Clinical trial results:
Phase IIA Exploratory Study of Oral Milciclib Maleate in Patients with Unresectable or Metastatic Hepatocellular Carcinoma

Summary

EudraCT number	2017-000144-18
Trial protocol	GR IT
Global end of trial date	20 June 2019

Results information

Result version number	v1 (current)
This version publication date	05 July 2020
First version publication date	05 July 2020

Trial information

Trial identification

Sponsor protocol code	CDKO-125a-010

Additional study identifiers

ISRCTN number	ISRCTN00000000
ClinicalTrials.gov id (NCT number)	NCT00000000
WHO universal trial number (UTN)	U0000-0000-0000
Other trial identifiers	NA: NA

Notes:

Sponsors

Sponsor organisation name	Tiziana Life Sciences Plc
Sponsor organisation address	55 Park Lane, London, United Kingdom, W1k 1NA
Public contact	Project Management, CLIOSS S.r.l., 0039 3480840579, monica.miani@clioss.com
Scientific contact	Project Management, CLIOSS S.r.l., 0039 3480840579, monica.miani@clioss.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 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety profile and tolerability of repeated administrations of milciclib in Child-Pugh "A" unresectable hepatocellular carcinoma (HCC) patients who failed or were not eligible for sorafenib or who actively refused it (presenting as naïve, progressing, recurrent or metastatic disease).
There was no primary efficacy endpoint in this study.

Protection of trial subjects:

The study was conducted in accordance with the the principles of the Declaration of Helsinki and Good Clinical Practice.
Patients were instructed on procedures in case of accidental opening of capsules and inhalation, skin, or eye contact with a cytotxic product (such as milciclib).
Dose modifications required due to drug-related toxicity were detailed in the study protocol.
Evaluation of safety data was performed by an Independent Data Monitoring Committee (IDMC) as soon as the 10th treated patient had completed as per protocol the first cycle of treatment. The IDMC had the power to recommend early trermination of the study in case of safety concerns.

Background therapy:

No background therapy was specified.
All patients had previously failed sorafenib treatment, were intolerant of sorafenib, or actively refused treatment with sorafenib.
Second line therapy with regorafenib discontinued for intolerance was allowed if lasting < 14 days.

Evidence for comparator:

This was a single-arm study with no comparator.

Actual start date of recruitment	02 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Israel: 7
Worldwide total number of subjects	31
EEA total number of subjects	24

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	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 14 July 2017 and 29 November 2018.

Pre-assignment

Screening details:

Patients were screened prior to study entry, up to 2 weeks before study start, to ensure eligibility criteria were met.

Period 1

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

Arms

Arm title	Milciclib

Arm description:

This was a single-arm study. All patients started treatment on the same dose of milciclib.

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

Dosage and administration details:

100 mg/day once a day for 4-day on/3-day off every week for 4 consecutive weeks. This 4-week dosing period constituted a full treatment cycle. Each patient was to receive three full cycles (12-weeks total). Milciclib was administered on Days 1 to 4, Days 8 to 11, Days 15 to 18, Day 22 to Day 25 of each cycle.

Number of subjects in period 1	Milciclib
Started	31
Treated	31
Completed	13
Not completed	18
Adverse event, serious fatal	3
Physician decision	1
New anticancer therapy	5
Consent withdrawn by subject	2
Lost to follow-up	7

Baseline characteristics

Reporting groups	
Reporting group title	Milciclib
Reporting group description:	
This was a single-arm study. All patients started treatment on the same dose of milciclib.	

Reporting group values	Milciclib	Total	
Number of subjects	31	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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	67.5		
standard deviation	± 7.24	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	27	27	

End points

End points reporting groups

Reporting group title	Milciclib
Reporting group description:	
This was a single-arm study. All patients started treatment on the same dose of milciclib.	
Subject analysis set title	Evaluable patients
Subject analysis set type	Full analysis
Subject analysis set description:	
Treated patients with evaluable tumour response data were included in the evaluable set.	
Subject analysis set title	Pharmacokinetics
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who participated in the pharmacokinetic phase of the study.	

Primary: Objective response rate

End point title	Objective response rate[1]
End point description:	
Objective Response Rate (ORR), i.e., confirmed complete response (CR) + confirmed partial response (PR) (based on independent central review). The objective tumor assessment was made according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria for heaptcellular carcinomas (HCC). Conventional RECIST 1.1 was also assessed. ORR was assessed locally and confirmed by an Independent Central Review.	
End point type	Primary
End point timeframe:	
From baseline to end of participation in the trial.	
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: Note: all efficacy endpoints were defined as secondary endpoints in this study, which had a primary objective to evaluate the safety profile of milciclib. However, for the purpose of uploading into EudraCT, one endpoint had to be defined as primary. There is no statistical analysis of this 'primary' endpoint in this single-arm study.	

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate

End point title	Clinical benefit rate
End point description:	
Clinical benefit rate (CBR), calculated as the proportion of evaluable patients who have achieved (based on independent central review), as best overall response, confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) based on mRECIST tumor assessment out of the total number of evaluable patients.	

End point type	Secondary

End point timeframe:

From baseline to end of participation in the trial.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: subjects	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) evaluated since study treatment start to progression, based on mRECIST tumor assessment, or death for any causes.

End point type	Secondary

End point timeframe:

From baseline to end of participation in the trial.

End point values	Milciclib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: months				
median (confidence interval 95%)	5.9 (1.5 to 6.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression (TTP) evaluated since study treatment start to progression, based on mRECIST tumour assessment or death due to disease progression in the absence of previous documented PD.

End point type	Secondary

End point timeframe:

From baseline to end of participation in the trial.

End point values	Milciclib	Evaluable patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	28		
Units: months				
median (confidence interval 95%)	5.9 (1.5 to 6.7)	5.9 (1.5 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of evaluable patients known to be alive and progression free at ≥3 months

End point title	Proportion of evaluable patients known to be alive and progression free at ≥3 months

End point description:

Proportion of evaluable patients known to be alive and progression free based on mRECIST tumor assessment at ≥3 months since study treatment start out of the total number of evaluable patients (TTP-3 months).

End point type	Secondary

End point timeframe:

From baseline to end of participation in the trial.

End point values	Milciclib	Evaluable patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	28		
Units: Percent				
number (confidence interval 95%)	45.2 (27.32 to 63.97)	50.0 (30.65 to 69.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of evaluable patients known to be alive and progression free at ≥6 months

End point title	Proportion of evaluable patients known to be alive and progression free at ≥6 months

End point description:

Proportion of evaluable patients known to be alive and progression free based on mRECIST tumor assessment at ≥ 6 months since study treatment start out of the total number of evaluable patients

(TTP-6 months).

End point type	Secondary

End point timeframe:

From baseline to end of participation in the trial.

End point values	Milciclib	Evaluable patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	28		
Units: Subjects				
number (confidence interval 95%)	19.4 (7.45 to 37.47)	21.4 (8.30 to 40.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: Cmax

End point title	Milciclib Cycle-1, Day 4: Cmax

End point description:

Maximum observed concentration (µM).

End point type	Secondary

End point timeframe:

Cycle-1, Day 4

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM				
arithmetic mean (standard deviation)	0.527 (± 0.130)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: Tmax

End point title	Milciclib Cycle-1, Day 4: Tmax

End point description:

The time take to reach Cmax.

End point type	Secondary

End point timeframe:

Cycle-1, Day 4

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
median (inter-quartile range (Q1-Q3))	2 (1 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: AUC24

End point title	Milciclib Cycle-1, Day 4: AUC24

End point description:

Area under the curve from time zero to 24 h after study drug administration (h*µM).

End point type	Secondary

End point timeframe:

Cycle-1, Day 4

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM hours				
arithmetic mean (standard deviation)	9.31 (± 2.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 4: half-life

End point title	Milciclib Cycle-1, Day 4: half-life

End point description:

The time taken for the plasma concentration to fall by half its original value.

End point type	Secondary

End point timeframe:

Cycle-1, Day 4

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
arithmetic mean (standard deviation)	34.8 (± 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: Cmax

End point title	Milciclib Cycle-1, Day 25: Cmax
End point description: Maximum observed concentration (µM).	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM				
arithmetic mean (standard deviation)	0.731 (± 0.185)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: Tmax

End point title	Milciclib Cycle-1, Day 25: Tmax
End point description: The time take to reach Cmax.	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
median (inter-quartile range (Q1-Q3))	2.42 (2 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: AUC24

End point title	Milciclib Cycle-1, Day 25: AUC24
End point description: Area under the curve from time zero to 24 h after study drug administration (h*µM).	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM hours				
arithmetic mean (standard deviation)	12.4 (± 4.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Milciclib Cycle-1, Day 25: half-life

End point title	Milciclib Cycle-1, Day 25: half-life
End point description: The time taken for the plasma concentration to fall by half its original value.	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
arithmetic mean (standard deviation)	38.1 (± 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: Cmax

End point title	NMS-867734 Cycle-1, Day 4: Cmax
End point description: Maximum observed concentration (µM).	
End point type	Secondary
End point timeframe: Cycle-1, Day 4	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM				
arithmetic mean (standard deviation)	0.379 (± 0.133)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: Tmax

End point title	NMS-867734 Cycle-1, Day 4: Tmax
End point description: The time take to reach Cmax.	
End point type	Secondary
End point timeframe: Cycle-1, Day 4	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
median (inter-quartile range (Q1-Q3))	4 (3.92 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: AUC24

End point title	NMS-867734 Cycle-1, Day 4: AUC24
End point description:	
Area under the curve from time zero to 24 h after study drug administration (h*µM).	
End point type	Secondary
End point timeframe:	
Cycle-1, Day 4	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM hour				
arithmetic mean (standard deviation)	6.25 (± 2.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 4: half-life

End point title	NMS-867734 Cycle-1, Day 4: half-life
End point description:	
The time taken for the plasma concentration to fall by half its original value.	
End point type	Secondary
End point timeframe:	
Cycle-1, Day 4	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
arithmetic mean (standard deviation)	29.9 (± 8.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: Cmax

End point title	NMS-867734 Cycle-1, Day 25: Cmax
End point description: Maximum observed concentration (µM).	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM				
arithmetic mean (standard deviation)	0.330 (± 0.116)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: Tmax

End point title	NMS-867734 Cycle-1, Day 25: Tmax
End point description: The time take to reach Cmax.	
End point type	Secondary
End point timeframe: Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
median (inter-quartile range (Q1-Q3))	4 (2 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: AUC24

End point title	NMS-867734 Cycle-1, Day 25: AUC24
End point description:	
Area under the curve from time zero to 24 h after study drug administration (h*µM).	
End point type	Secondary
End point timeframe:	
Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: µM hours				
arithmetic mean (standard deviation)	5.79 (± 2.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: NMS-867734 Cycle-1, Day 25: half-life

End point title	NMS-867734 Cycle-1, Day 25: half-life
End point description:	
The time taken for the plasma concentration to fall by half its original value.	
End point type	Secondary
End point timeframe:	
Cycle-1, Day 25	

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: hours				
arithmetic mean (standard deviation)	37.4 (± 7.88)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event reporting period for this trial began upon signing of informed consent and ended 30 days after the last treatment administration.

Adverse event reporting additional description:

If the patient started a new anticancer therapy earlier than 30 days after the last dose of study drug, the adverse event reporting period ended at the time the new treatment was started.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Treated patients

Reporting group description:

Patients treated with Milciclib during treatment period.

Serious adverse events	Treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 31 (54.84%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Sciatica			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal tear			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinoschisis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Intra-abdominal haemorrhage				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Diabetic ulcer				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 31 (90.32%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Neutropenia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	9		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	6 / 31 (19.35%) 8		
Fatigue subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 7		
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 6		
Pyrexia subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 4		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Eye disorders Visual acuity reduced subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 8		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 5		
Ascites subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 5		
Constipation subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	13 / 31 (41.94%) 26		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 10 3 / 31 (9.68%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 4 / 31 (12.90%) 4 2 / 31 (6.45%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	 3 / 31 (9.68%) 3 2 / 31 (6.45%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported