Clinical trial results:
A PHASE I/II DOSE SCHEDULE FINDING STUDY OF CH14.18/CHO CONTINUOUS INFUSION COMBINED WITH SUBCUTANEOUS ALDESLEUKIN (IL-2) IN PATIENTS WITH PRIMARY REFRACTORY OR RELAPSED NEUROBLASTOMA. A SIOPEN STUDY.

Summary

EudraCT number	2009-018077-31
Trial protocol	AT ES DE IT GB IE PL BE
Global end of trial date	30 January 2025

Results information

Result version number	v1 (current)
This version publication date	04 March 2026
First version publication date	04 March 2026
Summary attachment (see zip file)	LTI_EoT Final Report Summary_Layperson Version_09-02-2026 (LTI_EoT Final Report Summary_Layperson Version_09-02-2026.pdf)

Trial information

Trial identification

Sponsor protocol code	012010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701479
WHO universal trial number (UTN)	-
Other trial identifiers	LTI - Long Term continuous Infusion: LTI

Notes:

Sponsors

Sponsor organisation name	St. Anna Kinderkrebsforschung
Sponsor organisation address	Zimmermannplatz 10, Wien, Austria, 1090
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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	31 January 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In the V1+V2 population the main objective was to to find an improved treatment schedule which reduces the pain-toxicity profile of ch14.18/CHO whilst maintaining immunomodulatory efficacy in patients (1-21 years old) with primary refractory (≥ 2 lines of conventional treatment) or relapsed neuroblastoma through prolonged continuous infusion in combination with s.c. aldesleukin (IL-2).

In the V3 population the main objective was the clarification of the role of sc IL-2 on event free survival by randomising the standard arm against the ch14.18/CHO only treatment arm. This decision was based on the V1+V2 population toxicity profiles and sc IL-2 toxicity data from the HR-NBL1 SIOPEN trial. The use of isotretinoin remained unchanged in both treatment arms.

Protection of trial subjects:

Detailed supportive care measures have been specified in the trial Protocol, section 8.6.
One aim of this study was to reduce the extent of neuropathic pain by administering the antibody as a prolonged continuous infusion to develop a schedule ultimately allowing for outpatient management of patients on trial. Therefore, this study aimed to establish a standard pain prophylaxis without the use of high doses of intravenous morphine. However, since neuropathic pain is an anticipated side effect even in a prolonged continuous infusion setting, children were to receive premedication with gabapentin (Neurontin®) from at least 3 days prior to the start of the ch14.18/CHO, as well as intravenous morphine prior to and during antibody infusion as required. Concomitant standard pain management was to be established with or without i.v. morphine and followed standard WHO guidelines including medications as follows:
Pain management/premedication:
- Prior to receiving ch14.18/CHO the patient should be primed with oral gabapentin, starting 3 days prior to the start of the ch14.18/CHO infusion. The recommended oral dose of gabapentin is 10 mg/kg/dose once daily on day 1, increasing to 10 mg/kg/dose twice daily on day 2 and 10 mg/kg three times a day thereafter. Gabapentin could either be stopped at the end of each continuous antibody infusion (and restarted 3 days prior to subsequent cycle) or continued throughout cycles and stopped after the end of the last infusion, according to local guidelines.
Gabapentin was available as oral solution containing 250 mg/5 mL of gabapentin or in capsules (100 mg, 300 mg, and 400 mg). The maximum single dose for Gabapentin is 300 mg.
- Premedication with anti-inflammatory drugs (e.g. paracetamol, metamizol according to local guidelines) was recommended prior to each dose of recombinant human Interleukin-2 (rhIL-2; Proleukin) to reduce anticipated toxicities.

Background therapy:

V1 and V2 (section 4 Trial Design) explored a feasible schedule for the LTI ch14.187CGO setting in patients with primary refractory or relapsed neuroblastoma. The dose and schedule of scIL-2 and isotretinoin (13-cis-RA) were constant. 20-40 patients were enrolled within the dose schedule finding part of the study with additional 20 patients enrolled during the confirmatory phase.
International Amendment 1 extended the confirmatory cohort to an expansion cohort of a total of 100 patients. Three dose levels of ch14.18/CHO dose levels were considered in V1 with respect to daily dose: 7 mg/m², 10 mg/m² and 15 mg/m² whilst the infusion durations in this design had a range from 10 to 21 days.
In V2 the ch14.18/CHO was administered as a diluted solution for infusion over a period of 10 days at a dose of 10 mg/m²/day within each treatment cycle by continuous infusion.

Evidence for comparator:

In V3 the LTI ch14.18/CHO only treatment arm was compared with the standard arm as established in V2.
The use of retinoid remained unchanged in both treatment arms.

Actual start date of recruitment	25 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United Kingdom: 50
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 53
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 50
Country: Number of subjects enrolled	Israel: 13
Worldwide total number of subjects	287
EEA total number of subjects	224

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)	7
Children (2-11 years)	254
Adolescents (12-17 years)	21
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

FPFV (first patient in): 25-Jan-2012
LPFV (last patient in): 05-Jul-2017
LPLV (last patient out): 30-Nov-2017
End of Global Recruitment: 11-Apr-2018
Total Number of Patients Recruited: 291
Number of Recruiting Countries: 10
Number of Sites with Recruited Subjects: 45

Pre-assignment

Screening details:

Patients with neuroblastoma >1 and ≤ 21 years of age (age limit for trial cohorts only), having received at least one previous high dose treatment followed by stem cell rescue after conventional therapy to reduce tumour burden. Treated and responding relapse after primary stage 4 disease, without signs of progression.

Period 1

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

Blinding implementation details:

Not blinded, open label study

Arms

Are arms mutually exclusive?	No
Arm title	Total Study Cohort

Arm description: -

Arm type	Total Study Cohort
Investigational medicinal product name	ch14.18/CHO
Investigational medicinal product code	NA
Other name	chimeric 14.18 anti-GD2, Dinutuximab beta, Qarziba
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A continuous infusion of ch14.18/CHO started on day 8. The duration of the infusion was dependent on the assigned infusion schedule. The duration ranged from 10 to 21 days.
Three dose levels were considered with respect to daily dose (7 mg/m², 10 mg/m², 15 mg/m²), which relates to total doses of 100 mg/m², 150 mg/m² and 210 mg/m².

Investigational medicinal product name	Aldesleukin (IL2)
Investigational medicinal product code	ATC code: L03AC01
Other name	Interleukin-2, Proleukin, IL2
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous aldesleukin (IL-2) was given at a dose of 6 x 106 IU/m²/day in two 5 day blocks (days 1-5 and 8-12).

Investigational medicinal product name	Isotretinoin
Investigational medicinal product code	ATC code: D10BA01
Other name	13-cis-RA, 13-cis-Retinoic Acid, Roaccutan
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients will receive isotretinoin (13-cis-RA) 160 mg/m²/day divided into two equal doses given orally twice a day for 14 days after the completion of the ch14.18/CHO infusion.
The starting day is dependent on the duration of ch14.18/CHO infusion and may be either day 19, 23, 24 or 30.

Arm title	Dose Finding & Confirmatory Cohort (V1+V2)

Arm description:

The Dose Finding Cohort used a continuous infusion of ch14.18/CHO which started on day 8. The duration of the infusion is dependent on the assigned infusion schedule. The duration ranged from 10 to 21 days.
Three dose levels were considered with respect to daily dose (7 mg/m², 10 mg/m², 15 mg/m²), which relates to total doses of 100 mg/m², 150 mg/m² and 210 mg/m².
The Confirmatory Cohort used the confirmed dose levels of 10 mg/m² of ch14.18/CHO over 10 days which relates to total dose of 100 mg/m².
In both cohorts subcutaneous aldesleukin (IL-2) was given at a dose of 6 x 106 IU/m²/day in two 5 day blocks (days 1-5 and 8-12).

Arm type	Single cohort
Investigational medicinal product name	ch14.18/CHO
Investigational medicinal product code	NA
Other name	chimeric 14.18 anti-GD2, Dinutuximab beta, Qarziba
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A continuous infusion of ch14.18/CHO started on day 8. The duration of the infusion was dependent on the assigned infusion schedule. The duration ranged from 10 to 21 days.
Three dose levels were considered with respect to daily dose (7 mg/m², 10 mg/m², 15 mg/m²), which relates to total doses of 100 mg/m², 150 mg/m² and 210 mg/m².

Investigational medicinal product name	Aldesleukin (IL2)
Investigational medicinal product code	ATC code: L03AC01
Other name	Interleukin-2, Proleukin, IL2
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous aldesleukin (IL-2) was given at a dose of 6 x 106 IU/m²/day in two 5 day blocks (days 1-5 and 8-12).

Arm title	Randomisation Cohort - Arm without IL-2 (V3)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	ch14.18/CHO
Investigational medicinal product code	NA
Other name	chimeric 14.18 anti-GD2, Dinutuximab beta, Qarziba
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A continuous infusion of ch14.18/CHO started on day 8. The confirmed dose level were used:
10 mg/m² over 10 days which relates to total dose of 100 mg/m².

Arm title	Randomisation Cohort - Arm with IL-2 (V3)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	ch14.18/CHO
Investigational medicinal product code	NA
Other name	chimeric 14.18 anti-GD2, Dinutuximab beta, Qarziba
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A continuous infusion of ch14.18/CHO started on day 8. The confirmed dose level were used: 10 mg/m² over 10 days which relates to total dose of 100 mg/m².

Investigational medicinal product name	Aldesleukin (IL2)
Investigational medicinal product code	ATC code: L03AC01
Other name	Interleukin-2, Proleukin, IL2
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous aldesleukin (IL-2) was given at a dose of 6 x 106 IU/m²/day in two 5 day blocks (days 1-5 and 8-12).

Number of subjects in period 1	Total Study Cohort	Dose Finding & Confirmatory Cohort (V1+V2)	Randomisation Cohort - Arm without IL-2 (V3)
Started	287	123	81
Completed	282	122	81
Not completed	5	1	0
Died during screening	1	1	-
Protocol deviation	4	-	-

Number of subjects in period 1	Randomisation Cohort - Arm with IL-2 (V3)
Started	79
Completed	79
Not completed	0
Died during screening	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Total Study Period
Reporting group description:	
Total cohort of patients (V1+V2+V3)	

Reporting group values	Total Study Period	Total	
Number of subjects	287	287	
Age categorical			
Age at study entry			
Units: Subjects			
<=1 year	0	0	
>1, <=1.5 years	2	2	
>1.5, <=5 years	125	125	
>5, <=10 years	114	114	
>10, <=21 years	46	46	
Age continuous			
Units: years			
median	5.3		
full range (min-max)	1.3 to 27.0	-	
Gender categorical			
Units: Subjects			
Female	118	118	
Male	169	169	

Subject analysis sets	
Subject analysis set title	Dose Finding & Confirmatory Cohort (V1+V2)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This subject analysis set contains the same cohort of patients as the already defined Dose Finding & Confirmatory Cohort (V1+V2) - arm.
According to the FAQ of EudraCT the cohort was defined in two different ways as a workaround to be able to enter the statistical analysis.

Reporting group values	Dose Finding & Confirmatory Cohort (V1+V2)		
Number of subjects	122		
Age categorical			
Age at study entry			
Units: Subjects			
<=1 year	0		
>1, <=1.5 years	2		
>1.5, <=5 years	50		
>5, <=10 years	48		
>10, <=21 years	23		

Age continuous Units: years			
median	5.7		
full range (min-max)	1.3 to 27.0		
Gender categorical Units: Subjects			
Female	53		
Male	70		

End points

End points reporting groups

Reporting group title	Total Study Cohort
Reporting group description: -	
Reporting group title	Dose Finding & Confirmatory Cohort (V1+V2)

Reporting group description:

The Dose Finding Cohort used a continuous infusion of ch14.18/CHO which started on day 8. The duration of the infusion is dependent on the assigned infusion schedule. The duration ranged from 10 to 21 days.
Three dose levels were considered with respect to daily dose (7 mg/m², 10 mg/m², 15 mg/m²), which relates to total doses of 100 mg/m², 150 mg/m² and 210 mg/m².
The Confirmatory Cohort used the confirmed dose levels of 10 mg/m² of ch14.18/CHO over 10 days which relates to total dose of 100 mg/m².
In both cohorts subcutaneous aldesleukin (IL-2) was given at a dose of 6 x 106 IU/m²/day in two 5 day blocks (days 1-5 and 8-12).

Reporting group title	Randomisation Cohort - Arm without IL-2 (V3)
Reporting group description: -	
Reporting group title	Randomisation Cohort - Arm with IL-2 (V3)
Reporting group description: -	
Subject analysis set title	Dose Finding & Confirmatory Cohort (V1+V2)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This subject analysis set contains the same cohort of patients as the already defined Dose Finding & Confirmatory Cohort (V1+V2) - arm.
According to the FAQ of EudraCT the cohort was defined in two different ways as a workaround to be able to enter the statistical analysis.

Primary: Composite (Primary End Point - Dose Finding & Confirmatory Cohort)

End point title	Composite (Primary End Point - Dose Finding & Confirmatory Cohort)

End point description:

For the evaluation of the primary endpoint only the first course will be taken into account :
A) Pain-toxicity endpoint: i.v. morphine free ch14.18/CHO infusion schedule after the first 5 days during the first cycle AND
B) Efficacy endpoint: on day 15 of the first cycle:
a. an increase of 500% and/or an absolute minimum increase to =100 cells/mcL of the CD16/CD56 positive activated NK cells, AND
b. a measurable ch14.18/CHO level of at least 1 µg/ml.

End point type	Primary

End point timeframe:

Start - end of first course of treatment

End point values	Total Study Cohort	Dose Finding & Confirmatory Cohort (V1+V2)	Randomisation Cohort - Arm without IL-2 (V3)	Randomisation Cohort - Arm with IL-2 (V3)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	287	122	81	79
Units: Patients with/without event	287	122	81	79

End point values	Dose Finding & Confirmatory Cohort (V1+V2)			
Subject group type	Subject analysis set			
Number of subjects analysed	122			
Units: Patients with/without event	122			

Statistical analyses

Statistical analysis title	Composite endpoint analysis

Statistical analysis description:

89/122 (73%) patients overall were intravenous morphine–free by day 5/cycle 1. Reasons for prolonged infusion in 33/122 patients were pain/discomfort (n=23, 19%) and other reasons (n=8, 7%), including investigator decision and hospital logistics. In patients with available data, 80/81 patients had dinutuximab beta concentration >1 µg/mL. On day 15 of cycle 1, 75/80 (94%) patients had a ≥500% increase (≥100 cells/µL) in NK cells.

Comparison groups	Dose Finding & Confirmatory Cohort (V1+V2) v Dose Finding & Confirmatory Cohort (V1+V2)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	0.99
Variability estimate	Standard deviation
Dispersion value	0.03

Primary: EFS (Primary End Point - Randomisation Cohort)

End point title	EFS (Primary End Point - Randomisation Cohort)[1]

End point description:

Disease progression or relapse and death from any cause were considered as events

End point type	Primary

End point timeframe:

Event Free Survival (EFS) is calculated from the date of randomisation.
The date of the first event (progression, relapse, death of any cause) or, if lost to follow up/censored the last examination date was taken as the end point of the time interval.

Notes:

[1] - 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: In the baseline period V1 + V2 dose finding & confirmation of the established dose with regards to pain and toxicity profile were the primary composite end points, but not EFS. Only in V3 EFS

was the primary end point.

End point values	Randomisation Cohort - Arm without IL-2 (V3)	Randomisation Cohort - Arm with IL-2 (V3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Patients with/without event	81	79		

Statistical analyses

Statistical analysis title	EFS comparison

Statistical analysis description:

The Cox proportional hazards method for treatment arm, stratified by country and stratum (relapsed prior study entry vs others) was used to calculate the hazard ratio (IL2+ vs IL2-) together with its confidence intervals and p-value.

Comparison groups	Randomisation Cohort - Arm with IL-2 (V3) v Randomisation Cohort - Arm without IL-2 (V3)
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.731
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.48
Variability estimate	Standard error of the mean
Dispersion value	0.241

Notes:

[2] - All analyses will be intention to treat, i.e. with all patients analysed in the arm to which they were randomised.

Secondary: EFS (Secondary End Point - Dose Finding & Confirmatory Cohort)

End point title	EFS (Secondary End Point - Dose Finding & Confirmatory Cohort)[3]

End point description:

Progression, relapse or death of any cause were defined as events

End point type	Secondary

End point timeframe:

To estimate the 2-years Event Free Survival (EFS) of the cohort, the date of the first event or, if lost to follow up/censored - the last examination date was taken as the end point of the time interval for each patient.

Notes:

[3] - 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: In the baseline period V1 + V2 dose finding & confirmation of the established dose with regards to pain and toxicity profile were the primary composite end points, but not EFS.

End point values	Dose Finding & Confirmatory Cohort (V1+V2)	Dose Finding & Confirmatory Cohort (V1+V2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	122	122		
Units: Patients with/without event	122	122		

Statistical analyses

Statistical analysis title	EFS

Statistical analysis description:

This is a single cohort analysis of the dose finding & confirmatory cohort (according to the FAQ of EudraCT the cohort was defined in two different ways as a workaround to be able to enter the stat. analysis).
The 2-years EFS was estimated using the Kaplan-Meier method. The date of the first event (progression, relapse or death of any cause) was taken as the endpoint of the time interval. Patients were censored at the date of the last contact if no events reported.

Comparison groups	Dose Finding & Confirmatory Cohort (V1+V2) v Dose Finding & Confirmatory Cohort (V1+V2)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Percent
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.64
Variability estimate	Standard deviation
Dispersion value	0.04

Notes:

[4] - Single cohort analysis

Secondary: OS (Secondary End Point - Dose Finding & Confirmatory Cohort)

End point title	OS (Secondary End Point - Dose Finding & Confirmatory Cohort)[5]

End point description:

Death of any cause was defined as event

End point type	Secondary

End point timeframe:

For the Overall Survival (OS), the date of death of any cause or, for patients without event, the last examination date was taken as the end point of the time interval for each patient.

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: OS was not a secondary end point.

End point values	Dose Finding & Confirmatory Cohort (V1+V2)	Dose Finding & Confirmatory Cohort (V1+V2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	122	122		
Units: Patients with/without event	122	122		

Statistical analyses

Statistical analysis title	OS

Statistical analysis description:

This is a single cohort analysis of the dose finding & confirmatory cohort (according to the FAQ of EudraCT the cohort was defined in two different ways as a workaround to be able to enter the stat. analysis).
The 2-years OS was estimated using the Kaplan-Meier method. Date of the first event (death of any cause) was taken as the endpoint of the time interval. Patients were censored at the date of the last contact if no events reported.

Comparison groups	Dose Finding & Confirmatory Cohort (V1+V2) v Dose Finding & Confirmatory Cohort (V1+V2)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Percent
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.81
Variability estimate	Standard deviation
Dispersion value	0.04

Notes:

[6] - Single group analysis (no group comparison)

Secondary: OS (Secondary End Point - Randomisation Cohort)

End point title	OS (Secondary End Point - Randomisation Cohort)[7]

End point description:

Death from any cause is considered an event

End point type	Secondary

End point timeframe:

The Overall Survival (OS) is calculated from the date of randomization. The date of death of any cause or, the last examination date (for lost to follow up/censored patients data) was taken as the end point of the time interval for each patient.

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: V1 and V2 had composite end points as outlined above but OS. Only V3 defined OS as secondary end point.

End point values	Randomisation Cohort - Arm without IL-2 (V3)	Randomisation Cohort - Arm with IL-2 (V3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Patients with/without event	81	79		

Statistical analyses

Statistical analysis title	OS comparison

Statistical analysis description:

The Cox proportional hazards method for treatment arm, stratified by country and stratum (relapsed prior study entry vs others) was used to calculate the hazard ratio (IL2+ vs IL2-) together with its confidence intervals and p-value.

Comparison groups	Randomisation Cohort - Arm without IL-2 (V3) v Randomisation Cohort - Arm with IL-2 (V3)
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.42
Variability estimate	Standard error of the mean
Dispersion value	0.27

Secondary: Response Rate (Secondary End Point - Randomisation Cohort)

End point title	Response Rate (Secondary End Point - Randomisation

End point description:

Response rate for patients with measurable disease at study entry

End point type	Secondary

End point timeframe:

End of treatment

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: In V3 response rate was a secondary end point but not in V1 and V2.

End point values	Randomisation Cohort - Arm without IL-2 (V3)	Randomisation Cohort - Arm with IL-2 (V3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Patients				
No evidence of/improved disease	22	21		
Stable/progressive disease	25	23		
Not evaluable	34	35		

Statistical analyses

Statistical analysis title	Response comparison

Statistical analysis description:

The response rate for each arm was defined as the patients with No evidence of/improved disease at end of MRD treatment divided by all evaluable patients.

Comparison groups	Randomisation Cohort - Arm without IL-2 (V3) v Randomisation Cohort - Arm with IL-2 (V3)
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.765
Method	Chi-squared

Notes:

[9] - Comparison of non time to event variables

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs observed from the time of registration up to 90 days after the last study drug administration will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

Adverse event reporting additional description:

All SAEs that are at least possibly related to the ch14.18/CHO, Aldesleukin (IL-2) or 13-cis-RA and are still present at the end of the study must be followed at least until the final outcome is determined, even if it implies that the follow-up continues after the patient leaves the trial and when appropriate until the end of planned f-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	Dose Finding & Confirmatory Cohort

Reporting group description:

Consisting of Dose Finding and Confirmatory subgroups

Reporting group title	Randomisation: ch14.18/CHO with IL2

Reporting group description:

ch14.18/CHO + IL2

Reporting group title	Randomisation: ch14.18/CHO without IL2

Reporting group description:

ch14.18/CHO -IL2

Reporting group title	Not Randomised

Reporting group description:

Not Randomised

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious Adverse Events were not MedDRA coded but encountered toxicities were captured according to CTS coding in the clinical trial database.

Serious adverse events	Dose Finding & Confirmatory Cohort	Randomisation: ch14.18/CHO with IL2	Randomisation: ch14.18/CHO without IL2
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 123 (56.91%)	49 / 79 (62.03%)	30 / 81 (37.04%)
number of deaths (all causes)	30	21	9
number of deaths resulting from adverse events	1	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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			

Capillary leak syndrome			
subjects affected / exposed	5 / 123 (4.07%)	10 / 79 (12.66%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distributive shock			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	5 / 123 (4.07%)	5 / 79 (6.33%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Venoocclusive disease			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Fatigue			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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

Gait disturbance			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Influenza like illness			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Pyrexia			
subjects affected / exposed	17 / 123 (13.82%)	14 / 79 (17.72%)	12 / 81 (14.81%)
occurrences causally related to treatment / all	0 / 17	0 / 14	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Cytokine release syndrome			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Hypersensitivity			

subjects affected / exposed	4 / 123 (3.25%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolar proteinosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Asthma			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Bronchospasm			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Cough			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Hypoxia			
subjects affected / exposed	3 / 123 (2.44%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Pneumonitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
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 distress			
subjects affected / exposed	3 / 123 (2.44%)	4 / 79 (5.06%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
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 tract infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Depressed mood			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Depression			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Irritability			

subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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			
Alanine aminotransferase			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Aspartate aminotransferase			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 123 (0.00%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood culture positive			
subjects affected / exposed	0 / 123 (0.00%)	2 / 79 (2.53%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CSF protein increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Eosinophil count increased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve conduction studies abnormal			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Platelet count decreased			
subjects affected / exposed	5 / 123 (4.07%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Weight decreased			
subjects affected / exposed	0 / 123 (0.00%)	3 / 79 (3.80%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital central hypoventilation syndrome			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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			

Cardiac arrest			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Nervous system disorders			
Allodynia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Brain injury			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Brain oedema			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Demyelination			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Diplegia			

subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Dyskinesia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperaesthesia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Paraplegia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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	0 / 123 (0.00%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	3 / 123 (2.44%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord paralysis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Haemoglobinaemia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Thrombocytopenia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Eye disorders			

Iridoplegia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mydriasis			
subjects affected / exposed	3 / 123 (2.44%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photophobia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Visual acuity reduced			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Abdominal pain			
subjects affected / exposed	2 / 123 (1.63%)	2 / 79 (2.53%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Constipation			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Diarrhoea			

subjects affected / exposed	4 / 123 (3.25%)	1 / 79 (1.27%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	3 / 123 (2.44%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Intestinal obstruction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Nausea			
subjects affected / exposed	3 / 123 (2.44%)	0 / 79 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 123 (2.44%)	4 / 79 (5.06%)	4 / 81 (4.94%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venoocclusive liver disease			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Chronic kidney disease			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
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 failure			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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

Urinary retention			
subjects affected / exposed	0 / 123 (0.00%)	3 / 79 (3.80%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Pain in extremity			
subjects affected / exposed	0 / 123 (0.00%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Acinetobacter infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Arthritis bacterial			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Bacteraemia			
subjects affected / exposed	3 / 123 (2.44%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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

Candida sepsis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Catheter site infection			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Cystitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Device related bacteraemia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	6 / 123 (4.88%)	3 / 79 (3.80%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	3 / 123 (2.44%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Gastroenteritis			

subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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 infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Herpes simplex			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 123 (0.81%)	3 / 79 (3.80%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	3 / 123 (2.44%)	3 / 79 (3.80%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 123 (0.00%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterium avium complex infection			

subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Parvovirus infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Pharyngitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Pneumococcal infection			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			

subjects affected / exposed	0 / 123 (0.00%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 123 (0.81%)	4 / 79 (5.06%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Pyelonephritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Respiratory tract infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Rhinovirus infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Rotavirus infection			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	4 / 123 (3.25%)	0 / 79 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Staphylococcal sepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Staphylococcal skin infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Stenotrophomonas infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Streptococcal infection			

subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Tonsillitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Tooth infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Urinary tract infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Urinary tract infection bacterial			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Varicella			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	3 / 123 (2.44%)	3 / 79 (3.80%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Vulvitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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			
Decreased appetite			
subjects affected / exposed	0 / 123 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Dehydration			
subjects affected / exposed	2 / 123 (1.63%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 79 (1.27%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 79 (0.00%)	0 / 81 (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
Hyponatraemia			
subjects affected / exposed	1 / 123 (0.81%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Not Randomised		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Distributive shock			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venoocclusive disease			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaphylactic shock				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytokine release syndrome				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alveolar proteinosis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed mood				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Irritability				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood culture positive				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CSF protein increased				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eosinophil count increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nerve conduction studies abnormal				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urine output decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				

Congenital central hypoventilation syndrome				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Allodynia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain injury				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Depressed level of consciousness				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Demyelination				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diplegia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyskinesia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperaesthesia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensorimotor neuropathy				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord paralysis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobinaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Iridoplegia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mydriasis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Photophobia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal adhesions				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic cytolysis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venoocclusive liver disease				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Chronic kidney disease				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Mobility decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Acarodermatitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acinetobacter infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Bacteraemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related bacteraemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterobacter sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngitis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mycobacterium avium complex infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myelitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes zoster				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parvovirus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal skin infection				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stenotrophomonas infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella				

subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vulvitis				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Dose Finding & Confirmatory Cohort	Randomisation: ch14.18/CHO with IL2	Randomisation: ch14.18/CHO without IL2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 123 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)

Non-serious adverse events	Not Randomised		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2012	International Amendment 1, Protocol version 2.0.
26 February 2014	International Amendment 2, Protocol version 3.0.
28 October 2016	International Amendment 3, Protocol version 4.0.
22 December 2016	Non-substantial Amendment 3, Protocol version 4.1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The limitation of the trial cohorts lies in the underlying disease presenting a rare paediatric tumour entity and ideally recruitment would have happened in a more stringent time period.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/40940820

http://www.ncbi.nlm.nih.gov/pubmed/37444475

http://www.ncbi.nlm.nih.gov/pubmed/37834840

http://www.ncbi.nlm.nih.gov/pubmed/39796776

http://www.ncbi.nlm.nih.gov/pubmed/40627545

http://www.ncbi.nlm.nih.gov/pubmed/30442501

http://www.ncbi.nlm.nih.gov/pubmed/32013055

http://www.ncbi.nlm.nih.gov/pubmed/23924804

http://www.ncbi.nlm.nih.gov/pubmed/15950727

http://www.ncbi.nlm.nih.gov/pubmed/29120699

http://www.ncbi.nlm.nih.gov/pubmed/26785755

http://www.ncbi.nlm.nih.gov/pubmed/30336605

http://www.ncbi.nlm.nih.gov/pubmed/31741754

http://www.ncbi.nlm.nih.gov/pubmed/35454826