



Clinical trial results:

An Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects 1 and 30 Years of Age With Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

Summary

EudraCT number	2017-003377-34
Trial protocol	GB DE BE FR ES SE NL IT Outside EU/EEA
Global end of trial date	22 September 2022

Results information

Result version number	v1 (current)
This version publication date	07 April 2023
First version publication date	07 April 2023

Trial information

Trial identification

Sponsor protocol code	54767414ALL2005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03384654
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002152-PIP01-17
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 September 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this trial was to evaluate the efficacy of daratumumab in addition to standard chemotherapy in pediatric subjects with relapse/refractory B-cell acute lymphoblastic leukemia (ALL) and T-cell ALL as measured by complete response (CR) rate.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 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	Germany: 2
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	46
EEA total number of subjects	28

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)	24
Adolescents (12-17 years)	15
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One subject of Cohort 1: B-cell ALL (1-17 Years) was not enrolled in the study and thus 46 subjects were enrolled in the study and treated with study drug. Out of 46 subjects, 45 subjects completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)

Arm description:

Subjects with relapsed/refractory B-cell ALL received intrathecal methotrexate (MTX) 8milligrams(mg):1-less than(<)2 years (y), 10mg:2- <3 Y, 12mg:3- <9 Y and 15 mg:greater than or equal to(>=) 9 Y on Cycle(C) 1 Day(D) 1(all) and C2 and later D1 each C (CNS negative); for CNS positive, with MTX, hydrocortisone(HC)/cytarabine(ARA-C) was used per local standard practice; daratumumab 16 milligrams per kilogram (mg/kg) as intravenous(IV) infusion weekly on D1,8,15 and 22 of C1 and 2 then every 2 weeks on D1,15 of C3 to 6 and every 4 weeks on D1 of C7 and onward;vincristine 1.5 milligrams per square meter(mg/m²) IV once weekly on D1,8,15 and 22 of C1, then every 2 weeks on D1 and 15 of C2 and every 4 weeks on D1 of C3 and onward;prednisone 40mg/m² once daily on D1 to 28 of C1 and on D1 to 5 of C2 onward. Subjects received treatment until disease progression, unacceptable toxicity, or proceeding hematopoietic stem cell transplant after CR whichever came first(maximum duration:2.3 months).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	JNJ-54767414
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) IV infusion weekly on Days 1, 8, 15 and 22 of Cycles 1 and 2 then every 2 weeks on Days 1 and 15 of Cycle 3 to 6 and every 4 weeks on Day 1 of Cycle 7 and onward.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received vincristine 1.5 mg/m² IV injection/infusion weekly on Days 1, 8, 15 and 22 of Cycle 1, then every 2 weeks on Days 1 and 15 of Cycle 2 and every 4 weeks on Day 1 of Cycle 3 and onward.

Investigational medicinal product name	Intrathecal Hydrocortisone (HC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intrathecal HC 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and Cycles 2 and later Day 1 of each cycle.

Investigational medicinal product name	Intrathecal methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intrathecal methotrexate 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Day 1 of Cycle 1 and 2 onwards.

Investigational medicinal product name	Intrathecal Cytarabine (ARA-C)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intrathecal ARA-C 16 mg for age 1- <2 years, 20 mg for age 2- <3 years, 24 mg for age 3- <9 years and 30 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and Cycles 2 and later Day 1 of each cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral liquid, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received prednisone 40 mg/m² orally daily on Days 1 to 28 of Cycle 1 and then on Days 1 to 5 of Cycle 2 and onward.

Arm title	Cohort 2: T-Cell ALL (1-17 Years)
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Arm description:

Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2Y, 10mg:2- <3Y, 12mg:3- <9Y and 15mg: ≥ 9 Y on C1 D1(all) each C (CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1, 8, 15 and 22; doxorubicin 60mg/m² IV once on D1; vincristine 1.5mg/m² IV injection/infusion weekly on D1, 8, 15 and 22; prednisone 40mg/m² orally daily on D1-28; peg-asparaginase 25000 units per square meter (U/m²) as intramuscular (IM) injection/IV infusion on D2, 16. In C2, subjects received intrathecal MTX 8mg:1- <2Y, 10mg:2- <3Y, 12mg:3- <9Y and 15mg: ≥ 9 Y on C2 D2, 15 (CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1, 8, 15 and 22; MTX 5g/m² as IV once on D2, cyclophosphamide IV 1g/m² once on D15; cytarabine 75mg/m² IV/subcutaneous (SC) on D16-19 and D23-26; 6-mercaptopurine 60mg/m² orally daily on D15-28 (max. duration: 2.9 months).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	JNJ-54767414
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received daratumumab 16 mg/kg IV weekly for 4 doses on Days 1, 8, 15, and 22 during cycle 1 and 2.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Subjects received doxorubicin 60 mg/m ² IV once on Day 1 during cycle 1 alone.	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received vincristine 1.5 mg/m ² as IV injection/infusion weekly on Days 1, 8, 15 and 22 during cycle 1 alone.	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral liquid, Oral suspension
Routes of administration	Oral use
Dosage and administration details:	
Subjects received prednisone 40 mg/m ² orally daily on Days 1 to 28 during cycle 1 alone.	
Investigational medicinal product name	Methotrexate (MTX)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received MTX 5 grams per square meter (g/m ²) as IV once on Day 2 during cycle 2 alone.	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received cyclophosphamide IV 1 g/m ² once on Day 15 during cycle 2 alone.	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details:	
Subjects received cytarabine 75 mg/m ² either IV or subcutaneously on Days 16 to 19 and 23 to 26 during cycle 2 alone.	
Investigational medicinal product name	6-mercaptopurine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received 6-mercaptopurine 60 mg/m ² orally daily for 14 doses on Days 15 to 28 during cycle 2 alone.	
Investigational medicinal product name	Intrathecal methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal methotrexate 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Days 1 (all subjects), 15 and 22 (CNS negative subjects) during Cycle 1 and on Days 2 and 15 (CNS negative subjects) during Cycle 2.

Investigational medicinal product name	Intrathecal Hydrocortisone (HC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal HC 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Intrathecal Cytarabine (ARA-C)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal ARA-C 16 mg for age 1- <2 years, 20 mg for age 2- <3 years, 24 mg for age 3- <9 years and 30 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Peg-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Intramuscular and intravenous use

Dosage and administration details:
Subject received peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16 during Cycle 1.

Arm title	Cohort 2: T-Cell ALL (18-30 Years)
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Arm description:

Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg: ≥ 9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m² IV once on D1; vincristine 1.5mg/m² IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m² orally daily on D1-28 and peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg: ≥ 9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m² as IV once on D2, cyclophosphamide 1g/m² once on D15; cytarabine 75mg/m² IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m² orally daily on D15 to 28 (maximum duration:2.1 months).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	JNJ-54767414
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received daratumumab 16 mg/kg IV weekly for 4 doses on Days 1, 8, 15, and 22 during cycle 1 and 2.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received doxorubicin 60 mg/m² IV once on Day 1 during cycle 1 alone.

Investigational medicinal product name	MTX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received MTX 5 g/m² as IV once on Day 2 during cycle 2 alone.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral liquid, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects received prednisone 40 mg/m² orally daily on Days 1 to 28 during cycle 1 alone.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received vincristine 1.5 mg/m² as IV injection/infusion weekly on Days 1, 8, 15 and 22 during cycle 1 alone.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cyclophosphamide IV 1 g/m² once on Day 15 during cycle 2 alone.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects received cytarabine 75 mg/m² either IV or subcutaneously on Days 16 to 19 and 23 to 26 during cycle 2 alone.

Investigational medicinal product name	6-mercaptopurine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 6-mercaptopurine 60 mg/m² orally daily for 14 doses on Days 15 to 28 during cycle 2 alone.

Investigational medicinal product name	Intrathecal methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal methotrexate 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Days 1 (all subjects), 15 and 22 (CNS negative subjects) during Cycle 1 and on Days 2 and 15 (CNS negative subjects) during Cycle 2.

Investigational medicinal product name	Intrathecal Hydrocortisone (HC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal HC 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Intrathecal Cytarabine (ARA-C)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received intrathecal ARA-C 16 mg for age 1- <2 years, 20 mg for age 2- <3 years, 24 mg for age 3- <9 years and 30 mg for ≥ 9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Peg-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:
Subject received peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16 during Cycle 1.

Arm title	Cohort 2: T-Cell LL (1-30 Years)
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Arm description:

Subjects with relapsed/refractory T-cell LL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg: ≥ 9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m² IV once on D1; vincristine 1.5mg/m² IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m² orally daily on D1-28 and peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg: ≥ 9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m² as IV once on D2, cyclophosphamide 1g/m² once on D15; cytarabine 75mg/m² IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m² orally daily on D15 to 28 (maximum duration:2.1 months).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	JNJ-54767414
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Subjects received daratumumab 16 mg/kg IV weekly for 4 doses on Days 1, 8, 15, and 22 during cycle 1 and 2.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Subjects received doxorubicin 60 mg/m ² IV once on Day 1 during cycle 1 alone.	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received vincristine 1.5 mg/m ² as IV injection/infusion weekly on Days 1, 8, 15 and 22 during cycle 1 alone.	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral liquid, Oral suspension
Routes of administration	Oral use
Dosage and administration details:	
Subjects received prednisone 40 mg/m ² orally daily on Days 1 to 28 during cycle 1 alone.	
Investigational medicinal product name	MTX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received MTX 5 g/m ² as IV once on Day 2 during cycle 2 alone.	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received cyclophosphamide IV 1 g/m ² once on Day 15 during cycle 2 alone.	
Investigational medicinal product name	Intrathecal methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received intrathecal methotrexate 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥9 years on Days 1 (all subjects), 15 and 22 (CNS negative subjects) during Cycle 1 and on Days 2 and 15 (CNS negative subjects) during Cycle 2.	
Investigational medicinal product name	6-mercaptopurine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received 6-mercaptopurine 60 mg/m ² orally daily for 14 doses on Days 15 to 28 during cycle 2 alone.	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects received cytarabine 75 mg/m² either IV or subcutaneously on Days 16 to 19 and 23 to 26 during cycle 2 alone.

Investigational medicinal product name	Intrathecal Hydrocortisone (HC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intrathecal HC 8 mg for age 1- <2 years, 10 mg for age 2- <3 years, 12 mg for age 3- <9 years and 15 mg for ≥9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Intrathecal Cytarabine (ARA-C)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intrathecal ARA-C 16 mg for age 1- <2 years, 20 mg for age 2- <3 years, 24 mg for age 3- <9 years and 30 mg for ≥9 years on Cycle 1 Days 8, 15, 22, 28 and on Days 2 and 15 of Cycle 2.

Investigational medicinal product name	Peg-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Subject received peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16 during Cycle 1.

Number of subjects in period 1	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)
Started	7	24	5
Completed	7	24	4
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Number of subjects in period 1	Cohort 2: T-Cell LL (1-30 Years)
Started	10
Completed	10
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)
Reporting group description:	
Subjects with relapsed/refractory B-cell ALL received intrathecal methotrexate (MTX) 8milligrams(mg):1-less than(<)2 years (y), 10mg:2- <3 Y, 12mg:3- <9 Y and 15 mg:greater than or equal to(>=) 9 Y on Cycle(C) 1 Day(D) 1(all) and C2 and later D1 each C (CNS negative); for CNS positive, with MTX, hydrocortisone(HC)/cytarabine(ARA-C) was used per local standard practice; daratumumab 16 milligrams per kilogram (mg/kg) as intravenous(IV) infusion weekly on D1,8,15 and 22 of C1 and 2 then every 2 weeks on D1,15 of C3 to 6 and every 4 weeks on D1 of C7 and onward;vincristine 1.5 milligrams per square meter(mg/m^2) IV once weekly on D1,8,15 and 22 of C1, then every 2 weeks on D1 and 15 of C2 and every 4 weeks on D1 of C3 and onward;prednisone 40mg/m^2 once daily on D1 to 28 of C1 and on D1 to 5 of C2 onward. Subjects received treatment until disease progression, unacceptable toxicity, or proceeding hematopoietic stem cell transplant after CR whichever came first(maximum duration:2.3 months).	
Reporting group title	Cohort 2: T-Cell ALL (1-17 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2Y,10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9Y on C1 D1(all) each C (CNS negative);for CNS positive,with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1;vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22;prednisone 40mg/m^2 orally daily on D1-28;peg-asparaginase 25000 units per square meter(U/m^2) as intramuscular(IM) injection/IV infusion on D2,16. In C2, subjects received intrathecal MTX 8mg:1- <2Y, 10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;MTX 5g/m^2 as IV once on D2, cyclophosphamide IV 1g/m^2 once on D15;cytarabine 75mg/m^2 IV/subcutaneous(SC) on D16-19 and D23-26;6-mercaptopurine60mg/m^2 orally daily on D15-28 (max. duration:2.9months).	
Reporting group title	Cohort 2: T-Cell ALL (18-30 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1; vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m^2 orally daily on D1-28 and peg-asparaginase 25000 U/m^2 as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m^2 as IV once on D2, cyclophosphamide 1g/m^2 once on D15; cytarabine 75mg/m^2 IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m^2 orally daily on D15 to 28 (maximum duration:2.1 months).	
Reporting group title	Cohort 2: T-Cell LL (1-30 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell LL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1; vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m^2 orally daily on D1-28 and peg-asparaginase 25000 U/m^2 as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m^2 as IV once on D2, cyclophosphamide 1g/m^2 once on D15; cytarabine 75mg/m^2 IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m^2 orally daily on D15 to 28 (maximum duration:2.1 months).	

Reporting group values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)

Number of subjects	7	24	5
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	5	16	0
Adolescents (12-17 years)	2	8	0
Adults (18-64 years)	0	0	5
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	8.1	9.8	22.2
standard deviation	± 5.01	± 4.17	± 2.77
Title for Gender			
Units: subjects			
Female	4	10	0
Male	3	14	5

Reporting group values	Cohort 2: T-Cell LL (1-30 Years)	Total	
Number of subjects	10	46	
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	3	24	
Adolescents (12-17 years)	5	15	
Adults (18-64 years)	2	7	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous			
Units: years			
arithmetic mean	13.5	-	
standard deviation	± 5.68	-	
Title for Gender			
Units: subjects			
Female	1	15	
Male	9	31	

End points

End points reporting groups

Reporting group title	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)
Reporting group description:	
Subjects with relapsed/refractory B-cell ALL received intrathecal methotrexate (MTX) 8milligrams(mg):1-less than(<)2 years (y), 10mg:2- <3 Y, 12mg:3- <9 Y and 15 mg:greater than or equal to(>=) 9 Y on Cycle(C) 1 Day(D) 1(all) and C2 and later D1 each C (CNS negative); for CNS positive, with MTX, hydrocortisone(HC)/cytarabine(ARA-C) was used per local standard practice; daratumumab 16 milligrams per kilogram (mg/kg) as intravenous(IV) infusion weekly on D1,8,15 and 22 of C1 and 2 then every 2 weeks on D1,15 of C3 to 6 and every 4 weeks on D1 of C7 and onward;vincristine 1.5 milligrams per square meter(mg/m^2) IV once weekly on D1,8,15 and 22 of C1, then every 2 weeks on D1 and 15 of C2 and every 4 weeks on D1 of C3 and onward;prednisone 40mg/m^2 once daily on D1 to 28 of C1 and on D1 to 5 of C2 onward. Subjects received treatment until disease progression, unacceptable toxicity, or proceeding hematopoietic stem cell transplant after CR whichever came first(maximum duration:2.3 months).	
Reporting group title	Cohort 2: T-Cell ALL (1-17 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2Y,10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9Y on C1 D1(all) each C (CNS negative);for CNS positive,with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1;vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22;prednisone 40mg/m^2 orally daily on D1-28;peg-asparaginase 25000 units per square meter(U/m^2) as intramuscular(IM) injection/IV infusion on D2,16. In C2, subjects received intrathecal MTX 8mg:1- <2Y, 10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;MTX 5g/m^2 as IV once on D2, cyclophosphamide IV 1g/m^2 once on D15;cytarabine 75mg/m^2 IV/subcutaneous(SC) on D16-19 and D23-26;6-mercaptopurine60mg/m^2 orally daily on D15-28 (max. duration:2.9months).	
Reporting group title	Cohort 2: T-Cell ALL (18-30 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1; vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m^2 orally daily on D1-28 and peg-asparaginase 25000 U/m^2 as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m^2 as IV once on D2, cyclophosphamide 1g/m^2 once on D15; cytarabine 75mg/m^2 IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m^2 orally daily on D15 to 28 (maximum duration:2.1 months).	
Reporting group title	Cohort 2: T-Cell LL (1-30 Years)
Reporting group description:	
Subjects with relapsed/refractory T-cell LL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m^2 IV once on D1; vincristine 1.5mg/m^2 IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m^2 orally daily on D1-28 and peg-asparaginase 25000 U/m^2 as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m^2 as IV once on D2, cyclophosphamide 1g/m^2 once on D15; cytarabine 75mg/m^2 IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m^2 orally daily on D15 to 28 (maximum duration:2.1 months).	

Primary: Percentage of Subjects with Complete Response (CR) for B-cell Acute Lymphoblastic Leukemia (ALL)

End point title	Percentage of Subjects with Complete Response (CR) for B-cell Acute Lymphoblastic Leukemia (ALL) ^{[1][2]}
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End point description:

Complete response based on the modified National Comprehensive Cancer Network (NCCN) criteria is defined as: less than 5 percent (%) blasts in the bone marrow; no evidence of circulating blasts or extramedullary disease; full recovery of peripheral blood counts: platelets greater than ($>$) 100×10^9 cells/liter (L) and absolute neutrophil count (ANC) $> 1.0 \times 10^9$ cells/L. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab. This endpoint was planned to be analysed for specified arm only as pre specified in protocol.

End point type	Primary
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End point timeframe:

Up to 2 cycles (each cycle of 28-days)

Notes:

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

Justification: No inferential statistics was planned for this primary endpoint.

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

Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of Subjects				
number (confidence interval 90%)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with CR for T-cell ALL

End point title	Percentage of Subjects with CR for T-cell ALL ^{[3][4]}
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End point description:

CR based on the modified NCCN criteria is defined as: less than 5% blasts in the bone marrow; no evidence of circulating blasts or extramedullary disease; full recovery of peripheral blood counts: platelets $> 100 \times 10^9$ cell/L and ANC $> 1.0 \times 10^9$ cell/L. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab. This endpoint was planned to be analysed for specified arm only as pre specified in protocol.

End point type	Primary
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End point timeframe:

End of Cycle 1 (ie., up to 28 days)

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 inferential statistics was planned for this primary endpoint.

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

Justification: This endpoint was planned to be analysed for specified arms only.

End point values	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	5	10	
Units: Percentage of subjects				
number (confidence interval 90%)	41.7 (24.6 to 60.3)	60.0 (18.9 to 92.4)	30.0 (8.7 to 60.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
ORR is defined as percentage of ALL subjects who achieved CR with only partial hematological recovery (CRi) according to NCCN criteria. Per NCCN criteria, CR for ALL is defined as: Less than 5 % blasts in the bone marrow; no evidence of circulating blasts or extramedullary disease; full recovery of peripheral blood counts: Platelets $>100 \times 10^9$ cell/L and ANC $>1.0 \times 10^9$ cell/L; CRi for ALL: less than 5% blasts in the bone marrow; no evidence of circulating blasts or extramedullary disease; partial recovery of peripheral blood counts not meeting criteria for CR. For LL subjects, ORR was defined as the percentage of subjects who achieved CR or partial response (PR) during or after treatment administration but prior to the start of subsequent anti-cancer therapy or allogeneic hematopoietic stem cell transplant (HSCT). The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab.	
End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Percentage of subjects				
number (confidence interval 90%)	14.3 (0.7 to 52.1)	83.3 (65.8 to 94.1)	80.0 (34.3 to 99.0)	50.0 (22.2 to 77.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)
End point description:	
EFS is defined as the time (in months) from the date of first treatment to the first documented treatment failure (that is [ie], disease progression) or date of relapse from CR or death due to any	

cause, whichever occurs first. Per NCCN criteria, relapse from CR is defined as: reappearance of leukemia blasts in the peripheral blood or >5% blasts in the bone marrow; reappearance of extramedullary disease or new extramedullary disease. Progressive disease: increase of at least 25% in the absolute number of circulating peripheral or bone marrow blasts, or development of new extramedullary disease. Kaplan-Meier method was used for the analysis. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab. Here, '99999' indicates that data were not evaluable due to less number of subjects with events.

End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Months				
median (confidence interval 90%)	1.1 (0.9 to 2.1)	8.9 (5.3 to 99999)	10.3 (2.6 to 99999)	2.9 (1.3 to 4.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free Survival (RFS)

End point title	Relapse-free Survival (RFS)
End point description:	
RFS is defined as the time (in months) from CR to relapse from CR or disease progression or death due to any cause, whichever occurs first. Per NCCN criteria, relapse from CR is defined as: reappearance of leukemia blasts in the peripheral blood or >5% blasts in the bone marrow, or reappearance of extramedullary disease or new extramedullary disease. Progressive disease: increase of at least 25% in absolute number of circulating peripheral or bone marrow blasts, or development of new extramedullary disease. Kaplan-Meier method was used for analysis. The response evaluable analysis set included all enrolled subjects who received at least 1 dose of daratumumab and had at least 1 adequate post-baseline disease assessment. Here, 'N' (number of subject analysed) signifies all treated who achieved a complete response. Here, '99999' indicate that data were not evaluable due to less number of subjects with events.	
End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[5]	12	3	4
Units: Months				
median (confidence interval 90%)	(to)	19.4 (5.3 to 99999)	9.4 (3.6 to 99999)	99999 (1.8 to 99999)

Notes:

[5] - RFS was not evaluable for this arm as no subjects achieved CR.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time (in months) from the date of first study drug administration to the date of death due to any cause. Kaplan-Meier method was used for the analysis. Subjects who died after consent withdrawal were considered as having an OS event. If the subject was alive or the survival status was unknown, then the subject's data were censored at the last known alive date. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab. Here,'99999' indicates that data were not evaluable due to less number of subjects with events.	
End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Months				
median (confidence interval 90%)	3.2 (1.0 to 3.6)	10.9 (6.7 to 99999)	12.0 (4.5 to 99999)	4.9 (1.7 to 5.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD) Negative Rate

End point title	Minimal Residual Disease (MRD) Negative Rate
End point description:	
MRD negative rate was defined as the percentage of subjects who were considered MRD negative after MRD testing by bone marrow aspirate at any timepoint after first study treatment administration and before disease progression or starting subsequent anti-cancer therapy or allogeneic HSCT. MRD negative	

is defined as <0.01% abnormal population counts to nucleated mononuclear cells when measured by flow cytometry. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab.

End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Percentage of subjects				
number (confidence interval 90%)	0 (0 to 0)	45.8 (28.2 to 64.2)	20.0 (1.0 to 65.7)	50.0 (22.2 to 77.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT)

End point title	Percentage of Subjects who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT)
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End point description:

Percentage of subjects who received an allogeneic HSCT after treatment with daratumumab were assessed. The allogeneic HSCT rate was defined as the percentage of subjects who received an allogeneic HSCT after treatment with daratumumab. The all treated analysis set included all enrolled subjects who received at least 1 dose of daratumumab.

End point type	Secondary
End point timeframe:	
Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Percentage of subject				
number (confidence interval 90%)	14.3 (0.7 to 52.1)	75.0 (56.5 to 88.5)	60.0 (18.9 to 92.4)	30.0 (8.7 to 60.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Daratumumab

End point title	Maximum Observed Serum Concentration (Cmax) of Daratumumab
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End point description:

Cmax is defined as maximum observed serum concentration. The serum pharmacokinetics (PK) evaluable analysis set included all enrolled subjects who received at least 1 dose of daratumumab and provided at least 1 post-infusion blood sample for serum daratumumab concentrations. Here, follow-up indicated 8 week post treatment. EOI: End of infusion.

End point type	Secondary
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End point timeframe:

B-cell ALL: Predose and EOI on Day 1 of Cycles 1 and 2, EOT and follow-up; T-cell ALL: Predose and EOI on Day 1 of Cycles 1 and 2, Cycle 2 Day 22, EOT and follow-up

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: Micrograms per millilitre (mcg/mL)				
arithmetic mean (standard deviation)	494 (± 184)	763 (± 185)	501 (± 347)	758 (± 157)

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Daratumumab

End point title	Minimum Observed Serum Concentration (Cmin) of Daratumumab
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End point description:

Cmin is defined as minimum observed serum concentration. The serum PK evaluable analysis set included all enrolled subjects who received at least 1 dose of daratumumab and provided at least 1 post-infusion blood sample for serum daratumumab concentrations. Here, follow-up indicated 8 week post treatment.

End point type	Secondary
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End point timeframe:

B-cell ALL: Predose and EOI on Day 1 of Cycles 1 and 2, EOT and follow-up; T-cell ALL: Predose and EOI on Day 1 of Cycles 1 and 2, Cycle 2 Day 22, EOT and follow-up

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	24	5	10
Units: mcg/mL				
arithmetic mean (standard deviation)	172 (± 115)	369 (± 105)	172 (± 177)	365 (± 204)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-daratumumab Antibody

End point title	Number of Subjects with Anti-daratumumab Antibody
End point description: Number of subjects with anti-daratumumab antibody was reported. The immunogenicity evaluable analysis set included all enrolled subjects who received at least 1 dose of daratumumab and had at least 1 post-infusion sample for detection of anti-daratumumab antibodies.	
End point type	Secondary
End point timeframe: Up to 4 years 4 months	

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	22	5	9
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Daratumumab in Cerebrospinal Fluid (CSF)

End point title	Concentration of Daratumumab in Cerebrospinal Fluid (CSF)
End point description: Concentration of daratumumab in CSF was reported. The CSF PK evaluable analysis set included all enrolled subjects who received at least 1 dose of daratumumab and provided at least 1 post-infusion CSF sample for daratumumab concentrations. Here, 'N' (number of subject analysed) signifies number of subjects who were evaluable for this endpoint and 'n' (number analysed) represent number of subjects evaluable for specified timepoints. Here, '99999' indicates that data was not calculated due to the lower limit of quantification (LLOQ) limit in timepoint cycle 1: Day 1 predose and due to the less number of subject in timepoints cycle 1: Day 15 predose and cycle 2: Days 2, 15 predose.	
End point type	Secondary

End point timeframe:

Cohort 1: Cycle 1 and 2: Day 1 pre-dose; Cohort 2: Cycle 1 Day 1 and 15: pre-dose and Cycle 2 Day 2 and Day 15: pre-dose

End point values	Cohort 1: B-cell acute lymphoblastic leukemia(ALL) (1-17Years)	Cohort 2: T-Cell ALL (1-17 Years)	Cohort 2: T-Cell ALL (18-30 Years)	Cohort 2: T-Cell LL (1-30 Years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	21	5	10
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1: Day 1 predose (n=3, 18, 3, 10)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Cycle 1: Day 15 predose (n=0, 21, 5, 10)	99999 (± 99999)	0.907 (± 1.96)	0.319 (± 0.203)	0.456 (± 0.280)
Cycle 2: Day 1 predose (n=3, 0, 0, 0)	0.573 (± 0.545)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Cycle 2: Day 2 predose (n=0, 14, 3, 5)	99999 (± 99999)	0.915 (± 0.916)	0.296 (± 0.191)	1.23 (± 0.728)
Cycle 2: Day 15 predose (n=0, 16, 1, 5)	99999 (± 99999)	0.934 (± 0.549)	0.163 (± 99999)	1.06 (± 0.282)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 4 years 4 months

Adverse event reporting additional description:

The safety analysis set included all enrolled subjects who received at least 1 dose of daratumumab.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Cohort 1: B-Cell ALL (1-17 Years)
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Reporting group description:

Subjects aged 1 year to 17 years with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) received daratumumab 16 milligrams per kilogram (mg/kg) as intravenous (IV) infusion weekly on Days 1, 8, 15 and 22 of Cycles 1 and 2 then every 2 weeks on Days 1 and 15 of Cycle 3 to 6 and every 4 weeks on Day 1 of Cycle 7 and onward; vincristine 1.5 milligrams per square meter (mg/m²) as IV injection/infusion weekly on Days 1, 8, 15 and 22 of Cycle 1, then every 2 weeks on Days 1 and 15 of Cycle 2 and every 4 weeks on Day 1 of Cycle 3 and onward; prednisone 40 mg/m² orally daily on Days 1 to 28 of Cycle 1 and then on Days 1 to 5 of Cycle 2 and onward. Subjects received study drugs until disease progression, unacceptable toxicity, or achievement of complete response (CR) followed by hematopoietic stem cell transplant (HSCT), whichever occurred first (maximum duration: 2.3 months).

Reporting group title	Cohort 2: T-Cell LL (1-30 Years)
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Reporting group description:

Subjects with relapsed/refractory T-cell LL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m² IV once on D1; vincristine 1.5mg/m² IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m² orally daily on D1-28 and peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m² as IV once on D2, cyclophosphamide 1g/m² once on D15; cytarabine 75mg/m² IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m² orally daily on D15 to 28 (maximum duration:2.1 months).

Reporting group title	Cohort 2: T-Cell ALL (18-30 Years)
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Reporting group description:

Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C1 D1(all) and on C1 D15 and 22 (CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m² IV once on D1; vincristine 1.5mg/m² IV injection/infusion weekly on D1,8,15 and 22; prednisone 40mg/m² orally daily on D1-28 and peg-asparaginase 25000 U/m² as IM injection/IV infusion on D2 and 16. In C2, subjects received intrathecal MTX 8mg:1- <2 Y, 10mg:2- <3 Y, 12mg:3- <9 Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX, HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22; MTX 5g/m² as IV once on D2, cyclophosphamide 1g/m² once on D15; cytarabine 75mg/m² IV/SC on D16 to 19 and D23 to 26 and 6-mercaptopurine 60mg/m² orally daily on D15 to 28 (maximum duration:2.1 months).

Reporting group title	Cohort 2: T-Cell ALL (1-17 Years)
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Reporting group description:

Subjects with relapsed/refractory T-cell ALL in C1 received intrathecal MTX 8mg:1- <2Y,10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9Y on C1 D1(all) each C (CNS negative);for CNS positive,with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;doxorubicin 60mg/m² IV once on D1;vincristine 1.5mg/m² IV injection/infusion weekly on D1,8,15 and 22;prednisone 40mg/m² orally daily on D1-28;peg-asparaginase 25000 units per square meter(U/m²) as intramuscular(IM) injection/IV infusion on D2,16. In C2, subjects received intrathecal MTX 8mg:1- <2Y, 10mg:2- <3Y, 12mg:3- <9Y and 15mg:>=9 Y on C2 D2,15(CNS negative); for CNS positive, with MTX,HC/ARA-C was used per local standard practice; daratumumab 16mg/kg IV infusion weekly on D1,8,15 and 22;MTX 5g/m² as IV once on D2, cyclophosphamide IV 1g/m² once on D15;

Serious adverse events	Cohort 1: B-Cell ALL (1-17 Years)	Cohort 2: T-Cell LL (1-30 Years)	Cohort 2: T-Cell ALL (18-30 Years)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	7 / 10 (70.00%)	4 / 5 (80.00%)
number of deaths (all causes)	3	6	2
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Blood Lactic Acid Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Pseudomonas Test Positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Staphylococcus Test Positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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

Weight Decreased subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Depressed Level of Consciousness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Dysarthria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukoencephalopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Posterior Reversible Encephalopathy Syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peripheral Nerve Palsy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 3	4 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mucosal Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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

General Physical Health Deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal Fistula			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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

Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Respiratory, thoracic and mediastinal disorders			
Pharyngeal Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory Distress			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (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
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Campylobacter Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter Bacteraemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Enterocolitis Infectious			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Mucormycosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Pseudomonas Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Respiratory Syncytial Virus Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (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
Sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (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	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2: T-Cell ALL (1-17 Years)		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 24 (66.67%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood Lactic Acid Increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonas Test Positive			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcus Test Positive			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Weight Decreased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Depressed Level of Consciousness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukoencephalopathy			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Posterior Reversible Encephalopathy			

Syndrome			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral Nerve Palsy			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences causally related to treatment / all	6 / 9		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Mucosal Inflammation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General Physical Health Deterioration			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences causally related to treatment / all	2 / 9		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal Fistula			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Proctalgia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hyperbilirubinaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pharyngeal Inflammation			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Distress			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic Disorder			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis Bacterial			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Campylobacter Infection			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Candida Infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter Bacteraemia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis Infectious				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucormycosis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas Infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Syncytial Virus Infection				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Staphylococcal Infection				

subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1: B-Cell ALL (1-17 Years)	Cohort 2: T-Cell LL (1-30 Years)	Cohort 2: T-Cell ALL (18-30 Years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	10 / 10 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	4 / 10 (40.00%)	1 / 5 (20.00%)
occurrences (all)	2	5	1
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Superficial Vein Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	4	2
Thrombophlebitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Catheter Site Haematoma			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	3 / 5 (60.00%)
occurrences (all)	0	1	3
Face Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injection Site Bruising			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Generalised Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Localised Oedema			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	4 / 7 (57.14%)	7 / 10 (70.00%)	3 / 5 (60.00%)
occurrences (all)	10	12	12
Oedema Peripheral			
subjects affected / exposed	0 / 7 (0.00%)	3 / 10 (30.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular Device Occlusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 10 (30.00%) 3	0 / 5 (0.00%) 0
Social circumstances Menopause subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all) Pelvic Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	0 / 5 (0.00%) 0 1 / 5 (20.00%) 1
Respiratory, thoracic and mediastinal disorders Allergic Cough subjects affected / exposed occurrences (all) Atelectasis subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Choking subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 3 / 7 (42.86%) 4 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 3 / 10 (30.00%) 3 5 / 10 (50.00%) 5 1 / 10 (10.00%) 1 2 / 10 (20.00%) 2	0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 2 / 5 (40.00%) 2 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1

Nasal Mucosal Disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nasal Congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hypoxia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 10 (0.00%)	3 / 5 (60.00%)
occurrences (all)	2	0	4
Oropharyngeal Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Pleural Effusion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	2
Pharyngeal Enanthema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pleuritic Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pulmonary Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Rhinitis Allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sneezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
Product issues			
Device Occlusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 7 (42.86%)	5 / 10 (50.00%)	3 / 5 (60.00%)
occurrences (all)	6	23	8
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	4 / 5 (80.00%)
occurrences (all)	0	0	8
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 7 (28.57%)	5 / 10 (50.00%)	3 / 5 (60.00%)
occurrences (all)	2	11	7
Antithrombin Iii Decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ammonia Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT Prolonged			

subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 7 (14.29%)	4 / 10 (40.00%)	1 / 5 (20.00%)
occurrences (all)	1	15	1
Blood Fibrinogen Decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Interleukin Level Increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
International Normalised Ratio Increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Lipase Increased			
subjects affected / exposed	0 / 7 (0.00%)	4 / 10 (40.00%)	2 / 5 (40.00%)
occurrences (all)	0	14	4
Urine Output Decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Weight Decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	2 / 5 (40.00%)
occurrences (all)	1	3	3
Weight Increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Wound Complication			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Wound			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Sinus Bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Sinus Tachycardia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	4	1	1
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Nervous system disorders			
Depressed Level of Consciousness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Facial Paralysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Encephalopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 7 (28.57%)	4 / 10 (40.00%)	2 / 5 (40.00%)
occurrences (all)	2	4	2
Peripheral Motor Neuropathy			

subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 10 (40.00%)	2 / 5 (40.00%)
occurrences (all)	2	4	4
Anaemia			
subjects affected / exposed	4 / 7 (57.14%)	10 / 10 (100.00%)	2 / 5 (40.00%)
occurrences (all)	13	49	5
Hypocoagulable State			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Lymph Node Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	3 / 7 (42.86%)	5 / 10 (50.00%)	1 / 5 (20.00%)
occurrences (all)	6	50	5
Lymphocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	1	2	1

Neutropenia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	6 / 10 (60.00%) 36	2 / 5 (40.00%) 6
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 10	9 / 10 (90.00%) 71	3 / 5 (60.00%) 11
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Eye disorders Eye Oedema subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Eye Pruritus subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Vision Blurred subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Visual Acuity Reduced subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3	4 / 10 (40.00%) 4	3 / 5 (60.00%) 3
Anal Fissure subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Anal Fistula subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Anal Inflammation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 10 (30.00%)	1 / 5 (20.00%)
occurrences (all)	2	4	1
Constipation			
subjects affected / exposed	2 / 7 (28.57%)	2 / 10 (20.00%)	4 / 5 (80.00%)
occurrences (all)	2	2	6
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gingival Bleeding			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	4 / 10 (40.00%)	2 / 5 (40.00%)
occurrences (all)	0	5	2
Lip Dry			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	5 / 10 (50.00%)	2 / 5 (40.00%)
occurrences (all)	3	10	3
Tongue Coated			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	7 / 10 (70.00%)	2 / 5 (40.00%)
occurrences (all)	0	12	4
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 10 (40.00%)	4 / 5 (80.00%)
occurrences (all)	0	14	9
Hepatomegaly			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Hepatic Cytolysis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	1 / 5 (20.00%) 1
Dermatitis Allergic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Petechiae subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 10 (10.00%) 1	2 / 5 (40.00%) 2
Rash Macular subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Rash Erythematous subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 10 (20.00%) 3	0 / 5 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 10 (20.00%) 5	2 / 5 (40.00%) 2
Rash Maculo-Papular subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Rash Papular			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Skin Striae subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Skin Ulcer subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Renal and urinary disorders Acute Kidney Injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 2	1 / 5 (20.00%) 1
Urinary Retention subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Renal Tubular Disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Renal Impairment subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 3	0 / 5 (0.00%) 0
Endocrine disorders Adrenal Insufficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	1 / 5 (20.00%) 1
Musculoskeletal and connective tissue disorders Bone Pain subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Back Pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 10 (30.00%) 3	1 / 5 (20.00%) 1
Arthralgia			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	2 / 10 (20.00%) 3	1 / 5 (20.00%) 4
Flank Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Muscular Weakness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	2 / 5 (40.00%) 2
Myalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Pain in Extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	1 / 5 (20.00%) 1
Pain in Jaw subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Spinal Pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Infections and infestations Clostridium Difficile Colitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 10 (0.00%) 0	0 / 5 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Clostridium Difficile Infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0

Device Related Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Herpes Simplex			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Kidney Infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oral Candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Otitis Externa			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Periorbital Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Splenic Infection Fungal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Vaginal Infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Metabolism and nutrition disorders			
Alkalosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Decreased Appetite subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 10 (10.00%) 1	2 / 5 (40.00%) 2
Dehydration subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	2 / 5 (40.00%) 2
Hyperammonaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 10 (0.00%) 0	1 / 5 (20.00%) 1
Fluid Retention subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	2 / 10 (20.00%) 3	0 / 5 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	1 / 5 (20.00%) 1
Hyperferritinaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 1	0 / 5 (0.00%) 0
Hyperamylasaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 10 (20.00%) 6	1 / 5 (20.00%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 10 (10.00%) 6	1 / 5 (20.00%) 1
Hypermagnesaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypervolaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	5 / 10 (50.00%)	3 / 5 (60.00%)
occurrences (all)	0	24	4
Hypocalcaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	2 / 5 (40.00%)
occurrences (all)	1	5	4
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 10 (30.00%)	1 / 5 (20.00%)
occurrences (all)	1	22	5
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	4 / 5 (80.00%)
occurrences (all)	0	2	5
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Tumour Lysis Syndrome			

subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Malnutrition			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	1 / 5 (20.00%)
occurrences (all)	1	7	4
Vitamin D Deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 2: T-Cell ALL (1-17 Years)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Flushing			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Superficial Vein Thrombosis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Thrombophlebitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Catheter Site Haematoma			

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Face Oedema			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	4		
Injection Site Bruising			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Generalised Oedema			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Localised Oedema			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	13 / 24 (54.17%)		
occurrences (all)	26		
Oedema Peripheral			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Vascular Device Occlusion			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		

Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2		
Social circumstances Menopause subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all) Pelvic Pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0 0 / 24 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Allergic Cough subjects affected / exposed occurrences (all) Atelectasis subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Choking subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 7 / 24 (29.17%) 10 0 / 24 (0.00%) 0 6 / 24 (25.00%) 6		

Nasal Mucosal Disorder			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Nasal Congestion			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Oropharyngeal Pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pleural Effusion			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pharyngeal Enanthema			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pleuritic Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pulmonary Oedema			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Rhinitis Allergic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sneezing			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Product issues			
Device Occlusion			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Alanine Aminotransferase Increased			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	41		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	21		
Antithrombin Iii Decreased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Ammonia Increased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Electrocardiogram QT Prolonged			

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	15		
Blood Fibrinogen Decreased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	10		
Interleukin Level Increased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
International Normalised Ratio Increased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Lipase Increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Urine Output Decreased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Weight Decreased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Weight Increased			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Wound Complication			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Wound			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Sinus Bradycardia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Sinus Tachycardia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Tachycardia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Nervous system disorders			
Depressed Level of Consciousness			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Facial Paralysis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Encephalopathy			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Dysarthria			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	18		
Peripheral Motor Neuropathy			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Peripheral Sensory Neuropathy			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Somnolence			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	12		
Anaemia			
subjects affected / exposed	16 / 24 (66.67%)		
occurrences (all)	109		
Hypocoagulable State			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Lymph Node Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	46		
Lymphocytosis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	12		

Neutropenia subjects affected / exposed occurrences (all)	15 / 24 (62.50%) 86		
Thrombocytopenia subjects affected / exposed occurrences (all)	18 / 24 (75.00%) 111		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Eye disorders Eye Oedema subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Eye Pruritus subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Vision Blurred subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Visual Acuity Reduced subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4		
Abdominal Pain subjects affected / exposed occurrences (all)	12 / 24 (50.00%) 37		
Anal Fissure subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Anal Fistula subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Anal Inflammation			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Colitis			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	6		
Dysphagia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gingival Bleeding			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Haematochezia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Haemorrhoids			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	11 / 24 (45.83%)		
occurrences (all)	17		
Lip Dry			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Odynophagia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pancreatitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Oesophagitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Proctalgia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	14 / 24 (58.33%)		
occurrences (all)	28		
Tongue Coated			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	18		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	17		
Hepatomegaly			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		

Hepatic Cytolysis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Dermatitis Allergic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rash Macular			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Rash Erythematous			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Rash Maculo-Papular			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Rash Papular			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin Striae</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin Ulcer</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 24 (0.00%)</p> <p>0</p> <p>0 / 24 (0.00%)</p> <p>0</p> <p>0 / 24 (0.00%)</p> <p>0</p> <p>4 / 24 (16.67%)</p> <p>5</p>		
<p>Renal and urinary disorders</p> <p>Acute Kidney Injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary Retention</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal Tubular Disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal Impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 24 (0.00%)</p> <p>0</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>1 / 24 (4.17%)</p> <p>1</p> <p>0 / 24 (0.00%)</p> <p>0</p>		
<p>Endocrine disorders</p> <p>Adrenal Insufficiency</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 24 (0.00%)</p> <p>0</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Bone Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p>	<p>2 / 24 (8.33%)</p> <p>3</p> <p>2 / 24 (8.33%)</p> <p>2</p>		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Flank Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Muscular Weakness			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Pain in Extremity			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Pain in Jaw			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Spinal Pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Clostridium Difficile Infection			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		

Device Related Infection			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Herpes Simplex			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Kidney Infection			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Oral Candidiasis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Otitis Externa			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Periorbital Cellulitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Splenic Infection Fungal			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		

Vaginal Infection subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Metabolism and nutrition disorders			
Alkalosis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Decreased Appetite subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4		
Dehydration subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Hyperammonaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Fluid Retention subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 10		
Hyperferritinaemia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Hyperamylasaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Hypermagnesaemia			

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Hyperuricaemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypervolaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	34		
Hypocalcaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	9		
Hypoglycaemia			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	24		
Hyponatraemia			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	7		
Hypomagnesaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Tumour Lysis Syndrome			

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Malnutrition			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	6		
Vitamin D Deficiency			
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2018	The purpose of this amendment was to include clarifications for the procedures to be conducted during the follow-up period and the addition of the collection of relevant information from subjects who proceeded to post-treatment, off-study bone marrow transplantation.
04 September 2018	The purpose of this amendment was to incorporate changes from country-specific amendments and to provide additional details and clarifications regarding study procedures.
22 January 2019	The purpose of this amendment was to include changes based on the identification of a new important risk (that is, hepatitis B virus [HBV] reactivation): the text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported