Clinical trial results:
A phase Ib, open-label, multicenter, dose escalation and expansion study, to evaluate the safety, pharmacokinetics and activity of INC280 in combination with cetuximab in c-MET positive CRC and HNSCC patients who have progressed after anti-EGFR monoclonal antibody therapy

Summary

EudraCT number	2014-000579-20
Trial protocol	ES IT DE BE
Global end of trial date	20 January 2017

Results information

Result version number	v1 (current)
This version publication date	27 January 2018
First version publication date	27 January 2018

Trial information

Trial identification

Sponsor protocol code	CINC280X2104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02205398
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the maximum tolerated dose (MTD) and/or recommended dose of INC280 in combination with cetuximab in c-MET positive mCRC and HNSCC patients.

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	28 July 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	United States: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	13
EEA total number of subjects	8

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)	9
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 13 patients were enrolled in the study between first patient first visit (FPFV, 28-Jul-2014) and last patient last visit (LPLV, 20-Jan-2017). All 13 patients discontinued treatment, among these, 12 patients discontinued due to progressive disease and one patient had AEs leading to study treatment discontinuation.

Pre-assignment

Screening details:

The patient population of the study consists of adult patients with K/NRAS WT and c-MET positive mCRC and c-MET positive recurrent/metastatic HNSCC who have received at least one previous line of treatment for the metastatic disease. The last treatment should include an anti-EGFR antibody (cetuximab/panitumumab or only cetuximab for HNSCC).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	INC280 150 mg BID + Cetuximab

Arm description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	INC280 and cetuximab
Investigational medicinal product code	
Other name	BID
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for INC280 was 150 mg bid, administered continuously twice a day (bid) dosing regimen and in combination with a fixed dose of intravenous infusion of cetuximab (400 mg/m2 initial infusion and 250 mg/m2 on subsequent infusions) every week (qwk) in 28-day cycles.

Arm title	INC280 300 mg BID + Cetuximab

Arm description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	INC280 and cetuximab
Investigational medicinal product code	
Other name	BID
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for INC280 was 300 mg bid, administered continuously twice a day (bid) dosing regimen and in combination with a fixed dose of intravenous infusion of cetuximab (400 mg/m2 initial infusion and 250 mg/m2 on subsequent infusions) every week (qwk) in 28-day cycles.

Arm title	INC280 400 mg BID + Cetuximab

Arm description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	INC280 and cetuximab
Investigational medicinal product code	
Other name	BID
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose for INC280 was 400 mg bid, administered continuously twice a day (bid) dosing regimen and in combination with a fixed dose of intravenous infusion of cetuximab (400 mg/m2 initial infusion and 250 mg/m2 on subsequent infusions) every week (qwk) in 28-day cycles.

Number of subjects in period 1	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab
Started	4	3	6
Completed	0	0	0
Not completed	4	3	6
INC280 150 mg BID + Cetuximab	4	3	-
Adverse event, non-fatal	-	-	1
Progressive disease	-	-	5

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	58.9		
standard deviation	± 12.97	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	11	11	

Subject analysis sets

Subject analysis set title	INC280 150 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Subject analysis set title	INC280 300 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Subject analysis set title	INC280 400 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Reporting group values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab
Number of subjects	4	3	6
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)	3	2	4
From 65-84 years	1	1	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.3	64.0	61.8
standard deviation	± 18.32	± 40.74	± 7.25
Gender categorical Units: Subjects			
Female	1	1	0
Male	3	2	6

End points

End points reporting groups

Reporting group title	INC280 150 mg BID + Cetuximab

Reporting group description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Reporting group title	INC280 300 mg BID + Cetuximab

Reporting group description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Reporting group title	INC280 400 mg BID + Cetuximab

Reporting group description:

The starting dose for INC280 was 150 mg bid, administered continuously in combination with a fixed dose of cetuximab of 400 mg/m2 as the initial dose (C1D1) and 250 mg/m2 as subsequent weekly doses in 28-day cycles.

Subject analysis set title	INC280 150 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Subject analysis set title	INC280 300 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Subject analysis set title	INC280 400 mg BID + Cetuximab
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

Primary: Maximum tolerated dose (MTD) and/or recommended dose of INC280 in combination with cetuximab in c-MET positive mCRC and HNSCC patients

End point title	Maximum tolerated dose (MTD) and/or recommended dose of INC280 in combination with cetuximab in c-MET positive mCRC and HNSCC patients[1]

End point description:

MTD and/or RP2D of INC280 in combination with cetuximab, by evaluating number of patients who experienced toxicity that fulfills the criteria for a DLT).
This analysis was done in the Dose Determining set (DDS). DDS consisted of all patients in the dose escalation part from the Safety Set who meet the minimum exposure to study treatment criterion and had sufficient safety evaluations during Cycle 1, or discontinued earlier due to DLT during Cycle 1.

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: No comparative statistical analysis was conducted for this endpoint. The relationship between dose and the probability of DLT was modelled using adaptive Bayesian logistic regression model with overdose control principle.

End point values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	3	6	
Units: Number of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Preliminary anti-tumor activity of the INC280 and cetuximab combination

End point title	Preliminary anti-tumor activity of the INC280 and cetuximab combination

End point description:

ORR is the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR).
This analysis was done in the full analysis set (FAS). FAS comprised of all patients who received at least one full or partial dose of INC280 or cetuximab. The FAS was used for all listings of raw data. Unless otherwise specified the FAS was the default analysis set used for all analyses.

End point type	Secondary

End point timeframe:

12 months

End point values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	3	6	
Units: Number of participants				
Complete response	0	0	0	
Partial response	0	0	0	
Stable disease	1	1	4	
Progressive disease	2	1	2	
Unknown	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

To assess additional clinical activity of the INC280 and cetuximab combination as measured by Overall Survival for patients in the expansion part of the study. The end of study was upon completion of the survival follow-up period of the last patient treated with the combination of INC280 and cetuximab.
The trial was terminated due to difficulties in identifying patients who met the eligibility criteria. As such the expansion arm was not opened and overall survival was not analyzed.

End point type	Secondary

End point timeframe:

Every 12 weeks until the end of the trial

End point values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Number of participants				

Notes:

[2] - As a result of early termination, overall survival was not analyzed.

[3] - As a result of early termination, overall survival was not analyzed.

[4] - As a result of early termination, overall survival was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time versus plasma concentration profiles and basic PK parameters of INC280

End point title	Time versus plasma concentration profiles and basic PK parameters of INC280

End point description:

To characterize the PK profile of INC280 with cetuximab combination as measured by time versus plasma concentration profiles and basic PK parameters of INC280. A treatment cycle was defined as 28 days with no scheduled break between cycles.
The trial was terminated because of difficulties in identifying patients who met the eligibility criteria.

End point type	Secondary

End point timeframe:

During the first 4 Cycles of treatment or up to 16 weeks from the time of study treatment start

End point values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: Number of participants				

Notes:

[5] - As a result of early termination, basic pharmacokinetic parameters were not analyzed.

[6] - As a result of early termination, basic pharmacokinetic parameters were not analyzed.

[7] - As a result of early termination, basic pharmacokinetic parameters were not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival of INC280 and cetuximab combination – expansion part

End point title	Progression Free Survival of INC280 and cetuximab combination – expansion part

End point description:

To assess preliminary anti-tumor activity of the INC280 and cetuximab combination as measured by Progression Free Survival in patients treated with the combination of INC280 and cetuximab.The end of study was upon completion of the survival follow-up period of the last patient treated with the combination of INC280 and cetuximab.
The trial was terminated because of difficulties in identifying patients who met the eligibility criteria.

End point type	Secondary

End point timeframe:

Every 8 weeks from C1D1 until the end of study for up to 3 years

End point values	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: Number of participants				

Notes:

[8] - As a result of early termination, progression free survival was not analyzed.

[9] - As a result of early termination, progression free survival was not analyzed.

[10] - As a result of early termination, progression free survival was not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first administration of any study drug to 30 days after date of last actual administration of any study drug (including start and stop date).

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	20.0

Reporting groups

Reporting group title	INC280 150 mg BID + Cetuximab
Reporting group description:	
INC280 150 mg BID + Cetuximab	
Reporting group title	INC280 300 mg BID + Cetuximab
Reporting group description:	
INC280 300 mg BID + Cetuximab	
Reporting group title	INC280 400 mg BID + Cetuximab
Reporting group description:	
INC280 400 mg BID + Cetuximab	
Reporting group title	All patients
Reporting group description:	
All patients	

Serious adverse events	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (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
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (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
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (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
Lung infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (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
Pneumonia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (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
Sepsis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	INC280 150 mg BID + Cetuximab	INC280 300 mg BID + Cetuximab	INC280 400 mg BID + Cetuximab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	2 / 3 (66.67%)	4 / 6 (66.67%)
occurrences (all)	2	2	4
Impaired healing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Oedema peripheral			
subjects affected / exposed	2 / 4 (50.00%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	1	3
Pyrexia			
subjects affected / exposed	4 / 4 (100.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	5	2	2
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 4 (100.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	5	0	3
Amylase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	4
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 4 (75.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood bilirubin increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
C-reactive protein increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Lymphocyte count decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Incisional hernia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infusion related reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	4
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	2 / 3 (66.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	7
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	3 / 3 (100.00%)	2 / 6 (33.33%)
occurrences (all)	4	3	2
Rectal haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	4	1	1
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dermatitis acneiform			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperkeratosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Photosensitivity reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 6 (66.67%)
occurrences (all)	0	0	4
Rash maculo-papular			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin fissures			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin toxicity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Spinal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Folliculitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Herpes zoster			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mucosal infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 4 (75.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	4	1	2
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Hypermagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	3 / 6 (50.00%)
occurrences (all)	3	2	3
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Hypomagnesaemia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 3 (100.00%)	2 / 6 (33.33%)
occurrences (all)	3	3	4
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	8		
Impaired healing			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oedema peripheral			

subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	9		
Systemic inflammatory response syndrome			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	8		
Amylase increased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	6		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
C-reactive protein increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Lymphocyte count decreased			

subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 4 1 / 13 (7.69%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Injury, poisoning and procedural complications Corneal abrasion subjects affected / exposed occurrences (all) Gastrointestinal stoma complication subjects affected / exposed occurrences (all) Incisional hernia subjects affected / exposed occurrences (all) Infusion related reaction subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Nervous system disorders Depressed level of consciousness subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Leukocytosis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	9		
Rectal haemorrhage			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	6		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dermatitis acneiform			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hyperkeratosis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pruritus			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Rash maculo-papular			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin toxicity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Folliculitis			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mucosal infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	7		
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Hypermagnesaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	8		
Hypocalcaemia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 13 (53.85%) 10		
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2014	The main reason for the this amendment was to comply with Health Authority request to revise the eligibility criteria in the protocol and extend the duration of use of highly effective methods of contraception during dosing and for at least 4 weeks after permanently discontinuing study treatment (by females and males).
22 September 2014	The main purpose of this amendment was to update the definition of c-MET positivity based on the recent preliminary data from the ongoing clinical studies with INC280.
16 July 2015	The main purpose of this amendment was to update the eligibility criteria to align with the current treatment paradigm for metastatic CRC and HNSCC by including patients who have received more than one prior regimen containing an anti-EGFR antibody.
29 March 2016	The major reason for this amendment was to optimize the management of liver toxicities and be consistent across the different INC280 studies.

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.

Recruitment in the CINC280X2104 study was halted due to difficulties in identifying patients who met the eligibility criteria.

Notes: