Clinical trial results:
A Multicenter, Single Arm, Phase Ib/II Study to Evaluate Efficacy, Safety, and PK of MSC2156119J as Monotherapy in Subjects with MET+ Advanced Hepatocellular Carcinoma with Child Pugh Class A Liver Function Who Have Failed Sorafenib Treatment

Summary

EudraCT number	2013-002053-30
Trial protocol	DE BE IT ES
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	02 March 2019
First version publication date	02 March 2019

Trial information

Trial identification

Sponsor protocol code	EMR200095_005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02115373
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250,, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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	14 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to determine the required Phase 2 dose and evaluate the efficacy of of MSC2156119J with MET+ advanced Hepatocellular Carcinoma (HCC) pretreated with sorafenib and child pugh class A liver function.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 May 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	Belgium: 1
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	66
EEA total number of subjects	62

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)	25
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant signed informed consent:18 May 2014, last participant last visit: 14th Feb 2018

Pre-assignment

Screening details:

In Phase 1b, 24 participants were screened of which, 17 started the treatment. In Phase 2 ,155 participants were screened, of which 49 participants started the treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Tepotinib 300 mg

Arm description:

Participants received a single oral dose of Tepotinib 300 milligram (mg) daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Arm type	Experimental
Investigational medicinal product name	Tepotinib
Investigational medicinal product code	
Other name	MSC2156119J
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single oral dose of Tepotinib 300 mg daily in each 21 days treatment cycle.

Arm title	Phase 1b: Tepotinib 500 mg

Arm description:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Arm type	Experimental
Investigational medicinal product name	Tepotinib
Investigational medicinal product code	
Other name	MSC2156119J
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle.

Arm title	Phase 2: Tepotinib 500 mg

Arm description:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Arm type	Experimental

Investigational medicinal product name	Tepotinib
Investigational medicinal product code	
Other name	MSC2156119J
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle.

Number of subjects in period 1	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg	Phase 2: Tepotinib 500 mg
Started	4	13	49
Completed	4	13	49

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1b: Tepotinib 300 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 300 milligram (mg) daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	
Reporting group title	Phase 1b: Tepotinib 500 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	
Reporting group title	Phase 2: Tepotinib 500 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	

Reporting group values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg	Phase 2: Tepotinib 500 mg
Number of subjects	4	13	49
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	1	3	21
>=65 years	3	10	28
Sex: Female, Male Units: Subjects			
Female	2	2	8
Male	2	11	41
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	1	8	26
More than one race	0	1	0
Unknown or Not Reported	3	4	20

Reporting group values	Total		
Number of subjects	66		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	25		
>=65 years	41		
Sex: Female, Male Units: Subjects			
Female	12		
Male	54		

End points

End points reporting groups

Reporting group title	Phase 1b: Tepotinib 300 mg

Reporting group description:

Participants received a single oral dose of Tepotinib 300 milligram (mg) daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Reporting group title	Phase 1b: Tepotinib 500 mg

Reporting group description:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Reporting group title	Phase 2: Tepotinib 500 mg

Reporting group description:

Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Subject analysis set title	Phase 1b: Tepotinib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received a single oral dose of Tepotinib 300 mg or 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.

Primary: Phase 1b: Number of Participants Experiencing Dose Limiting Toxicity (DLT) According to National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) for Adverse Events (AEs) Version 4.0

End point title	Phase 1b: Number of Participants Experiencing Dose Limiting Toxicity (DLT) According to National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) for Adverse Events (AEs) Version 4.0[1][2]

End point description:

DLT: defined using NCI-CTCAE for AEs Version 4.0, as any of following toxicities: Grade 4 neutropenia for more than 7 days; greater than or equal to (>=) Grade 3 febrile neutropenia for more than 1 day; Grade 4 or Grade 3 thrombocytopenia with nontraumatic bleeding; >=Grade 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate treatment for more than 3 days; >=Grade 3 any non-hematological AE. (DLT defined specifically for following cases: >=Grade 3 liver AE requiring recovery period of more than 7 days or to Grade 1 or less or Grade 2 with liver metastases ; >=Grade 3 lipase and/or amylase elevation with confirmation of pancreatitis. An isolated lipase and/or amylase elevation of >=Grade 3 without clinical/radiological evidence of pancreatitis was not classified as DLT); and AEs assessed by investigators to be exclusively related to the participant’s underlying disease or medical condition/concomitant treatment are not considered as DLTs. DLT analysis set.

End point type	Primary

End point timeframe:

Day 1 to Day 21 of Cycle 1 (each cycle was 21 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: Only descriptive statistics were planned to be analysed for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	11		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Participants who Were Progression-free at 12 weeks (PFS Status) as Assessed by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

End point title	Phase 2: Number of Participants who Were Progression-free at 12 weeks (PFS Status) as Assessed by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[3][4]

End point description:

PFS status was evaluated by the number of participants who were progression-free at 12 weeks according to RECIST Version 1.1. Participants were considered to be progression-free if the participant had a tumor assessment of Complete Response (CR) defined as disappearance of all target and non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response (PR) defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters, or Stable Disease (SD) defined as any cases that do not qualify for either partial response or progressive disease (an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started)12 weeks after start of treatment or later. Intent to Treat analysis set.

End point type	Primary

End point timeframe:

At 12 weeks post first-dose in Phase 2

Notes:

[3] - 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: Only descriptive statistics were planned to be analysed for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 2 arm only.

End point values	Phase 2: Tepotinib 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: participants	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Time to Progression According to Response

Evaluation Criteria in Solid Tumors (RECIST) version 1.1

End point title	Phase 1b and Phase 2: Time to Progression According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[5]

End point description:

TTP was the time (in months) from the date of first study drug administration to the date of radiological confirmation of PD performed according to RECIST Version 1.1. PD was defined as an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. ITT set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, Overall number of participants analyzed signified those participants who had progression. As per planned analysis, TTP was calculated for Tepotinib 300 mg and 500 mg arm combined in Phase 1b.

End point type	Secondary

End point timeframe:

Time from first study drug administration to the date of first occurrence of radiological progressive disease (PD), assessed up to 12 months after last participant's first dose (assessed maximum up to 1369 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Tepotinib 300 mg and Tepotinib 500mg arm from Phase 1b together.

End point values	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	36	12		
Units: months				
median (full range (min-max))	3.98 (0.03 to 16.53)	2.07 (0.03 to 22.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Progression-free survival (PFS) Time According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

End point title	Phase 1b and Phase 2: Progression-free survival (PFS) Time According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[6]

End point description:

PFS time was defined as the time from date of randomization until date of the first observation of progressive disease (PD) or death due to any cause within 12 weeks of the last tumor assessment in the absence of documented PD, whichever occurs first. PFS was assessed as per RECIST v1.1 as adjudicated by independent endpoint review committee (IERC). PD was defined as an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, Overall number of participants analyzed signified those participants who had progressive disease or death. As per planned analysis, PFS time was calculated for Tepotinib 300 mg and 500 mg arm combined in Phase 1b.

End point type	Secondary

End point timeframe:

From randomization up to first observation of PD or death, assessed maximum up to 1369 days

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Tepotinib 300 mg and Tepotinib 500mg arm from Phase 1b together.

End point values	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	16		
Units: months				
median (full range (min-max))	3.22 (0.03 to 16.53)	1.51 (0.69 to 22.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Progression-free survival (PFS) Time According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Hepatocellular Carcinoma (HCC)

End point title	Phase 1b and Phase 2: Progression-free survival (PFS) Time According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Hepatocellular Carcinoma (HCC)[7]

End point description:

PFS time was defined as the time from date of randomization until date of the first observation of progressive disease (PD) or death due to any cause within 12 weeks of the last tumor assessment in the absence of documented PD, whichever occurs first. PFS was assessed as per mRECIST for HCC as adjudicated by independent endpoint review committee (IERC). PD was defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, Overall number of participants analyzed signified those participants who had progressive disease or death. As per planned analysis, PFS time was calculated for Tepotinib 300 mg and 500 mg arm combined in Phase 1b.

End point type	Secondary

End point timeframe:

From randomization up to first observation of PD or death, assessed maximum up to 1369 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Tepotinib 300 mg and Tepotinib 500mg arm from Phase 1b together.

End point values	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	13		
Units: months				
median (full range (min-max))	3.35 (0.03 to 13.83)	1.48 (0.03 to 22.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time-to-symptomatic Progressionn (TTSP)

End point title	Phase 2: Time-to-symptomatic Progressionn (TTSP)[8]

End point description:

Time-to-symptomatic progression was defined as time (in months) from first study drug administration to the date of deterioration of symptoms assessed by Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8) (defined as at least a 4-point increase, i.e., higher score, compared with baseline value), or deterioration to Eastern Cooperative Oncology Group (ECOG) performance score 4, or death. FHSI-8 assesses hepatobiliary cancer symptoms with total score ranges from 0 to 32 (0 = the best quality of life; 32 = the worst quality of life with severe symptoms). ECOG assess participant's performance status on a scale of 0 to 5, where 0=fully active and 5=dead. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, Overall number of participants analysed signified those participants who had symptomatic progression. As per planned analysis, data for this outcome was analyzed for Phase 2 only.

End point type	Secondary

End point timeframe:

From date of randomization up to 1369 days

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 2 arm only.

End point values	Phase 2: Tepotinib 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (full range (min-max))	4.86 (0.03 to 17.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Overall Survival (OS) Time

End point title	Phase 1b and Phase 2: Overall Survival (OS) Time[9]

End point description:

The OS time was defined as the time from randomization to the date of death. The participants who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the participant was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, "number of participant analysed" signified the participants who had an event (death) . As per planned analysis, OS time was calculated for Tepotinib 300 mg and 500 mg arm combined in Phase 1b.

End point type	Secondary

End point timeframe:

From date of randomization up to the date of death, assessed maximum up to 1369 days

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Tepotinib 300 mg and Tepotinib 500mg arm

from Phase 1b together.

End point values	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	14		
Units: months				
median (full range (min-max))	5.55 (0.13 to 23.49)	7.20 (0.69 to 22.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Percentage of Participants With Best Overall Tumor Assessment of CR or PR According to RECIST v1.1

End point title	Phase 1b and Phase 2: Percentage of Participants With Best Overall Tumor Assessment of CR or PR According to RECIST v1.1

End point description:

Percentage of participants with best overall tumor assessment of (CR or PR) according to RECIST Version 1.1 was reported. CR defined as disappearance of all target and non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. PD was defined as an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J).

End point type	Secondary

End point timeframe:

From date of randomization up to first occurrence of PD, assessed maximum up to 1369 days

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg	Phase 2: Tepotinib 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	13	49	
Units: percentage of Participants				
number (confidence interval 90%)	50.0 (9.8 to 90.2)	0.0 (0.0 to 20.6)	8.2 (2.8 to 17.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Percentage of Participants With Disease Control

End point title	Phase 1b and Phase 2: Percentage of Participants With Disease Control

End point description:

Disease control was defined as CR, PR, or SD as the best overall response according to RECIST Version 1.1. Complete Response (CR) defined as disappearance of all target and non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response (PR) defined as at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters, or Stable Disease (SD) defined as any cases that do not qualify for either partial response or progressive disease (an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started)12 weeks after start of treatment or later. Percentage of Participants With Disease Control were reported. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J).

End point type	Secondary

End point timeframe:

From date of randomization up to first occurrence of PD, assessed maximum up to 1369 days

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg	Phase 2: Tepotinib 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	13	49	
Units: percentage of participants				
number (confidence interval 90%)	50.0 (9.8 to 90.2)	30.8 (11.3 to 57.3)	57.1 (44.4 to 69.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Percentage of Participants With Biological Response

End point title	Phase 1b and Phase 2: Percentage of Participants With Biological Response

End point description:

Percentage of participants with biological response was measured by serum Alpha-Fetoprotein (AFP), defined as a greater than 20% decrease in AFP level by Cycle 3 (each cycle is of 21 days) compared with baseline. ITT analysis set included all participants who had been administered at least one dose of Tepotinib (MSC2156119J). Here, "number of subjects analysed" signified the participants with baseline and post baseline AFP assessments.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 3 (each cycle is 21 days)

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg	Phase 2: Tepotinib 500 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	11	45	
Units: percentage of participants				
number (confidence interval 90%)	66.7 (13.5 to 98.3)	45.5 (20.0 to 72.9)	31.1 (19.9 to 44.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Sampling Time at Which the Concentration is at or Above the Lower Limit of Quantification (AUC0-t) of Tepotinib

End point title	Phase 1b: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Sampling Time at Which the Concentration is at or Above the Lower Limit of Quantification (AUC0-t) of Tepotinib[10]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, "n" is number of participants evaluable at a specified time-point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours Post-dose on Day 1 and Day 15 of Treatment Cycle 1 (each cycle was 21 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: nanogram hour per milliliter (ng*h/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=3,12) Cycle 1 Day 15(n=3,9)	4440 (± 6.7) 15200 (± 18.2)	5060 (± 38.9) 12900 (± 50.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Dose Normalized Area Under the Plasma Concentration-Time Curve From Zero to Last Sampling Time at Which the Concentration is at or Above

the Lower Limit of Quantification (AUC0-t) of Tepotinib

End point title	Phase 1b: Dose Normalized Area Under the Plasma Concentration-Time Curve From Zero to Last Sampling Time at Which the Concentration is at or Above the Lower Limit of Quantification (AUC0-t) of Tepotinib[11]

End point description:

Dose normalized was calculated as area under the plasma concentration versus time curve from time zero to the last sampling time t at which the concentration is at or above the lower limit of quantification (LLQ) divided by the dose. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, "n" is number of participants evaluable at a specified time-point.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: ng*h/mL/mg				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1(n=3,12)	14.8 (± 6.7)	10.1 (± 38.9)		
Cycle 1 Day 15(n=3,9)	50.7 (± 18.2)	25.8 (± 50.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUC0-inf) of Tepotinib

End point title	Phase 1b: Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUC0-inf) of Tepotinib[12]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, 99999 signified not applicable as dosing and sampling scheme in Phase Ib did not allow the reliable estimation of apparent terminal rate constant (λz), Therefore, AUC0-inf dependent on λz was not determined.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours Post-dose on Day 1 and Day 15 of Treatment Cycle 1 (each cycle was 21 days)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	13		
Units: nanogram hour per milliliter (ng*h/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	99999 (± 99999)	99999 (± 99999)		
Cycle 1 Day 15	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Maximum Observed Plasma Concentration (Cmax) of Tepotinib

End point title	Phase 1b: Maximum Observed Plasma Concentration (Cmax) of Tepotinib[13]

End point description:

Cmax is the maximum observed plasma concentration obtained directly from the concentration versus time curve. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, "n" is number of participants evaluable at a specified time-point.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1(n=3,12)	261 (± 8.4)	278 (± 39.3)		
Cycle 1 Day 15(n=3,10)	734 (± 19.6)	677 (± 44.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Dose Normalized Maximum Observed Plasma Concentration (Cmax) of Tepotinib

End point title	Phase 1b: Dose Normalized Maximum Observed Plasma Concentration (Cmax) of Tepotinib[14]

End point description:

Dose normalized was calculated as maximum observed plasma concentration obtained directly from the concentration versus time curve divided by dose. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, "n" is number of participants evaluable at a specified time-point.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	526 (± 28.0)	435 (± 57.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Time to Reach Maximum Plasma Concentration (Tmax) of Tepotinib

End point title	Phase 1b: Time to Reach Maximum Plasma Concentration (Tmax) of Tepotinib[16]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, "n" is number of participants evaluable at a specified time-point.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1(n=3,12)	10.0 (8.0 to 24.0)	8.0 (8.0 to 10.0)		
Cycle 1 Day 15(n=3,10)	8.0 (0.48 to 8.0)	6.1 (0.0 to 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Average Plasma Concentration at Steady State (Cav) of Tepotinib

End point title	Phase 1b: Average Plasma Concentration at Steady State (Cav) of Tepotinib[17]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	635 (± 18.2)	542 (± 50.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Apparent Total Body Clearance From Plasma (CL/f) of Tepotinib

End point title	Phase 1b: Apparent Total Body Clearance From Plasma (CL/f) of Tepotinib[18]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	17.7 (± 18.2)	34.9 (± 50.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Apparent Volume of Distribution During the Terminal Phase (Vz/f) of Tepotinib

End point title	Phase 1b: Apparent Volume of Distribution During the Terminal Phase (Vz/f) of Tepotinib[19]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, 99999 signified not applicable as dosing and sampling scheme in Phase Ib did not allow the reliable estimation of apparent terminal rate constant (λz), Therefore, Vz/F dependent on λz was not determined.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: liter				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	99999 (± 99999)	99999 (± 99999)		
Cycle 1 Day 15	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Apparent Volume of Distribution During the Steady State (Vss/f) of Tepotinib

End point title	Phase 1b: Apparent Volume of Distribution During the Steady State (Vss/f) of Tepotinib[20]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, 99999 signified not applicable as dosing and sampling scheme in Phase Ib did not allow the reliable estimation

of apparent terminal rate constant (λz), Therefore, Vss/F dependent on λz was not determined.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: liter				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	99999 (± 99999)	99999 (± 99999)		
Cycle 1 Day 15	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Apparent Terminal Elimination Rate Constant (λz) of Tepotinib

End point title	Phase 1b: Apparent Terminal Elimination Rate Constant (λz) of Tepotinib[21]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, 99999 signified not applicable as dosing and sampling scheme in Phase Ib did not allow the reliable estimation of apparent terminal rate constant (λz), Therefore, λz was not determined.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: 1 per hour				
geometric mean (geometric coefficient of variation)				

Cycle 1 Day 1 Cycle 1 Day 15	99999 (± 99999) 99999 (± 99999)	99999 (± 99999) 99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Apparent Terminal Half-life (t1/2) of Tepotinib

End point title	Phase 1b: Apparent Terminal Half-life (t1/2) of Tepotinib[22]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, 99999 signified not applicable as dosing and sampling scheme in Phase Ib did not allow the reliable estimation of apparent terminal rate constant (λz), Therefore, t1/2 dependent on λz was not determined.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: hours				
median (full range (min-max))				
Cycle 1 Day 1 Cycle 1 Day 15	99999 (99999 to 99999) 99999 (99999 to 99999)	99999 (99999 to 99999) 99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Time prior to the First Quantifiable (non-zero) Concentration (tlag) of Tepotinib

End point title	Phase 1b: Time prior to the First Quantifiable (non-zero) Concentration (tlag) of Tepotinib[23]

End point description:

PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 Cycle 1 (each Cycle is 21 days)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: hours				
median (full range (min-max))	0.53 (0.52 to 0.55)	0.50 (0.25 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Percentage Peak-Trough Fluctuation (PTF) Post First Dose of Tepotinib

End point title	Phase 1b: Percentage Peak-Trough Fluctuation (PTF) Post First Dose of Tepotinib[24]

End point description:

The peak trough fluctuation within complete dosing interval at steady state, calculated as PTF (%) = ([Cmax - Cmin]/Cav) multiplied by 100. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: percentage fluctuation				
geometric mean (geometric coefficient of variation)	31.5 (± 30.5)	35.9 (± 44.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Accumulation Ratio of Cmax (Racc (Cmax))

End point title	Phase 1b: Accumulation Ratio of Cmax (Racc (Cmax))[25]

End point description:

Accumulation ratio for Cmax was calculated as Cmax, after dosing on Day 15 divided by Cmax, after dosing on day 1 of cycle 1. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	10		
Units: ratio				
geometric mean (geometric coefficient of variation)	2.81 (± 24.1)	2.32 (± 23.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Accumulation Ratio of AUC (Racc (AUC)

End point title	Phase 1b: Accumulation Ratio of AUC (Racc (AUC)[26]

End point description:

Accumulation ratio for AUC was calculated as AUC, after dosing on Day 15 divided by AUC, after dosing on day 1 of cycle 1. PK population included all participants who have received Tepotinib (MSC2156119J) and who had at least one blood sample drawn that provided drug concentration data for PK evaluation. Here, number of subjects analyzed signified participants evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours post-dose; Day 1 and Day 15 of Cycle 1 (each Cycle is 21 days)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analysed for Phase 1b arm only.

End point values	Phase 1b: Tepotinib 300 mg	Phase 1b: Tepotinib 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: ratio				
geometric mean (geometric coefficient of variation)	3.43 (± 22.6)	2.51 (± 22.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From date of randomization up to 1369 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Phase 1b: Tepotinib 300 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 300 milligram (mg) daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	
Reporting group title	Phase 2: Tepotinib 500 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	
Reporting group title	Phase 1b: Tepotinib 500 mg
Reporting group description:	
Participants received a single oral dose of Tepotinib 500 mg daily in each 21 days treatment cycle until progressive disease, intolerable toxicity, death, or withdrawal from treatment.	

Serious adverse events	Phase 1b: Tepotinib 300 mg	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib 500 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	21 / 49 (42.86%)	5 / 13 (38.46%)
number of deaths (all causes)	3	40	11
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Investigations			
Blood bilirubin increased			

subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (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
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Hypoglycaemic coma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 4 (25.00%)	7 / 49 (14.29%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Vascular stent stenosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (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
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Jaundice			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Hepatorenal syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
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			
Pneumonia aspiration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Peritonitis bacterial			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (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			
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Hypercreatininaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Hyponatraemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (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
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase 1b: Tepotinib 300 mg	Phase 2: Tepotinib 500 mg	Phase 1b: Tepotinib 500 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	48 / 49 (97.96%)	12 / 13 (92.31%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Metastases to bone			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Peripheral venous disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Venous thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Deep vein thrombosis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Hypovolaemic shock			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	15 / 49 (30.61%)	2 / 13 (15.38%)
occurrences (all)	0	15	2
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Disease progression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	10 / 49 (20.41%)	2 / 13 (15.38%)
occurrences (all)	1	10	2
Generalised oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Localised oedema			

subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Oedema peripheral			
subjects affected / exposed	3 / 4 (75.00%)	32 / 49 (65.31%)	10 / 13 (76.92%)
occurrences (all)	3	32	10
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 49 (8.16%)	1 / 13 (7.69%)
occurrences (all)	1	4	1
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Acute respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			

subjects affected / exposed	0 / 4 (0.00%)	6 / 49 (12.24%)	0 / 13 (0.00%)
occurrences (all)	0	6	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
Depressed mood			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	3 / 49 (6.12%)	4 / 13 (30.77%)
occurrences (all)	2	3	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	6 / 49 (12.24%)	1 / 13 (7.69%)
occurrences (all)	1	6	1
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 4 (50.00%)	5 / 49 (10.20%)	2 / 13 (15.38%)
occurrences (all)	2	5	2
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	5 / 49 (10.20%)	1 / 13 (7.69%)
occurrences (all)	0	5	1
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)	7 / 49 (14.29%)	2 / 13 (15.38%)
occurrences (all)	1	7	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			

subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	2 / 13 (15.38%)
occurrences (all)	0	3	2
International normalised ratio increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	1 / 4 (25.00%)	5 / 49 (10.20%)	1 / 13 (7.69%)
occurrences (all)	1	5	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Urobilinogen urine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 49 (4.08%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Amylase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Haemoglobin decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Overdose			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Hepatic encephalopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Sciatica			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Migraine with aura			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	7 / 49 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	7	0
Coagulopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lymph node pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)	8 / 49 (16.33%)	2 / 13 (15.38%)
occurrences (all)	2	8	2
Abdominal pain upper			

subjects affected / exposed	0 / 4 (0.00%)	4 / 49 (8.16%)	1 / 13 (7.69%)
occurrences (all)	0	4	1
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	15 / 49 (30.61%)	2 / 13 (15.38%)
occurrences (all)	0	15	2
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	9 / 49 (18.37%)	0 / 13 (0.00%)
occurrences (all)	2	9	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	16 / 49 (32.65%)	2 / 13 (15.38%)
occurrences (all)	0	16	2
Dry mouth			
subjects affected / exposed	1 / 4 (25.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Gastric varices			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Haematemesis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Inguinal hernia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	11 / 49 (22.45%)	2 / 13 (15.38%)
occurrences (all)	1	11	2
Odynophagia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Varices oesophageal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	7 / 49 (14.29%)	0 / 13 (0.00%)
occurrences (all)	2	7	0
Eructation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hepatic pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hepatocellular injury			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	4 / 49 (8.16%)	0 / 13 (0.00%)
occurrences (all)	0	4	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0

Jaundice			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	5 / 49 (10.20%)	0 / 13 (0.00%)
occurrences (all)	0	5	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	4 / 49 (8.16%)	1 / 13 (7.69%)
occurrences (all)		4	1

subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)	3 / 49 (6.12%)	1 / 13 (7.69%)
occurrences (all)	1	3	1
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Renal impairment			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Glomerulonephritis membranoproliferative			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Ketonuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	5 / 49 (10.20%)	0 / 13 (0.00%)
occurrences (all)	1	5	0
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	4 / 49 (8.16%)	1 / 13 (7.69%)
occurrences (all)	0	4	1
Muscle spasms			

subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	1 / 49 (2.04%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Pain in jaw			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 49 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Hepatitis B			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Peritonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 49 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	0
Angular cheilitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Clostridium difficile colitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Genital herpes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Septic shock			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	8 / 49 (16.33%)	1 / 13 (7.69%)
occurrences (all)	0	8	1
Cell death			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypercreatininaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	5 / 49 (10.20%)	1 / 13 (7.69%)
occurrences (all)	0	5	1
Hyperlipasaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	13 / 49 (26.53%)	1 / 13 (7.69%)
occurrences (all)	0	13	1
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 49 (4.08%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Hypomagnesaemia			

subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	1 / 13 (7.69%)
occurrences (all)	0	3	1
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 49 (6.12%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Malnutrition			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 49 (2.04%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2015	Continuation of MSC2156119J in the event of persistent Grade 3 amylase/lipase elevations without clinical or radiological evidence of pancreatitis is allowed only if there is objectiveevidence of benefit, rather than the potential for benefit. For the second dose cohort (500 mg), the SMC will decide on actions to be taken if 2 or more subjects out of the first 3 experience a DLT during the first treatment cycle. Inclusion of an exploratory PK endpoint.
13 June 2016	It was added that administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported