony-stimulating growth factors; clarity on the definition of "women of childbearing potential"; and increase in the period for contraceptive measures for female participants to 1 month and 3 months for male participants after study drug discontinuation. FOR JAPAN ONLY: For patients under the age of 20 years additional written consent was needed from his/her legal representative and an Appendix 9 was provided to Protocol to add guidance for management of hepatitis B virus infection to raise awareness of the Investigators on this topic.
16 December 2014	Because laboratory assessments for pancreatic enzymes were not included in the laboratory parameters collection plan, lipase and amylase laboratory tests were now added to allow monitoring of pancreatic function. In addition sodium measurements were added to the laboratory collection plan to complete the electrolyte panel. QT prolonging agents were clarified to be prohibited throughout the study to align with the exclusion criteria. Clarification was provided regarding the operational aspects of the Novartis optional companion sample collection protocol studying treatment resistance. Integrated Response Technology was not used for Phase II due to system set -up limitations. The assignment of a patient to a particular group was coordinated by Novartis both in Phase I and Phase II. The duration of the follow-up period of the newborn and mother in case of pregnancy was missing and was added in this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported