Clinical trial results:
A Randomized, Open-Label Phase I/II Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with relapsed, Recurrent, or Refractory Synovial Sarcoma.

Summary

EudraCT number	2018-004243-23
Trial protocol	FR DE BE ES GB IT
Global end of trial date	23 February 2023

Results information

Result version number	v1 (current)
This version publication date	08 September 2023
First version publication date	08 September 2023

Trial information

Trial identification

Sponsor protocol code	J1S-MC-JV02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04145700
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 17306

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	23 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study is being conducted to test the safety and efficacy of ramucirumab in combination with other chemotherapy in the treatment of relapsed, recurrent, or refractory synovial sarcoma (SS) in children and young adults. This trial is part of the CAMPFIRE master protocol which is a platform to accelerate the development of new treatments for pediatric and young adult participants with cancer. Your participation in this trial could last 12 months or longer, depending on how you and your tumor respond.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 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	Australia: 2
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	23
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1

Adolescents (12-17 years)	7
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Completers included participants who died from any cause.

Pre-assignment

Screening details:

No Text Available

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab + Gemcitabine + Docetaxel

Arm description:

Participants received intravenous infusions of ramucirumab 9 milligrams per kilogram (mg/kg), gemcitabine 900 milligrams per meter square (mg/m2) on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	LY3009806
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received intravenous infusion of ramucirumab 9 mg/kg on days 1, 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received intravenous infusion of gemcitabine 900 mg/m2 on days 1, 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received intravenous infusion of docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Arm title	Gemcitabine + Docetaxel

Arm description:

Participants received intravenous infusions of gemcitabine 900 mg/m2 on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Arm type	Active comparator

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received intravenous infusion of gemcitabine 900 mg/m2 on days 1, 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received intravenous infusion of docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Number of subjects in period 1	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel
Started	16	7
Received at least one dose of study drug	16	6
Completed	8	4
Not completed	8	3
Consent withdrawn by subject	8	3

Baseline characteristics

Reporting groups	
Reporting group title	Ramucirumab + Gemcitabine + Docetaxel
Reporting group description:	
Participants received intravenous infusions of ramucirumab 9 milligrams per kilogram (mg/kg), gemcitabine 900 milligrams per meter square (mg/m2) on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.	
Reporting group title	Gemcitabine + Docetaxel
Reporting group description:	
Participants received intravenous infusions of gemcitabine 900 mg/m2 on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.	

Reporting group values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel	Total
Number of subjects	16	7	23
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	17.70	21.40	
standard deviation	± 4.22	± 4.58	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	10	3	13
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	14	6	20
Unknown or Not Reported	1	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	5	18
More than one race	1	0	1
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Australia	0	2	2
Italy	5	2	7
Spain	1	0	1
United Kingdom	6	2	8
United States	4	1	5

End points

End points reporting groups

Reporting group title	Ramucirumab + Gemcitabine + Docetaxel

Reporting group description:

Participants received intravenous infusions of ramucirumab 9 milligrams per kilogram (mg/kg), gemcitabine 900 milligrams per meter square (mg/m2) on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Reporting group title	Gemcitabine + Docetaxel

Reporting group description:

Participants received intravenous infusions of gemcitabine 900 mg/m2 on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from randomization until the first investigator-determined objective progression as defined by Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST v1.1) or death from any cause in the absence of progressive disease. Participants known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment or date of randomization, whichever is later.

Analysis Population Description: All randomized participants (including the censored participants). Number of participants censored in Ramucirumab + Gemcitabine + Docetaxel=4, Gemcitabine + Docetaxel=2.

End point type	Primary

End point timeframe:

Baseline to Objective Progression or Death Due to Any Cause (Up To 6.4 Months)

End point values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	7[1]		
Units: Months				
median (confidence interval 80%)	2.10 (2 to 6)	2.03 (1.38 to 9999)		

Notes:

[1] - 9999=NA=There were not enough events to estimate the upper confidence limit.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

To conclude success for the intervention, the Bayesian analysis must yield a minimum of 99% posterior probability for PFS Hazard ratio less than 1 [i.e., Pr(HR<1)>99%]. The Bayesian analyses below include posterior mean of Hazard ratio, posterior probabilities instead of p-values, and credible intervals instead of confidence intervals.

Comparison groups	Ramucirumab + Gemcitabine + Docetaxel v Gemcitabine + Docetaxel

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	Bayesian hierarchical model]
Parameter estimate	Posterior Mean Hazard Ratio
Point estimate	2.62
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.19
upper limit	4.46

Secondary: Overall Response Rate (ORR): Percentage of Participants Who Achieve Complete Response (CR) or Partial Response (PR)

End point title	Overall Response Rate (ORR): Percentage of Participants Who Achieve Complete Response (CR) or Partial Response (PR)

End point description:

ORR is the best overall tumor response of complete response (CR) or partial response (PR) as classified by the investigator according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1). CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of non-target lesions or appearance of new lesions.

Analysis Population Description: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline through Measured Progressive Disease (Up To 6.4 Months)

End point values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	7		
Units: Percentage of participants				
number (confidence interval 80%)	6.3 (0.7 to 22.2)	0 (0 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective disease progression is

observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

Analysis Population Description: All randomized participants who had CR or PR responses. For Gemcitabine + Docetaxel, there were no participants with CR or PR responses to evaluate DoR, hence, zero participants analysed.

End point type	Secondary

End point timeframe:

Date of CR or PR to Date of Objective Disease Progression or Death Due to Any Cause (Up To 4.13 Months)

End point values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[2]	0[3]		
Units: Months				
number (not applicable)	9999			

Notes:

[2] - 9999=N/A=DoR couldn't be calculated as the participant did not achieve the event and was censored.

[3] - Zero participants analysed as there were no participants with CR or PR responses to evaluate DoR.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR): Percentage of Participants Who Achieve CR

End point title	Complete Response (CR): Percentage of Participants Who Achieve CR

End point description:

CR is a disappearance of all target and non-target lesions and normalization of tumor marker level.

Analysis Population Description: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline Up to 6.94 months

End point values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	7		
Units: Percentage of participants				
number (confidence interval 80%)	0 (0 to 13.4)	0 (0 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Serum Concentration of Ramucirumab (Cmax)

End point title	Pharmacokinetics (PK): Maximum Serum Concentration of Ramucirumab (Cmax)[4]

End point description:

Cmax was the concentration of study drug in the blood after the dose is administered. It was measured post-dose and was summarized using descriptive statistics.

Analysis Population Description: All randomized participants who received at least one dose of Ramucirumab and had evaluable PK data.

End point type	Secondary

End point timeframe:

0.5 hours after the end of ramucirumab infusion on Day 1 of Cycle 1

Notes:

[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: This outcome is planned for Ramucirumab arm only.

End point values	Ramucirumab + Gemcitabine + Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)	231 (± 43)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Minimum Serum Concentration of Ramucirumab (Cmin)

End point title	PK: Minimum Serum Concentration of Ramucirumab (Cmin)[5]

End point description:

Cmin was the concentration of study drug in the blood immediately before the next dose was administered. It was measured pre-dose at all visits and was summarized using descriptive statistics.

Analysis Population Description: All randomized participants who received at least one dose of Ramucirumab and had evaluable PK data.

End point type	Secondary

End point timeframe:

Prior to ramucirumab infusion on Day 8 of Cycle 1, Day 1 of Cycle 2 and Day 1 of Cycle 5

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: This outcome is planned for Ramucirumab arm only.

End point values	Ramucirumab + Gemcitabine + Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	10[6]			
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Day 8 of Cycle 1, N=9	73.3 (± 39)			
Day 1 of Cycle 2, N=10	55.4 (± 24)			
Day 1 of Cycle 5, N=2	9999 (± 9999)			

Notes:

[6] - 9999=N/A due to insufficient participants. Individual values reported: 32.4 µg/mL, 41.3 µg/mL.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Anti-Drug Antibodies (TE-ADA)

End point title	Number of Participants with Treatment-Emergent Anti-Drug Antibodies (TE-ADA)

End point description:

A TE-ADA evaluable participant is considered to be TE-ADA positive if the participant has at least one post baseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment-boosted). If baseline result is ADA Not Present, then the participant is TE ADA positive if there is at least one post baseline result of ADA Present with titer >= 20 (treatment-induced).

Analysis Population Description: All randomized participants who received at least one dose of study drug and had at least one non-missing baseline, post baseline ADA value.

End point type	Secondary

End point timeframe:

Baseline Up to 6.94 months

End point values	Ramucirumab + Gemcitabine + Docetaxel	Gemcitabine + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline Up to 6.94 months	
Adverse event reporting additional description:	
All randomized participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Gemcitabine + Docetaxel
Reporting group description:	
Participants received intravenous infusions of gemcitabine 900 mg/m2 on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met.	
Reporting group title	Ramucirumab + Gemcitabine + Docetaxel
Reporting group description:	
Participants received intravenous infusions of ramucirumab 9 mg/kg, gemcitabine 900 mg/m2 on days 1, 8, and docetaxel 75 mg/m2 on day 8 of a 21-day cycle until disease progression or a criterion for discontinuation were met	

Serious adverse events	Gemcitabine + Docetaxel	Ramucirumab + Gemcitabine + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	8 / 16 (50.00%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events			
Investigations			
platelet count decreased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
embolism			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

febrile neutropenia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
pyrexia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
mallory-weiss syndrome			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
laryngeal haemorrhage			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
pneumonia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Gemcitabine + Docetaxel	Ramucirumab + Gemcitabine + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	15 / 16 (93.75%)	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
hypotension			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
lymphoedema			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
superficial vein thrombosis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	4	
fatigue			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	4 / 6 (66.67%)	4 / 16 (25.00%)	
occurrences (all)	5	6	
mucosal inflammation			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
non-cardiac chest pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	3	
oedema peripheral			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	1 / 6 (16.67%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
pyrexia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	5 / 16 (31.25%)	
occurrences (all)	0	9	
Respiratory, thoracic and mediastinal disorders			
epistaxis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	6 / 16 (37.50%)	
occurrences (all)	1	8	
emphysema			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
dyspnoea			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
cough			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
nasal congestion			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
nasal dryness			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
productive cough			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
pleuritic pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
pneumothorax			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
rhinalgia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			
activated partial thromboplastin time prolonged			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
alanine aminotransferase			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
blood glucose increased			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	6 / 16 (37.50%)	
occurrences (all)	1	10	
alanine aminotransferase increased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	2 / 6 (33.33%)	7 / 16 (43.75%)	
occurrences (all)	3	14	
lymphocyte count decreased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	3	
neutrophil count decreased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	5 / 16 (31.25%)	
occurrences (all)	0	10	
platelet count decreased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	6 / 16 (37.50%)	
occurrences (all)	4	10	
weight increased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
white blood cell count decreased			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	4 / 16 (25.00%)	
occurrences (all)	7	8	

Injury, poisoning and procedural complications			
wound dehiscence			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cardiac disorders			
sinus tachycardia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	2 / 6 (33.33%)	4 / 16 (25.00%)	
occurrences (all)	2	4	
dizziness			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
presyncope			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
neuropathy peripheral			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	1	2	
sciatic nerve neuropathy			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

syncope			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
taste disorder			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	2 / 6 (33.33%)	7 / 16 (43.75%)	
occurrences (all)	4	8	
leukopenia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
neutropenia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	5 / 16 (31.25%)	
occurrences (all)	4	11	
thrombocytopenia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
ear pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorders			
blepharitis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
periorbital oedema			

alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
retinal haemorrhage			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	4 / 16 (25.00%)	
occurrences (all)	1	4	
aphthous ulcer			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
abdominal pain upper			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
gingival pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
enterocolitis haemorrhagic			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
dyspepsia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
diarrhoea			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	2 / 6 (33.33%)	3 / 16 (18.75%)	
occurrences (all)	2	4	
constipation			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	6 / 16 (37.50%)	
occurrences (all)	1	8	
nausea			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	5 / 16 (31.25%)	
occurrences (all)	1	11	
odynophagia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
vomiting			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	7 / 16 (43.75%)	
occurrences (all)	3	9	
stomatitis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	2 / 6 (33.33%)	5 / 16 (31.25%)	
occurrences (all)	3	6	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
erythema			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
dry skin			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
dermatitis acneiform			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
nail disorder			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
onychomadesis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
pain of skin			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	9	
pruritus			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
rash			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	1	2	
rash maculo-papular			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

skin discolouration			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
skin disorder			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
skin ulcer			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Renal and urinary disorders			
haematuria			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
proteinuria			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	4	
urinary retention			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
bone pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
back pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	3 / 16 (18.75%)	
occurrences (all)	0	4	
arthralgia			

alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
muscle spasms			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
muscular weakness			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
musculoskeletal chest pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
myalgia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	2 / 16 (12.50%)	
occurrences (all)	1	3	
neck pain			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
pain in extremity			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	6 / 16 (37.50%)	
occurrences (all)	0	7	
Infections and infestations			
cellulitis			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
covid-19			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
asymptomatic covid-19				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
folliculitis				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)		
occurrences (all)	0	3		
eye infection				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
conjunctivitis				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)		
occurrences (all)	1	1		
paronychia				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
pneumonia				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
urinary tract infection				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	2		
skin infection				
alternative dictionary used: MedDRA 25.1				
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		

Metabolism and nutrition disorders			
hyperglycaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
fluid retention			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
decreased appetite			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
hyperkalaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
hyperphosphataemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
hypoalbuminaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
hypocalcaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
hypoglycaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 6 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
hypokalaemia			
alternative dictionary used: MedDRA 25.1			

subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
hypomagnesaemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
hyponatraemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
hypophosphataemia			
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	0 / 6 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The limitation to this study was the highly varied estimates of the PFS HR and the probability of PFS HR < 1 due to influence from the matched historical controls whose PFS substantially outperformed PFS from the prospectively randomized control.

Notes: