Clinical trial results:
A Phase 1b/2 Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Efavaleukin Alfa in Adult Subjects With Steroid Refractory Chronic Graft Versus Host Disease

Summary

EudraCT number	2017-000763-33
Trial protocol	BE
Global end of trial date	13 October 2022

Results information

Result version number	v1 (current)
This version publication date	21 October 2023
First version publication date	21 October 2023

Trial information

Trial identification

Sponsor protocol code	20160283

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03422627
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	Study Director, Amgen Inc., medinfo@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the safety and tolerability of multiple ascending doses of efavaleukin alfa in participants with steroid refractory chronic graft versus host disease (cGVHD) in order to estimate the maximum tolerated dose (MTD) and establish the recommended phase 2 dose (RP2D).

Only the Phase 1b portion of this trial was completed. Phase 2 never opened.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312. All participants provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	32
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

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

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled into this study at sites in Belgium, France, Japan, and the United States.

Pre-assignment

Screening details:

Screening tests and procedures were performed up to 28 days preceding treatment. The study was planned to have a Phase 1b part and a Phase 2 part. The study was cancelled before enrolling participants into the Phase 2 part. Therefore, results presented only include data for the Phase 1b part.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Participants in Cohort 1 received efavaleukin alfa subcutaneously (SC) once every 2 weeks (Q2W) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 1 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Arm type	Experimental
Investigational medicinal product name	Efavaleukin alfa
Investigational medicinal product code	
Other name	AMG 592
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received efavaleukin alfa subcutaneously (SC) plus protocol permitted background therapy for 52 weeks.

Arm title	Cohort 2

Arm description:

Participants in Cohort 2 received efavaleukin alfa SC once every week (QW) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 2 received dose 1. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Arm type	Experimental

Investigational medicinal product name	Efavaleukin alfa
Investigational medicinal product code	
Other name	AMG 592
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received efavaleukin alfa subcutaneously (SC) plus protocol permitted background therapy for 52 weeks.

Arm title	Cohort 3

Arm description:

Participants in Cohort 3 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 3 received dose 3. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Arm type	Experimental
Investigational medicinal product name	Efavaleukin alfa
Investigational medicinal product code	
Other name	AMG 592
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received efavaleukin alfa subcutaneously (SC) plus protocol permitted background therapy for 52 weeks.

Arm title	Cohort 4

Arm description:

Participants in Cohort 4 received efavaleukin alfa SC QW plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 4 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Arm type	Experimental
Investigational medicinal product name	Efavaleukin alfa
Investigational medicinal product code	
Other name	AMG 592
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received efavaleukin alfa subcutaneously (SC) plus protocol permitted background therapy for 52 weeks.

Arm title	Cohort 5

Arm description:

Participants in Cohort 5 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 5 received dose 4. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Arm type	Experimental

Investigational medicinal product name	Efavaleukin alfa
Investigational medicinal product code	
Other name	AMG 592
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received efavaleukin alfa subcutaneously (SC) plus protocol permitted background therapy for 52 weeks.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	7	7	7
Completed Wk52 Opted for Extended Dosing	2	1 [1]	2 [2]
Completed Wk52 Didn't Opt Extend Dosing	0 [3]	1 [4]	1 [5]
Completed	2	2	3
Not completed	5	5	4
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	-	-	-
Ineligibility Determined	-	1	-
Adverse event, non-fatal	2	1	-
Requirement for Alternative Therapy	1	1	2
Protocol-specified Criteria	1	1	-
Disease Progression	1	-	1

Number of subjects in period 1	Cohort 4	Cohort 5
Started	6	5
Completed Wk52 Opted for Extended Dosing	3	0 [6]
Completed Wk52 Didn't Opt Extend Dosing	0 [7]	1
Completed	3	1
Not completed	3	4
Adverse event, serious fatal	-	-
Consent withdrawn by subject	1	-
Ineligibility Determined	-	-
Adverse event, non-fatal	-	2
Requirement for Alternative Therapy	-	-
Protocol-specified Criteria	-	2
Disease Progression	2	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of participants who completed Week 52 who did not opt for extended dosing.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1

Reporting group description:

Participants in Cohort 1 received efavaleukin alfa subcutaneously (SC) once every 2 weeks (Q2W) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 1 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 2

Reporting group description:

Participants in Cohort 2 received efavaleukin alfa SC once every week (QW) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 2 received dose 1. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 3

Reporting group description:

Participants in Cohort 3 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 3 received dose 3. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 4

Reporting group description:

Participants in Cohort 4 received efavaleukin alfa SC QW plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 4 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 5

Reporting group description:

Participants in Cohort 5 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 5 received dose 4. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	7	7	7

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	5	7
From 65-84 years	1	2	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	48.9	52.9	49.4
standard deviation	± 12.5	± 17.4	± 12.2
Sex: Female, Male Units: participants			
Female	3	3	2
Male	4	4	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	1	5	6
Unknown or Not Reported	5	2	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	2	4	4
More than one race	0	0	0
Unknown or Not Reported	5	2	1

Reporting group values	Cohort 4	Cohort 5	Total
Number of subjects	6	5	32
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	2	26
From 65-84 years	0	3	6
85 years and over	0	0	0

Age Continuous Units: years			
arithmetic mean	55.3	64.6	
standard deviation	± 7.6	± 5.9	-
Sex: Female, Male Units: participants			
Female	3	1	12
Male	3	4	20
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	6	5	23
Unknown or Not Reported	0	0	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	4	3	17
More than one race	0	0	0
Unknown or Not Reported	0	0	8

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Participants in Cohort 1 received efavaleukin alfa subcutaneously (SC) once every 2 weeks (Q2W) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 1 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 2

Reporting group description:

Participants in Cohort 2 received efavaleukin alfa SC once every week (QW) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 2 received dose 1. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 3

Reporting group description:

Participants in Cohort 3 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 3 received dose 3. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 4

Reporting group description:

Participants in Cohort 4 received efavaleukin alfa SC QW plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 4 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 5

Reporting group description:

Participants in Cohort 5 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 5 received dose 4. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Primary: Phase 1b: Number of Participants Who Experienced a Dose-limiting Toxicity (DLT)

End point title	Phase 1b: Number of Participants Who Experienced a Dose-limiting Toxicity (DLT)[1]

End point description:

A DLT was defined as a:
- Non-hematological toxicity ≥grade-4(per common terminology criteria for adverse events [CTCAE] v4.03) related to efavaleukin alfa. Non-hematological lab abnormalities without clinical significance weren't considered DLTs.
- Hematological toxicity ≥grade 4 related to efavaleukin alfa defined as decreases in peripheral counts (absolute neutrophil count or platelets) persisting longer than 72 hrs, as measured by 2 separate results, that were not related to malignant disease relapse, infection, or other etiologies.
- Constitutional events (ie, fever, fatigue) ≥grade 3 that were classified as serious adverse events by the investigator and related to efavaleukin alfa.
- Infection is considered an expected complication of chronic graft versus host disease (cGVHD) and its treatment. Only grade 4 or 5 infections considered by the investigator to be related to efavaleukin alfa were reviewed by the dose level review meeting to determine whether it was considered a DLT.

End point type	Primary

End point timeframe:

Up to 4 weeks after first dose of study drug administration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	7	6	6
Units: participants	0	0	0	0

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants Who Experienced a Treatment-related Adverse Event (AE)

End point title	Phase 1b: Number of Participants Who Experienced a Treatment-related Adverse Event (AE)[2]

End point description:

A treatment-related AE was any untoward medical occurrence in a clinical study participant deemed to have a possibly causal relationship to the study treatment as determined by the investigator.
Measured in the safety analysis set, which included all participants who received at least 1 dose of efavaleukin alfa.

End point type	Primary

End point timeframe:

Day 1 until the end of study; median (min, max) duration was 38.01 (3.27, 139.81) weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	6
Units: participants	5	5	6	6

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants Who Experienced a Treatment-emergent AE

End point title	Phase 1b: Number of Participants Who Experienced a Treatment-emergent AE[3]

End point description:

A treatment-emergent AE was any untoward medical occurrence in a clinical study participant that occurred after first dose.
Measured in the safety analysis set, which included all participants who received at least 1 dose of efavaleukin alfa.

End point type	Primary

End point timeframe:

Day 1 until the end of study; median (min, max) duration was 38.01 (3.27, 139.81) weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	6
Units: participants	6	6	7	6

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants Who Experienced a Treatment-emergent Serious AE

End point title	Phase 1b: Number of Participants Who Experienced a Treatment-emergent Serious AE[4]

End point description:

A treatment-emergent serious AE was any untoward medical occurrence in a clinical study participant that occurred after first dose that resulted in death, was immediately life threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect or another medically important serious event.
Measured in the safety analysis set, which included all participants who received at least 1 dose of efavaleukin alfa.

End point type	Primary

End point timeframe:

Day 1 until the end of study; median (min, max) duration was 38.01 (3.27, 139.81) weeks

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	7	6
Units: participants	5	3	3	4

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: participants	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Mortality: from enrollment until the end of study; median (min, max) duration was 38.44 (3.56, 140.09) weeks. Serious and non-serious adverse events: from Day 1 until the end of study; median (min, max) duration was 38.01 (3.27, 139.81) weeks.

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled/randomized in the study. Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Participants in Cohort 1 received efavaleukin alfa subcutaneously (SC) once every 2 weeks (Q2W) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 1 received dose 2.

At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 2

Reporting group description:

Participants in Cohort 2 received efavaleukin alfa SC once every week (QW) plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 2 received dose 1.

At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 3

Reporting group description:

Participants in Cohort 3 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 3 received dose 3. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 4

Reporting group description:

Participants in Cohort 4 received efavaleukin alfa SC QW plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 4 received dose 2. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 259 weeks (QW dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Reporting group title	Cohort 5

Reporting group description:

Participants in Cohort 5 received efavaleukin alfa SC Q2W plus protocol permitted background therapy for 52 weeks. Four ascending dose levels of efavaleukin alfa were administered between the 5 cohorts as follows. Dose 1 (low dose), dose 2 (low-mid dose), dose 3 (high-mid dose), dose 4 (high dose). Participants in Cohort 5 received dose 4. At the discretion of the sponsor, following discussion and agreement between the principal investigator and medical monitor, participants that responded to efavaleukin alfa were permitted to continue to receive efavaleukin alfa treatment at their current dosing regimen for up to a maximum of 258 weeks (Q2W dose), if they remained eligible for extended dosing. Participants then completed the 6-week safety follow up after their last dose of efavaleukin alfa.

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	3 / 7 (42.86%)	3 / 7 (42.86%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Vena cava thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Cardiac arrest			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Ischaemic stroke			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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
Immune system disorders			
Chronic graft versus host disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft versus host disease in skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Chronic graft versus host disease in skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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			
Large intestine polyp			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Duodenal ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (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 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Klebsiella bacteraemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Enterococcal sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Candida sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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 / 7 (14.29%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Pseudomonal sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (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
Vascular device infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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
Septic shock			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (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

Serious adverse events	Cohort 4	Cohort 5	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	3 / 5 (60.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Chronic graft versus host disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Graft versus host disease in skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease in skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Klebsiella bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Parainfluenzae virus infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	6 / 7 (85.71%)	7 / 7 (100.00%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vena cava thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chest pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	0 / 7 (0.00%)
occurrences (all)	1	4	0
Gait disturbance			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Injection site erythema			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Injection site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injection site pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Injection site reaction			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	4 / 7 (57.14%)
occurrences (all)	0	9	6
Localised oedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	7	3	4
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Immune system disorders			
Graft versus host disease in skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Acute graft versus host disease oral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Chronic graft versus host disease			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Chronic graft versus host disease in skin			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Graft versus host disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Graft versus host disease in eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			

Cervix oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vasomotor rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pulmonary thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pharyngeal enanthema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Dysphonia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	1	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Delirium			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Enterovirus test positive			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eosinophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Human rhinovirus test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pelvic fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Procedural nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin laceration			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Monoparesis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	2	2
Facial paresis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dizziness			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aphasia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nervous system disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	1 / 7 (14.29%)
occurrences (all)	1	3	1
Eosinophilia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ocular hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Eye pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Keratitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Meibomianitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Vision blurred			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Large intestine polyp			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Melaena			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Odynophagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral lichen planus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Oral pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Periodontal disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hepatic cytolysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hepatomegaly			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Drug eruption			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Ingrowing nail			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Skin lesion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Skin induration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Rash			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	3 / 7 (42.86%)
occurrences (all)	3	0	3
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Lichenoid keratosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Palmar erythema			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Plantar erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Skin ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Chronic kidney disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 7 (28.57%)
occurrences (all)	0	2	2
Trismus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Scleroderma			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	5	0	1
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Catheter site infection			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Enterococcal sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Fungal disease carrier			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Keratitis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Lip infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Mastitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Onychomycosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pathogen resistance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Tinea pedis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vascular device infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	3	2	0
Zinc deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Steroid diabetes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Cohort 4	Cohort 5	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 5 (60.00%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vena cava thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypotension			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Venous thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	7	
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Disease progression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			

subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Injection site pruritus			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Injection site rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)	
occurrences (all)	2	2	
Localised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Graft versus host disease in skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Acute graft versus host disease oral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	

Chronic graft versus host disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Chronic graft versus host disease in skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Graft versus host disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Graft versus host disease in eye			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Cervix oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Vasomotor rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pulmonary embolism			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pharyngeal enanthema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Laryngeal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dysphonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Delirium			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	

Agitation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Blood glucose increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Enterovirus test positive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Eosinophil count increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Weight increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pelvic fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Procedural nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Spinal compression fracture			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Tachycardia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Monoparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Facial paresis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Aphasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Motor dysfunction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Presyncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Nervous system disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Ocular hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Keratitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Meibomianitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cataract			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Large intestine polyp			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Oral lichen planus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Periodontal disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholestasis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hepatic cytolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hepatomegaly			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Drug eruption			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin induration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Rash pruritic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	2 / 6 (33.33%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Lichenoid keratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Palmar erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Plantar erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin ulcer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Renal failure			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Incontinence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Chronic kidney disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Trismus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Scleroderma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Catheter site infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cellulitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	
occurrences (all)	1	2	
Clostridium difficile colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ear infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Enterococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Fungal disease carrier			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Herpes simplex			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Keratitis bacterial			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Lip infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Mastitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pathogen resistance			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Subcutaneous abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Tinea pedis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Tracheitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Oral herpes			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Zinc deficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Steroid diabetes			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	
Dehydration subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 5 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2017	- Key Sponsor Contact and supporting information was updated - The primary objective for the phase 1b portion of the study was updated to clarify the intent to use the phase 1 data to determine the maximum tolerated dose and support the determination of the recommended phase 2 dose. - Updated the phase 2 primary endpoint and all related descriptions to reflect a change to analyze the best overall response rate (ORR) during the study. In addition, week 8 is included in the secondary endpoint analysis. - Updated the maximum dose to be administered in the study. - To accommodate the change in formulation, the information regarding product packaging was updated to indicate that AMG 592 is a liquid formulation that was provided in glass vials. - Updated the cGVHD response assessment - Updated Schedule of Activities and eligibility - Clarified that pharmacokinetics was determined using serum samples rather than plasma samples. - Subgroup analyses were updated to include prior radiation status and conditioning regimen (myeloablative versus non-myeloablative). - The Safety Follow-Up Visit was updated to require in-clinic assessment of the participants rather than a phone call assessment. Urine pregnancy testing was also added for women of childbearing potential to confirm pregnancy status up to 6 weeks posttreatment.
04 December 2018	- Changes to study design: Increased Phase 1b cohort size of future dosing cohorts from n = 3 to up to n = 6, clarified that dosing cohorts may be added or removed at any time after completion of the first cohorts, removed optional cohorts 1b/2b,a dded 1a/2a dose expansion cohorts to align with DLRM decision, made final dose expansion cohort of n = 10 participants optional. - Clarified entry criteria and study conduct rules - Revised entry criterion 104, definition of moderate to severe steroid refractory cGVHD: o Removed requirement for diagnosis within the past 2 years o Removed requirement to be steroid refractory within the past 12 months - Modified alcohol restrictions after the 4-week DLT evaluation period in eligible participants - Increased visit window duration after the week 16 visit - Clarified that direct genital exams are not require as part of the Staging and National Institutes of Health (NIH) Form A evaluations. - Miscellaneous changes made to schedule of assessments - Changed to 1-sided test with a significance level of 0.025
26 August 2019	- Updated the phase 1b part of the study to allow for continued access to AMG 592 for up to an additional 52 weeks following week 50 (Q2W dose) or week 51 (QW dose) at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, for participants who were responding to AMG 592 (as assessed by week 50) and who wished to continue on treatment. - Clarified that phase 1b participants who were still receiving or planned to receive AMG 592 treatment at the time that the RP2D was established may change their AMG 592 dose to the RP2D dose at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, and may continue study treatment until completion of the week104/EOT visit. - Corrected inconsistencies in the Schedules of Assessments for the phase 1b part of the study with regard to corticosteroid use, adverse events, serious adverse events, and disease-related events. - Clarified requirements for recording and reporting disease-related events

08 December 2020	- Added cohort 5 for the purpose of exploring the safety, pharmacokinetics (PK), pharmacodynamics (PD) of higher efavaleukin alfa (AMG 592) doses in participants with steroid refractory chronic graft versus host disease. - Included description of cohort 5 and enrollment to cohort 5 to study design - Removed statement regarding efavaleukin alfa dose level weekly limit - Updated study schema phase 1b to include cohort 5 - Increased the sample size from up to 34 participants to approximately 40 participants sample size to reflect the addition of cohort 5 - Updated human exposure and justification for investigational product dose sections to support the cohort 5 dose - Edited a secondary PK endpoint to be consistent to evaluate PK parameters on week 4 instead of week 16 - Updated risk assessment - Updated footnotes and timing windows for assessments - Updated eligibility criteria - Clarified that the medical monitor was to be informed when efavaleukin alfa was withheld for acute clinical events - Minor corrections to statistical considerations section to provide additional clarity - Provided more details for serious adverse event reporting via the electronic data collection tool - Clarified that the disease-related events table presented in Appendix 11 was not inclusive
22 June 2021	- Updated the phase 1b part of the study to allow for continued access to efavaleukin alfa for up to an additional 156 weeks following week 102 (Q2W dose) or week 103 (QW dose) at the discretion of the Sponsor, following discussion and agreement between the principal investigator and medical monitor, for participants who were responding to efavaleukin alfa (as assessed by week 104) and who wished to continue on treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported