



Clinical trial results:

Activity of Lorlatinib based on ALK resistance mutations on blood in ALK positive NSCLC patients previously treated with 2nd generation ALK inhibitor

Summary

EudraCT number	2019-003862-41
Trial protocol	NO NL FR IT ES
Global end of trial date	29 November 2024

Results information

Result version number	v1 (current)
This version publication date	20 November 2025
First version publication date	20 November 2025

Trial information

Trial identification

Sponsor protocol code	EORTC-1825-LCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04127110
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for the Research and Treatment of Cancer, 0032 27741066, regulatory@eortc.org
Scientific contact	Regulatory Affairs Department, European Organisation for the Research and Treatment of Cancer, 0032 27741066, regulatory@eortc.org

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	16 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2024
Global end of trial reached?	Yes
Global end of trial date	29 November 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main aim of this trial is to assess the progression-free survival rate at 12 months (PFSR12) to lorlatinib in ALK positive advanced NSCLC patients, who progressed on second generation ALK TKI with the presence of ALK resistance mutations on blood (liquid biopsies) by Independent Central Review (ICR) assessment per RECIST v1.1

Protection of trial subjects:

Safety data were reviewed within EORTC Headquarters on a regular basis as part of the Medical Review process. Safety information was included in trial status reports which served as a basis of discussion during EORTC Group meetings

Background therapy:

Previous treatment with at least one 2nd-generation ALK inhibitor. The 2nd-generation ALK TKI (including but not limited to ceritinib, alectinib, brigatinib) was the latest therapy.

Evidence for comparator:

This was not a randomized controlled trial. Each cohort in the trial received lorlatinib at the same dose and frequency. The cohort allocation was based on ALK mutations and alterations. Specifically, Cohort A consisted of patients with presence of 1 or more ALK mutation(s) and represented the cohort of primary interest. Cohort B consisted of patients with absence of ALK mutation, but presence of any other non-ALK mutation. Cohort C consisted of patients with negative ctDNA or absence of any alteration.

Actual start date of recruitment	04 May 2020
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	Netherlands: 12
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Jordan: 8
Worldwide total number of subjects	64
EEA total number of subjects	56

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)	46
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Cohort A for patients with presence of ≥ 1 ALK mutation(s) (target 42 patients and primary cohort of interest for the trial). Cohort B for Patients with absence of ALK mutation, but presence of any other non-ALK mutation (target 21 patients). Cohort C for patients with negative ctDNA or absence of any ALK alteration (target 21 patients).

Pre-assignment

Screening details:

The main inclusion criteria were: advanced (stage III not eligible for local therapy, or stage IV) NSCLC with ALK rearrangement, progressed on and with last treatment second generation ALK inhibitor TKIs (alectinib, ceritinib or brigatinib). Treated and/or untreated brain or leptomeningeal metastases were allowed if asymptomatic and/or controlled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Patients with the presence of 1 or more ALK mutation(s)

Arm type	Experimental
Investigational medicinal product name	Lorlatinib
Investigational medicinal product code	L01XE44
Other name	Lorviqua, PF-06463922, Lorbrena
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lorlatinib is administered orally at the daily dose of 100 mg (four tablets of 25 mg).

Lorlatinib must be swallowed with a glass of water and must not be mashed or chewed. The tablets can be taken with or without food.

Treatment cycles are defined as a four-week period (28 days) to facilitate scheduling of visits and assessments and will always be considered 4 weeks irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle

Arm title	Cohort B
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Arm description:

Patients with absence of ALK mutation, but presence of any other non-ALK mutation

Arm type	Experimental
Investigational medicinal product name	Lorlatinib
Investigational medicinal product code	L01XE44
Other name	Lorviqua, PF-06463922, Lorbrena
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lorlatinib is administered orally at the daily dose of 100 mg (four tablets of 25 mg).

Lorlatinib must be swallowed with a glass of water and must not be mashed or chewed. The tablets can be taken with or without food.

Treatment cycles are defined as a four-week period (28 days) to facilitate scheduling of visits and

assessments and will always be considered 4 weeks irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle

Arm title	Cohort C
Arm description: Patients with negative ctDNA or absence of any ALK alteration	
Arm type	Experimental
Investigational medicinal product name	Lorlatinib
Investigational medicinal product code	L01XE44
Other name	Lorviqua, PF-06463922, Lorbrena
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lorlatinib is administered orally at the daily dose of 100 mg (four tablets of 25 mg).

Lorlatinib must be swallowed with a glass of water and must not be mashed or chewed. The tablets can be taken with or without food.

Treatment cycles are defined as a four-week period (28 days) to facilitate scheduling of visits and assessments and will always be considered 4 weeks irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle

Number of subjects in period 1	Cohort A	Cohort B	Cohort C
Started	8	22	34
Completed	8	22	34

Baseline characteristics

Reporting groups

Reporting group title	Cohort A
Reporting group description:	
Patients with the presence of 1 or more ALK mutation(s)	
Reporting group title	Cohort B
Reporting group description:	
Patients with absence of ALK mutation, but presence of any other non-ALK mutation	
Reporting group title	Cohort C
Reporting group description:	
Patients with negative ctDNA or absence of any ALK alteration	

Reporting group values	Cohort A	Cohort B	Cohort C
Number of subjects	8	22	34
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	15	28
From 65-84 years	5	7	6
85 years and over	0	0	0
Age continuous			
Units: years			
median	65.5	59	55.5
inter-quartile range (Q1-Q3)	49.5 to 74.0	49 to 68	49 to 62
Gender categorical			
Units: Subjects			
Female	4	14	19
Male	4	8	15
ECOG WHO Performance Score			
ECOG WHO Performance Score is a 6 point item scale (0-5) which determines the patients to assess the patient's functional status or performance status			
Units: Subjects			
PS 0	1	7	14
PS 1	6	11	18
PS 2	1	4	2
PS 3	0	0	0
PS 4	0	0	0
PS 5	0	0	0
Histopathological type			
Units: Subjects			
Adenocarcinoma	7	20	29
Adenocarcinoma in situ	0	0	1

Carcinoma, NOS	0	0	2
Invasive mucinous adenocarcinoma	0	1	1
Large cell neuroendocrine carcinoma	0	1	0
Squamous cell carcinoma	1	0	1
Stage at first diagnosis			
according to UICC TNM staging v8.0			
Units: Subjects			
Missing	1	2	5
IIB	0	0	1
IIIA	0	1	2
IIIB	0	0	1
IIIC	0	2	1
IV	0	3	3
IVA	3	5	10
IVB	4	9	11
Brain or leptomeningeal metastases at screening			
Units: Subjects			
No	5	14	19
Yes	3	8	15

Reporting group values	Total		
Number of subjects	64		
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)	46		
From 65-84 years	18		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	37		
Male	27		
ECOG WHO Performance Score			
ECOG WHO Performance Score is a 6 point item scale (0-5) which determines the patients to assess the patient's functional status or performance status			
Units: Subjects			
PS 0	22		
PS 1	35		
PS 2	7		
PS 3	0		

PS 4	0		
PS 5	0		
Histopathological type			
Units: Subjects			
Adenocarcinoma	56		
Adenocarcinoma in situ	1		
Carcinoma, NOS	2		
Invasive mucinous adenocarcinoma	2		
Large cell neuroendocrine carcinoma	1		
Squamous cell carcinoma	2		
Stage at first diagnosis			
according to UICC TNM staging v8.0			
Units: Subjects			
Missing	8		
IIB	1		
IIIA	3		
IIIB	1		
IIIC	3		
IV	6		
IVA	18		
IVB	24		
Brain or leptomeningeal metastases at screening			
Units: Subjects			
No	38		
Yes	26		

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description:	
Patients with the presence of 1 or more ALK mutation(s)	
Reporting group title	Cohort B
Reporting group description:	
Patients with absence of ALK mutation, but presence of any other non-ALK mutation	
Reporting group title	Cohort C
Reporting group description:	
Patients with negative ctDNA or absence of any ALK alteration	

Primary: PFSR-12

End point title	PFSR-12 ^{[1][2]}
End point description:	
Progression-free survival rate at 12 months (PFSR-12) is defined as the proportion of patients at 12 months who are alive and non-progressing. It is based on independent central review. Progression of disease is assessed as per RECIST v1.1 criteria.	
Patients without adequate disease assessment at 12 months are considered as failures.	
End point type	Primary
End point timeframe:	
12 months after enrolment	

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: Due to early termination of this trial due to poor accrual no formal hypothesis tests were conducted. Only exploratory results were provided.

In this case the rate of patients progression-free and alive after 12 months in cohort A (in the per-protocol population and as per central review) was 1 out of 7, i.e. 1 success and 6 failures. This corresponds to a rate of 0.143 (with 95% C.I. of 0.00-0.579).

[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: PFSR-12 was only pre-planned and considered relevant for patients in Cohort A. The landmark time point of 12 months was neither planned nor considered relevant for cohorts B and C.

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	7 ^[3]			
Units: patients				
Succes	1			
Fail	6			

Notes:

[3] - Analysis done in the per-protocol population.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as the time interval between the date of enrolment and the date of death from any cause, whichever occurs first. If no event has been observed, then the patient is censored at the last date known to be alive.

End point type	Secondary
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End point timeframe:

From enrolment until the end of study.

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7 ^[4]	21 ^[5]	34 ^[6]	
Units: Patients				
Alive	2	4	22	
Dead	5	17	12	

Notes:

[4] - Analysis done in the per-protocol population.

[5] - Analysis done in the per-protocol population.

[6] - Analysis done in the per-protocol population.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

Progression-free survival is defined as the time interval between the date of enrolment and the date of disease progression or death, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination.

Progression of disease is defined as per RECIST v1.1 criteria (and assessed as per central review).

End point type	Secondary
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End point timeframe:

From enrolment until the end of study

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7 ^[7]	21 ^[8]	34 ^[9]	
Units: patients				
Progressive disease	2	9	13	
Death	3	11	8	
Progression-free and alive	2	1	13	

Notes:

[7] - Analysis done in the per-protocol population

[8] - Analysis done in the per-protocol population

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression-free survival

End point title	Median Progression-free survival
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End point description:

Progression-free survival was determined as per RECIST v1.1 criteria (and assessed as per central review).

The median overall progression-free survival and its 95% confidence interval for each cohort are presented.

Note: the value 99999 indicates that the median or lower/upper bound of the 95% confidence interval was not reached.

End point type	Secondary
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End point timeframe:

From enrolment until end of study

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7 ^[10]	21 ^[11]	34 ^[12]	
Units: Months				
median (confidence interval 95%)	7.2 (2.0 to 99999)	2.0 (1.6 to 10.3)	10.8 (5.4 to 25.9)	

Notes:

[10] - Analysis done in the per-protocol population

[11] - Analysis done in the per-protocol population

[12] - Analysis done in the per-protocol population

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival

End point title	Median Overall Survival
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End point description:

The median overall survival and its 95% confidence interval for each cohort are presented.

Note: the value 99999 indicates that the median or lower/upper bound of the 95% confidence interval was not reached.

End point type	Secondary
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End point timeframe:

From enrolment until the end of study

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7 ^[13]	21 ^[14]	34 ^[15]	
Units: months				
median (confidence interval 95%)	9.9 (2.0 to 99999)	9.0 (2.4 to 21.7)	99999 (11.3 to 99999)	

Notes:

[13] - Analysis was done in the per-protocol population

[14] - Analysis was done in the per-protocol population

[15] - Analysis was done in the per-protocol population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The number of patients who had specific adverse events in the period during treatment, which starts at the date the first dose of lorlatinib was taken until 30 days after the last date a dose of lorlatinib is taken.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Cohort A
Reporting group description: -	
Reporting group title	Cohort B
Reporting group description: -	
Reporting group title	Cohort C
Reporting group description: -	

Serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	9 / 22 (40.91%)	13 / 34 (38.24%)
number of deaths (all causes)	6	18	12
number of deaths resulting from adverse events	3	3	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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			
Hydronephrosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	3 / 22 (13.64%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Organising pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (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
Cardiac disorders			
Aortic valve calcification			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Brain oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
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 ischaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lethargy			

subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Motor dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Seizure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (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
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (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

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 Infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	4 / 34 (11.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (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	Cohort A	Cohort B	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	22 / 22 (100.00%)	34 / 34 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other, Neoplasms benign, malignant and unspecified			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Hot flashes			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	2 / 8 (25.00%)	2 / 22 (9.09%)	3 / 34 (8.82%)
occurrences (all)	2	2	3
Superficial thrombophlebitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Superior vena cava syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Thromboembolic Event			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
General disorders and administration site conditions			
Oedema Limbs			
subjects affected / exposed	3 / 8 (37.50%)	5 / 22 (22.73%)	9 / 34 (26.47%)
occurrences (all)	3	5	9
Fatigue			
subjects affected / exposed	2 / 8 (25.00%)	3 / 22 (13.64%)	4 / 34 (11.76%)
occurrences (all)	2	3	4
Fever			

subjects affected / exposed	2 / 8 (25.00%)	0 / 22 (0.00%)	7 / 34 (20.59%)
occurrences (all)	2	0	7
Flu like symptoms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
Gait disturbance			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Irritability			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Localised oedema			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	1	1	1
Other, General disorders			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Gynaecomastia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	2 / 8 (25.00%)	2 / 22 (9.09%)	5 / 34 (14.71%)
occurrences (all)	2	2	5
Dyspnoea			
subjects affected / exposed	2 / 8 (25.00%)	9 / 22 (40.91%)	6 / 34 (17.65%)
occurrences (all)	2	9	6
Hypoxia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Pleural effusion			
subjects affected / exposed	2 / 8 (25.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	2	0	1
Pleuratic pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Respiratory failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Sore throat			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Voice alteration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Other, Respiratory and mediastinal disorder			

subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Anxiety disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Delirium			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Euphoria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hallucination			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	5 / 34 (14.71%)
occurrences (all)	0	2	5
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
Psychosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Other, Psychiatric disorder			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Alkaline Phosphatase Increased			

subjects affected / exposed	0 / 8 (0.00%)	3 / 22 (13.64%)	5 / 34 (14.71%)
occurrences (all)	0	3	5
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	4 / 34 (11.76%)
occurrences (all)	1	0	4
Cholesterol high			
subjects affected / exposed	4 / 8 (50.00%)	14 / 22 (63.64%)	29 / 34 (85.29%)
occurrences (all)	4	14	29
Creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Creatine urine increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	1 / 8 (12.50%)	2 / 22 (9.09%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Serum amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Weight increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	4 / 34 (11.76%)
occurrences (all)	0	2	4
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Eosinophilia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Dysuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Atrial flutter			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Pericardial effusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pericardial tamponade			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Ventricular arrhythmia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Amnesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Aphonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Cognitive disturbance			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	4 / 34 (11.76%)
occurrences (all)	0	1	4
Concentration impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)	3 / 22 (13.64%)	5 / 34 (14.71%)
occurrences (all)	2	3	5
Dysarthria			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	3 / 34 (8.82%)
occurrences (all)	0	2	3
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Oedema cerebral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Encephalopathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	5 / 34 (14.71%)
occurrences (all)	1	1	5
Ischemia cerebrovascular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Memory impairment			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	8 / 34 (23.53%)
occurrences (all)	0	1	8
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Paresthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	4 / 34 (11.76%)
occurrences (all)	0	1	4
Peripheral motor neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	1	1	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	4 / 34 (11.76%)
occurrences (all)	0	2	4
Seizure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Stroke			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Syncope			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Other, Nervous system disorders			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Generalised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 8 (12.50%)	4 / 22 (18.18%)	6 / 34 (17.65%)
occurrences (all)	1	4	6
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Other, Blood and Lymphatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Vestibular disorder			
subjects affected / exposed	2 / 8 (25.00%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	2	0	3
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Eye pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Retinopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Watering eyes			

subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Other, Eye disorders			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	4 / 34 (11.76%)
occurrences (all)	1	0	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	6 / 34 (17.65%)
occurrences (all)	1	0	6
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	4 / 34 (11.76%)
occurrences (all)	0	0	4
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	4 / 22 (18.18%)	9 / 34 (26.47%)
occurrences (all)	0	4	9
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Oesophageal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Mucositis Oral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0

Nausea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
Other, Gastrointestinal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Other, Hepatobiliary			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Rash acneiform			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Skin induration			

subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Other, skin and subcutaneous tissue disorders			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Urinary incontinence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Urinary tract pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Other, Renal and urinary disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	7 / 34 (20.59%)
occurrences (all)	0	2	7
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	4 / 22 (18.18%)	8 / 34 (23.53%)
occurrences (all)	1	4	8
Bone pain			

subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Generalised muscle weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Muscle weakness left-sided			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	4 / 34 (11.76%)
occurrences (all)	0	0	4
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
neck contracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Sprained ankle			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Muscle cramp			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Spinal cord compression			

subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Scapular pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Hand cramps			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Appendicitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Bladder infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Bronchial infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	3 / 34 (8.82%)
occurrences (all)	0	0	3
Lung infection			
subjects affected / exposed	1 / 8 (12.50%)	4 / 22 (18.18%)	7 / 34 (20.59%)
occurrences (all)	1	4	7
Otitis externa			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Rhinitis infective			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Upper respiratory infection			
subjects affected / exposed	2 / 8 (25.00%)	0 / 22 (0.00%)	5 / 34 (14.71%)
occurrences (all)	2	0	5
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	1	1	1
Other, Infections and infestations			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Herpes simplex oral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Shingles			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Alcohol intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Anorexia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 22 (9.09%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Hypercalcaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hypertriglyceridemia			
subjects affected / exposed	3 / 8 (37.50%)	9 / 22 (40.91%)	25 / 34 (73.53%)
occurrences (all)	3	9	25
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 22 (0.00%)	0 / 34 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 22 (4.55%)	1 / 34 (2.94%)
occurrences (all)	1	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Other, Metabolism and nutrition disorders			
subjects affected / exposed	0 / 8 (0.00%)	0 / 22 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	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? Yes

Date	Interruption	Restart date
01 July 2023	<p>Accrual in this study was permanently discontinued on July 1st 2023 following an Independent Data Monitoring Committee (IDMC) recommendation based on poor accrual in cohort A. The primary objective and endpoint (progression-free survival rate at 12 months in cohort A) of this study was based and driven by cohort A; therefore, the statistical analysis plan foreseen in the protocol was modified considering the observed poor accrual in cohort A. The statistical guidelines for data analysis stated in the protocol were modified and documented in a revised SAP.</p> <p>Following this study's premature closing to patient entry for accrual in cohort A, 8 (7 in per-protocol population) patients were enrolled in cohort A, 22 (21 in per-protocol) population patients in cohort B and 34 patients (all 34 part of the per-protocol population) in cohort C. It was anticipated that 50% of accrued patients would satisfy the characteristics of cohort A, with an anticipated sample size of 42 to satisfy the power calculation. With the current sample size, after premature stopping of the accrual, this study was underpowered for the primary endpoint.</p> <p>As a consequence, the presented results are descriptive and thus decision rules and boundaries corresponding to the primary endpoint are not used to declare whether cohort A-based treatment is worthwhile for further exploration. The report also includes descriptive analyses of the endpoints relating to cohorts B and C, which are also descriptive, without any decision rules and boundaries.</p>	-

Notes:

Limitations and caveats

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

This phase II, multi-cohort, multicentre, clinical trial was stopped early due to poor accrual in cohort A, the cohort of primary interest. As a consequence, no hypothesis testing was performed and only exploratory descriptive values were presented.

Notes: