



Clinical trial results:

A Phase 1b/2 Study of Blinatumomab in Japanese Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Summary

EudraCT number	2017-003778-15
Trial protocol	Outside EU/EEA
Global end of trial date	04 July 2019

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	20130265
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02412306
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 July 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Phase 1b part: to determine the maximum tolerated dose (MTD) of blinatumomab in adult and pediatric subjects with R/R B precursor ALL
- Phase 2 part: to further evaluate in adults the recommended dose identified in the phase 1b portion of the study and to evaluate the rate of complete remission/complete remission with partial hematological recovery (CR/CRh*) in adult subjects with R/R B precursor ALL who receive blinatumomab
- Expansion part: to observe the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in adult and pediatric subjects with R/R B precursor ALL

Protection of trial subjects:

The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an institutional review board (IRB) at each center. This study was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 66
Worldwide total number of subjects	66
EEA total number of subjects	0

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)	1

Children (2-11 years)	17
Adolescents (12-17 years)	8
Adults (18-64 years)	37
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 16 centers in Japan. Cohort enrollment periods were: adult phase 1b, from 04 Jun 2015 to 13 Jan 2016; pediatric phase 1b, from 17 Feb 2016 to 20 Jun 2016; adult phase 2, from 11 Apr 2016 to 12 Jun 2017; adult expansion cohort, from 04 Dec 2017 to 13 Nov 2018; pediatric expansion cohort, from 05 Nov 2017 to 05 Sep 2018.

Pre-assignment

Screening details:

After a 2-week screening and pre-phase period, participants were treated in an open-label phase 1b part (adult or pediatric), a phase 2 part (adult), or in an expansion cohort (adult or pediatric).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Blinatumomab 9/28 µg/day (Adults)

Arm description:

Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from week 2 and all cycles thereafter.

Arm type	Experimental
Investigational medicinal product name	blinatumomab
Investigational medicinal product code	
Other name	Blincyto®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

Arm title	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)
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Arm description:

Participants received blinatumomab by CIV over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m²/day for the first week of cycle 1, escalated to 15 µg/m²/day starting from week 2 and all cycles thereafter.

Arm type	Experimental
Investigational medicinal product name	blinatumomab
Investigational medicinal product code	
Other name	Blincyto®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

Arm title	Phase 2: Blinatumomab 9/28 µg/day (Adults)
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Arm description:

Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.

Arm type	Experimental
Investigational medicinal product name	blinatumomab
Investigational medicinal product code	
Other name	Blincyto®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

Arm title	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)
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Arm description:

Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.

Arm type	Experimental
Investigational medicinal product name	blinatumomab
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Other name	Blincyto®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

Arm title	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day (Pediatric)
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Arm description:

Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m²/day for the first week of cycle 1, escalated to 15 µg/m²/day starting from week 2 and all cycles thereafter.

Arm type	Experimental
Investigational medicinal product name	blinatumomab
Investigational medicinal product code	
Other name	Blincyto®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered per protocol for a maximum of 5 treatment cycles, or until documented disease progression, intolerable adverse event, or withdrawal of consent.

Number of subjects in period 1	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)
Started	5	9	21
Completed	0	1	5
Not completed	5	8	16
Adverse event, serious fatal	5	7	15
Consent withdrawn by subject	-	-	1
Lost to follow-up	-	1	-

Number of subjects in period 1	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day (Pediatric)
Started	14	17
Completed	14	15
Not completed	0	2
Adverse event, serious fatal	-	2
Consent withdrawn by subject	-	-
Lost to follow-up	-	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b: Blinatumomab 9/28 µg/day (Adults)
Reporting group description:	
Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from week 2 and all cycles thereafter.	
Reporting group title	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)
Reporting group description:	
Participants received blinatumomab by CIV over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	
Reporting group title	Phase 2: Blinatumomab 9/28 µg/day (Adults)
Reporting group description:	
Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.	
Reporting group title	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)
Reporting group description:	
Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.	
Reporting group title	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day (Pediatric)
Reporting group description:	
Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	

Reporting group values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)
Number of subjects	5	9	21
Age, Customized			
Units: Subjects			
< 2 years	0	0	0
2 to 6 years	0	0	0
7 to 17 years	0	9	0
18 to 34 years	1	0	6
35 to 54 years	1	0	14
55 to 64 years	2	0	1
≥ 65 years	1	0	0
Sex: Female, Male			
Units: Subjects			
Female	4	5	12
Male	1	4	9
Race/Ethnicity, Customized			
Units: Subjects			
Japanese	5	9	21

Reporting group values	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day	Total
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		(Pediatric)	
Number of subjects	14	17	66
Age, Customized			
Units: Subjects			
< 2 years	0	1	1
2 to 6 years	0	5	5
7 to 17 years	0	11	20
18 to 34 years	5	0	12
35 to 54 years	6	0	21
55 to 64 years	1	0	4
≥ 65 years	2	0	3
Sex: Female, Male			
Units: Subjects			
Female	9	8	38
Male	5	9	28
Race/Ethnicity, Customized			
Units: Subjects			
Japanese	14	17	66

End points

End points reporting groups

Reporting group title	Phase 1b: Blinatumomab 9/28 µg/day (Adults)
Reporting group description: Participants received blinatumomab by continuous intravenous (CIV) infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from week 2 and all cycles thereafter.	
Reporting group title	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)
Reporting group description: Participants received blinatumomab by CIV over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	
Reporting group title	Phase 2: Blinatumomab 9/28 µg/day (Adults)
Reporting group description: Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.	
Reporting group title	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)
Reporting group description: Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from Week 2 and all cycles thereafter.	
Reporting group title	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day (Pediatric)
Reporting group description: Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	
Subject analysis set title	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received blinatumomab by CIV infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from week 2 and all cycles thereafter.	
Subject analysis set title	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received blinatumomab by CIV over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	
Subject analysis set title	Blinatumomab 9/28 µg/day (Phase 1b Only Adults)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received blinatumomab by CIV infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 9 µg/day for the first week of cycle 1, escalated to 28 µg/day starting from week 2 and all cycles thereafter.	
Subject analysis set title	Blinatumomab 5/15 µg/m ² /day (Phase 1b Only Pediatric)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received blinatumomab by CIV over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m ² /day for the first week of cycle 1, escalated to 15 µg/m ² /day starting from week 2 and all cycles thereafter.	

Primary: Phase 1b: Number of Participants with Dose-limiting Toxicities

End point title	Phase 1b: Number of Participants with Dose-limiting
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End point description:

Dose-limiting toxicities (DLTs) were defined as any Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade ≥ 3 adverse event related to blinatumomab, excluding specific CTCAE grade ≥ 3 adverse events considered consistent with the current known safety profile of blinatumomab, CTCAE grade ≥ 3 fever or infection, and laboratory parameters of CTCAE grade ≥ 3 not considered clinically relevant and/or responding to routine medical management.

Analysis Population Description: Phase 1b participants in who received any infusion of blinatumomab.

End point type	Primary
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End point timeframe:

Days 1 to 14

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: Percentages are presented in the data table per protocol.

[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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	9		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment

End point title	Phase 2: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment ^{[3][4]}
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End point description:

Hematological assessments were performed from bone marrow biopsy samples. All hematological assessments of bone marrow were reviewed in a central reference laboratory. Hematological remissions were defined by the following criteria: - Complete Remission (CR) is defined as $\leq 5\%$ blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets $> 100,000/\mu\text{l}$ and absolute neutrophil count (ANC) $> 1,000/\mu\text{l}$. - Complete Remission With Partial Hematological Recovery (CRh*) is defined as $\leq 5\%$ blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts: platelets $> 50,000/\mu\text{l}$ and ANC $> 500/\mu\text{l}$.

Analysis Population Description: Phase 2 participants who received any infusion of blinatumomab.

End point type	Primary
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End point timeframe:

Within the first 2 cycles of treatment, 12 weeks

Notes:

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

Justification: Percentages are presented in the data table per protocol.

[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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 2: Blinatumomab 9/28 µg/day (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	38.1 (18.1 to 61.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Expansion Cohort: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point title	Expansion Cohort: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs ^[5]
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End point description:

TEAEs are defined as those that start between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the treatment period. The severity of adverse events was assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as follows: Grade 1 – Mild AE; Grade 2 – Moderate AE; Grade 3 – Severe AE; Grade 4 – Life-threatening or disabling AE; Grade 5 – Death. The investigator used medical judgment to determine if there was a causal relationship (ie, related, unrelated) between an adverse event and blinatumomab.

Analysis Population Description: Expansion Cohort participants in the who received any infusion of blinatumomab.

End point type	Primary
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End point timeframe:

From the start of the first infusion to 30 days after the end of the last infusion; median (min, max) treatment duration was 55.6 (25, 140) and 28.0 (8, 56) days in the adult and pediatric expansion cohorts, respectively.

Notes:

[5] - 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: Descriptive statistics are presented in the data table per protocol.

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: participants				

All TEAEs	14	17		
TEAEs ≥ Grade 3	11	15		
TEAEs ≥ Grade 4	7	7		
Serious TEAEs (STEAEs)	2	3		
TEAEs Leading to Interruption of Blinatumomab	2	2		
STEAEs Leading to Interruption of Blinatumomab	0	0		
TEAEs Leading to Blinatumomab Discontinuation	0	1		
STEAEs Leading to Blinatumomab Discontinuation	0	0		
Fatal TEAEs	0	2		
All Treatment-Related (TR) TEAEs	14	14		
TR TEAEs ≥ Grade 3	9	9		
TR TEAEs ≥ Grade 4	5	5		
TR STEAEs	0	0		
TR TEAEs Leading to Blinatumomab Interruption	2	1		
TR STEAEs Leading to Blinatumomab Interruption	0	0		
TR TEAEs Leading to Blinatumomab Discontinuation	0	1		
TR STEAEs Leading to Blinatumomab Discontinuation	0	0		
TR Fatal TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b Adults: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment

End point title	Phase 1b Adults: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment ^[6]
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End point description:

Hematological assessments were performed from bone marrow biopsy samples. All hematological assessments of bone marrow were reviewed in a central reference laboratory. Hematological remissions were defined by the following criteria: - Complete Remission (CR) is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/μl and absolute neutrophil count (ANC) > 1,000/μl. - Complete Remission With Partial Hematological Recovery (CRh*) is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/μl and ANC > 500/μl.

Analysis Population Description: Phase 1b adult participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Within the first 2 cycles of treatment, 12 weeks

Notes:

[6] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of participants				
number (confidence interval 95%)	80.0 (28.4 to 99.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b Pediatric: Percentage of Participants with M1 Remission Within 2 Cycles of Treatment

End point title	Phase 1b Pediatric: Percentage of Participants with M1 Remission Within 2 Cycles of Treatment ^[7]
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End point description:

M1 remission for pediatric participants was defined as ≤ 5% blasts (M1 bone marrow) in the bone marrow and no evidence of disease.

Analysis Population Description: Phase 1b pediatric participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

The first 2 cycles of treatment, 12 weeks

Notes:

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

Justification: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of participants				
number (confidence interval 95%)	55.6 (21.2 to 86.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Duration of Response

End point title	Phase 1b and Phase 2: Duration of Response ^[8]
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End point description:

Duration of response was calculated from the date of bone marrow aspiration when response (CR/CRh*) was detected for the first time during the first 2 cycles of treatment until the earlier of the following events:

- the date of bone marrow aspiration at which hematological relapse or progressive disease (PD) was first detected,
- the date of diagnosis on which the hematological or extra medullary relapse was documented,
- the date of death if patient died due to PD
- the date of end of induction phase if primary reason for treatment termination was hematological or extramedullary relapse.

For a responder who did not report an event and was alive during the study, the end date of duration (censoring) was based on the date of the last available bone marrow aspiration prior to the data cutoff date for the analysis. Participants with response who did not report an event and who died due to reasons other than PD, were censored on the date of death, with death treated as a competing risk.

End point type	Secondary
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End point timeframe:

Median (minimum [min], maximum [max]) follow-up time was 6.3 (2.4, 13.6) months for Phase 1b and 26.7 (3.0, 28.5) months for Phase 2.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4 ^[9]	5 ^[10]	8 ^[11]	
Units: months				
median (confidence interval 95%)	13.0 (4.2 to 19.7)	2.3 (1.1 to 6.8)	13.1 (3.5 to 20.7)	

Notes:

[9] - participants who received any infusion of blinatumomab and achieved CR/CRh* during the 1st 2 cycles

[10] - participants who received any infusion of blinatumomab and achieved CR/CRh* during the 1st 2 cycles

[11] - participants who received any infusion of blinatumomab and achieved CR/CRh* during the 1st 2 cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Relapse-free Survival

End point title	Phase 1b and Phase 2: Relapse-free Survival ^[12]
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End point description:

Relapse-free survival (RFS) was defined for participants who achieved a response (CR/CRh*) during the first 2 cycles of treatment. RFS was calculated from the date of bone marrow aspiration when response was detected for the first time to the date of bone marrow aspiration at which hematological relapse was first detected or the date of diagnosis on which the hematological or extra medullary relapse was documented or the date of death due to any cause, whichever was earlier. Participants who did not experience hematological relapse and did not die were censored on the date of the last available bone marrow aspiration prior to the data cutoff date for the analysis.

Analysis Population Description: Phase 1b and Phase 2 participants who received any infusion of blinatumomab and achieved CR/CRh* during the first 2 cycles of treatment.

End point type	Secondary
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End point timeframe:

Median (min, max) follow-up time was 6.3 (2.4, 13.6) months for Phase 1b and 26.7 (3.0, 28.5) months for Phase 2.

Notes:

[12] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	8	
Units: months				
median (confidence interval 95%)	11.4 (4.2 to 19.7)	2.3 (1.1 to 6.8)	13.1 (3.5 to 20.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Overall Survival

End point title	Phase 1b and Phase 2: Overall Survival ^[13]
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End point description:

Overall survival (OS) was calculated from the start date of blinatumomab infusion in the first treatment cycle. All deaths were counted as events on the date of death. Participants still alive were censored on the last documented visit date or the date of the last phone contact when the participant was last known to have been alive. For participants who withdrew their informed consent, only information until the date of withdrawal was used in the analysis.

Analysis Population Description: Phase 1b and Phase 2 participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Median (min, max) follow-up time was 6.3 (2.4, 13.6) months for Phase 1b and 26.7 (3.0, 28.5) months for Phase 2.

Notes:

[13] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	9 ^[14]	21	
Units: months				
median (confidence interval 95%)	11.0 (9.3 to 20.7)	10.6 (0.9 to 99999)	14.8 (2.7 to 21.6)	

Notes:

[14] - 99999=not applicable (could not be estimated due to the low number of events)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Best Overall Response Within 2 Cycles of Treatment

End point title	Phase 2: Best Overall Response Within 2 Cycles of
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End point description:

Best response was defined as one of the following:

CR: $\leq 5\%$ blasts in the bone marrow (BM); No evidence of disease; Full recovery of peripheral blood counts: Platelets $> 100,000/\mu\text{l}$, and absolute neutrophil count (ANC) $> 1,000/\mu\text{l}$

CRh*: $\leq 5\%$ blasts in BM; No evidence of disease; Partial recovery of peripheral blood counts: Platelets $> 50,000/\mu\text{l}$, and ANC $> 500/\mu\text{l}$

CRi: CR with incomplete count recovery without CRh*

Blast free hypoplastic or aplastic BM: $\leq 5\%$ blasts in BM; No evidence of disease; Insufficient recovery of peripheral blood counts: platelets $\leq 50,000/\mu\text{l}$ and/or ANC $\leq 500/\mu\text{l}$

Partial Remission: BM blasts > 5 to $< 25\%$ with at least a 50% reduction from baseline

Hematological Relapse: $> 5\%$ blasts in BM or blasts in peripheral blood after documented CR/CRh* during the study

PD: An increase from baseline of $\geq 25\%$ of BM blasts or an absolute increase of $\geq 5,000$ cells/ μL in the number of circulating leukemia cells.

End point type	Secondary
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End point timeframe:

Within the first 2 cycles of treatment, 12 weeks

Notes:

[15] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 2: Blinatumomab 9/28 $\mu\text{g/day}$ (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	21 ^[16]			
Units: participants				
CR	5			
CRh*	3			
CRi	0			
Blast-free hypoplastic or aplastic bone marrow	6			
Partial remission	0			
Hematological relapse	0			
Progressive disease	2			
No response (none of the above)	5			

Notes:

[16] - participants who received any infusion of blinatumomab.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) During Blinatumomab Induced Remission

End point title	Phase 2: Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) During Blinatumomab Induced Remission ^[17]
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End point description:

Participants who were eligible for allogeneic HSCT were those who achieved remission (complete response or complete response with partial recovery of peripheral blood counts) after 2 cycles of blinatumomab treatment, and no further anti-leukemic medication was given before HSCT.

Analysis Population Description: Phase 2 participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Median (min, max) follow-up time was 26.7 (3.0, 28.5) months.

Notes:

[17] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 2: Blinatumomab 9/28 µg/day (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	81.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: 100-Day Mortality After Allogeneic HSCT

End point title	Phase 2: 100-Day Mortality After Allogeneic HSCT ^[18]
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End point description:

The analysis of 100-day mortality after allogeneic HSCT was assessed for all participants who received an allogeneic HSCT while in any CR following treatment with blinatumomab. 100-day mortality after allogeneic HSCT was calculated relative to the date of allogeneic HSCT. Participants still alive were censored on the last documented visit date or the date of the last phone contact when the patient was last known to have been alive. The 100-day mortality rate after allogeneic HSCT was defined as the percentage of patients having died up to 100 days after allogeneic HSCT estimated using the estimated

time to death in percent calculated by Kaplan-Meier methods.

Analysis Population Description: Phase 2 participants who received an allogeneic HSCT.

End point type	Secondary
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End point timeframe:

100 days, from the date of allogeneic HSCT; median (min, max) follow-up time was 26.7 (3.0, 28.5)

Notes:

[18] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 2: Blinatumomab 9/28 µg/day (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (not applicable)	11.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Number of Participants with TEAEs

End point title	Phase 1b and Phase 2: Number of Participants with TEAEs ^[19]
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End point description:

TEAEs are defined as those that start between the start of the first infusion of blinatumomab and 30 days after the end of the last infusion during the treatment period. The severity of adverse events was assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as follows: Grade 1 – Mild AE; Grade 2 – Moderate AE; Grade 3 – Severe AE; Grade 4 – Life-threatening or disabling AE; Grade 5 – Death. The investigator used medical judgment to determine if there was a causal relationship (ie, related, unrelated) between an adverse event and blinatumomab.

Analysis Population Description: Phase 1b and Phase 2 participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

From the start of the first infusion to 30 days after the end of the last infusion; median (min, max) treatment duration was 108 (56, 140), 56.0 (5, 84), and 56.0 (11, 115) days in adult phase 1b, adult phase 2 and pediatric phase 1b cohort respectively.

Notes:

[19] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	9	21	
Units: participants				
All TEAEs	5	9	21	
TEAEs ≥ Grade 3	4	9	21	
TEAEs ≥ Grade 4	2	7	14	
Serious TEAEs (STEAEs)	0	1	7	
TEAEs Leading to Blinatumomab Interruption	1	6	3	
STEAEs Leading to Blinatumomab Interruption	0	0	0	
TEAEs Leading to Blinatumomab Discontinuation	0	1	1	
STEAEs Leading to Blinatumomab Discontinuation	0	0	1	
Fatal TEAEs	0	1	1	
All Treatment-Related (TR) TEAEs	5	8	21	
TR TEAEs ≥ Grade 3	2	8	18	
TR TEAEs ≥ Grade 4	1	5	11	
TR STEAEs	0	0	4	
TR TEAEs Leading to Blinatumomab Interruption	1	6	1	
TR STEAEs Leading to Blinatumomab Interruption	0	0	0	
TR TEAEs Leading to Blinatumomab Discontinuation	0	1	1	
TR STEAEs Leading to Blinatumomab Discontinuation	0	0	1	
TR Fatal TEAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Serum Blinatumomab Concentration at Steady State

End point title	Phase 1b and Phase 2: Serum Blinatumomab Concentration at Steady State
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End point description:

The steady-state concentration (C_{ss}) of serum blinatumomab was summarized as the average of the observed concentrations collected after 5 half-lives or after 24 hours from the start of continuous IV (CIV) infusion. Cycle 1, day 2 values represent steady-state concentration after CIV with the initial dose of blinatumomab (9 µg/day for adults and 5 µg/m²/day for pediatric patients). All other time points were measured after the dose step to 28 µg/day (adults) / 15 µg/m²/day (pediatric participants).

Analysis Population Description: phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacokinetic sample collected with available data.

End point type	Secondary
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End point timeframe:

After 24 hours from the start of infusion: Cycle 1 (before dose step) day 2; Cycle 1 (after dose step) days 15 and 29; Cycle 2 onwards day 8 (pediatric and adult), days 15 and 29 (adult).

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)	Blinatumomab 9/28 µg/day (Phase 1b Only Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b Only Pediatric)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25 ^[20]	7 ^[21]	5 ^[22]	7 ^[23]
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 before dose step; n=23, 7, 4, 7	191 (± 90.8)	113 (± 65.0)	135 (± 41.7)	107 (± 42.7)
Cycle 1 after dose step; n=25, 7, 5, 7	948 (± 488)	361 (± 137)	907 (± 403)	361 (± 137)
Cycle 2; n=21, 6, 5, 6	1150 (± 575)	427 (± 66.0)	1040 (± 493)	427 (± 66.0)
Cycle 3+; n=8, 1, 4, 0	1420 (± 685)	780 (± 99999)	1280 (± 396)	999999 (± 999999)

Notes:

[20] - n=participants with available data at each time point.

[21] - n=participants with available data at each time point; 99999=not applicable (n=1)

[22] - n=participants with available data at each time point.

[23] - n=participants with available data at each time point; 999999=not applicable (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Systemic Clearance of Blinatumomab

End point title	Phase 1b and Phase 2: Systemic Clearance of Blinatumomab
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End point description:

Systemic clearance (CL) was calculated as $CL = R0/C_{ss}$, where R0 is the infusion rate (µg/hour or µg/m²/hour).

Analysis Population Description: phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacokinetic sample collected with available data.

End point type	Secondary
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End point timeframe:

After 24 hours from the start of infusion: Cycle 1 (before dose step) day 2; Cycle 1 (after dose step) days 15 and 29; Cycle 2 onwards day 8 (pediatric and adult), days 15 and 29 (adult).

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)	Blinatumomab 9/28 µg/day (Phase 1b Only Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b Only Pediatric)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	9	5	9
Units: liters/hour				
arithmetic mean (standard deviation)	1.59 (± 0.812)	1.88 (± 0.789)	1.59 (± 0.998)	1.83 (± 0.801)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Terminal Half-life of Blinatumomab

End point title	Phase 1b and Phase 2: Terminal Half-life of Blinatumomab
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End point description:

Analysis Population Description: phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacokinetic sample collected with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 day 1 predose, 2, 6 (adults), 10, 24 hours; day 8 (prior to dose step) 0 hour (adults); day 15 any time during infusion; day 29 prior to end of infusion, 1 (adults), 2, 4 (adults), 6 hours after end of infusion

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)	Blinatumomab 9/28 µg/day (Phase 1b Only Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b Only Pediatric)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	5	5	5
Units: hours				
arithmetic mean (standard deviation)	2.38 (± 1.36)	1.92 (± 1.12)	2.60 (± 2.03)	2.62 (± 1.67)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Volume of Distribution of Blinatumomab

End point title	Phase 1b and Phase 2: Volume of Distribution of Blinatumomab
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End point description:

Analysis Population Description: phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacokinetic sample collected with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 day 1 predose, 2, 6 (adults), 10, 24 hours; day 8 (prior to dose step) 0 hour (adults); day 15 any time during infusion; day 29 prior to end of infusion, 1 (adults), 2, 4 (adults), 6 hours after end of infusion

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)	Blinatumomab 9/28 µg/day (Phase 1b Only Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b Only Pediatric)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	5	5	5
Units: liters				
arithmetic mean (standard deviation)	6.02 (± 6.09)	5.05 (± 3.35)	8.22 (± 11.7)	6.38 (± 3.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Number of Participants who Developed Anti-blinatumomab Antibodies

End point title	Phase 1b and Phase 2: Number of Participants who Developed Anti-blinatumomab Antibodies ^[24]
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End point description:

Antibodies to blinatumomab were detected using an electrochemiluminescence (ECL)-based assay.

Analysis Population Description: Phase 1b and Phase 2 participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Day 1 before first dose; cycles 1 and 2 day 29, 6 hours after end of infusion; 30 days after last dose.

Notes:

[24] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Phase 1b: Blinatumomab 9/28 µg/day (Adults)	Phase 1b: Blinatumomab 5/15 µg/m ² /day (Pediatric)	Phase 2: Blinatumomab 9/28 µg/day (Adults)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	9	21	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Interleukin-2 Concentration

End point title	Phase 1b and Phase 2: Interleukin-2 Concentration
End point description:	
The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon gamma (IFN-γ) using multiplex cytometric bead assays. The lower limit of quantification (LLOQ) was 125 pg/mL and the limit of detection (LOD) was 20 pg/mL. For calculations of mean cytokine concentrations at every time point across all participants, samples with concentrations below LLOQ were included in the calculation as ½ LLOQ (= 62.5 pg/mL); samples with values below LOD were included as ½ LOD (= 10 pg/mL).	
Analysis Population Description: Phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected, with available data at each time point.	
End point type	Secondary
End point timeframe:	
Adults: cycle 1, day 1: 2, 6, 10, 24 hrs after infusion start; day 8: 2, 6, 10 hrs after dose step. Cycles 2-5, day 1: 6 hrs after infusion start. Pediatric: cycle 1, day 1: 6, 10, 24 hrs after infusion start; Cycles 2-5, day 1: 6 hrs after infusion start	

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[25]	9 ^[26]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 day 1, 2 hrs after infusion start; n=26,0	16.1 (± 17.1)	999999 (± 999999)		
Cycle 1 day 1, 6 hrs after infusion start; n=26,9	30.2 (± 72.8)	10.0 (± 0.0)		
Cycle 1 day 1, 10 hrs after infusion start; n=26,9	32.6 (± 85.0)	10.0 (± 0.0)		
Cycle 1 day 1, 24 hrs after infusion start; n=26,9	17.2 (± 36.7)	29.8 (± 55.9)		
Cycle 1 day 8, 2 hrs after infusion start; n=25,0	10.0 (± 0.0)	999999 (± 999999)		
Cycle 1 day 8, 6 hrs after infusion start; n=25,0	10.0 (± 0.0)	999999 (± 999999)		
Cycle 1 day 8, 10 hrs after infusion start; n=25,0	10.0 (± 0.0)	999999 (± 999999)		
Cycle 2 day 1, 6 hrs after infusion start; n=20,7	12.6 (± 11.7)	10.0 (± 0.0)		
Cycle 3 day 1, 6 hrs after infusion start; n=8,2	10.0 (± 0.0)	10.0 (± 0.0)		
Cycle 4 day 1, 6 hrs after infusion start; n=3,1	10.0 (± 0.0)	10.0 (± 99999)		
Cycle 5 day 1, 6 hrs after infusion start; n=2,1	10.0 (± 0.0)	10.0 (± 99999)		

Notes:

[25] - n=participants with an assessment at given time point

[26] - 999999=not applicable (n=1); 999999=not applicable (n=0)

Statistical analyses

Secondary: Phase 1b and Phase 2: Interleukin-6 Concentration

End point title	Phase 1b and Phase 2: Interleukin-6 Concentration
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End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)- α and interferon gamma (IFN- γ) using multiplex cytometric bead assays. The lower limit of quantification (LLOQ) was 125 pg/mL and the limit of detection (LOD) was 20 pg/mL. For calculations of mean cytokine concentrations at every time point across all participants, samples with concentrations below LLOQ were included in the calculation as $\frac{1}{2}$ LLOQ (= 62.5 pg/mL); samples with values below LOD were included as $\frac{1}{2}$ LOD (= 10 pg/mL).

Analysis Population Description: Phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected, with available data at each time point.

End point type	Secondary
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End point timeframe:

Adults: cycle 1, day 1: 2, 6, 10, 24 hrs after infusion start; day 8: 2, 6, 10 hrs after dose step. Cycles 2-5, day 1: 6 hrs after infusion start. Pediatric: cycle 1, day 1: 6, 10, 24 hrs after infusion start; Cycles 2-5, day 1: 6 hrs after infusion start

End point values	Blinatumomab 9/28 μ g/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 μ g/m ² /day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[27]	9 ^[28]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 day 1, 2 hrs after infusion start; n=26,0	29.1 (\pm 40.1)	999999 (\pm 999999)		
Cycle 1 day 1, 6 hrs after infusion start; n=26,9	173 (\pm 198.1)	275 (\pm 371)		
Cycle 1 day 1, 10 hrs after infusion start; n=26,9	186 (\pm 301.5)	317 (\pm 358)		
Cycle 1 day 1, 24 hrs after infusion start; n=26,9	246 (\pm 907.6)	3714 (\pm 10740)		
Cycle 1 day 8, 2 hrs after infusion start; n=25,0	14.2 (\pm 14.5)	999999 (\pm 999999)		
Cycle 1 day 8, 6 hrs after infusion start; n=25,0	10.0 (\pm 0.0)	999999 (\pm 999999)		
Cycle 1 day 8, 10 hrs after infusion start; n=25,0	10.0 (\pm 0.0)	999999 (\pm 999999)		
Cycle 2 day 1, 6 hrs after infusion start; n=20,7	20.3 (\pm 35.6)	17.5 (\pm 19.8)		
Cycle 3 day 1, 6 hrs after infusion start; n=8,2	16.6 (\pm 18.6)	36.3 (\pm 37.1)		
Cycle 4 day 1, 6 hrs after infusion start; n=3,1	10.0 (\pm 0.0)	62.5 (\pm 99999)		
Cycle 5 day 1, 6 hrs after infusion start; n=2,1	10.0 (\pm 0.0)	62.5 (\pm 99999)		

Notes:

[27] - n=participants with an assessment at given time point

[28] - 99999=not applicable (n=1); 999999=not applicable (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Interleukin-10 Concentration

End point title	Phase 1b and Phase 2: Interleukin-10 Concentration
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End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)- α and interferon gamma (IFN- γ) using multiplex cytometric bead assays. The lower limit of quantification (LLOQ) was 125 pg/mL and the limit of detection (LOD) was 20 pg/mL. For calculations of mean cytokine concentrations at every time point across all participants, samples with concentrations below LLOQ were included in the calculation as $\frac{1}{2}$ LLOQ (= 62.5 pg/mL); samples with values below LOD were included as $\frac{1}{2}$ LOD (= 10 pg/mL).

Analysis Population Description: Phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected, with available data at each time point.

End point type	Secondary
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End point timeframe:

Adults: cycle 1, day 1: 2, 6, 10, 24 hrs after infusion start; day 8: 2, 6, 10 hrs after dose step. Cycles 2-5, day 1: 6 hrs after infusion start. Pediatric: cycle 1, day 1: 6, 10, 24 hrs after infusion start; Cycles 2-5, day 1: 6 hrs after infusion start

End point values	Blinatumomab 9/28 μ g/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 μ g/m ² /day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[29]	9 ^[30]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 day 1, 2 hrs after infusion start; n=26,0	101 (\pm 81.1)	999999 (\pm 999999)		
Cycle 1 day 1, 6 hrs after infusion start; n=26, 9	597 (\pm 637)	153 (\pm 94.7)		
Cycle 1 day 1, 10 hrs after infusion start; n=26,9	423 (\pm 373)	230 (\pm 178)		
Cycle 1 day 1, 24 hrs after infusion start; n=26,9	400 (\pm 699)	641 (\pm 1168)		
Cycle 1 day 8, 2 hrs after infusion start; n=25,0	28.9 (\pm 25.7)	999999 (\pm 999999)		
Cycle 1 day 8, 6 hrs after infusion start; n=25,0	33.1 (\pm 26.6)	999999 (\pm 999999)		
Cycle 1 day 8, 10 hrs after infusion start; n=25,0	33.1 (\pm 26.6)	999999 (\pm 999999)		

Cycle 2 day 1, 6 hrs after infusion start; n=20,7	220 (± 357)	142 (± 173)		
Cycle 3 day 1, 6 hrs after infusion start; n=8,2	121 (± 146)	62.5 (± 0.0)		
Cycle 4 day 1, 6 hrs after infusion start; n=3,1	88.2 (± 93.7)	62.5 (± 99999)		
Cycle 5 day 1, 6 hrs after infusion start; n=2,1	36.3 (± 37.1)	62.5 (± 99999)		

Notes:

[29] - n=participants with an assessment at given time point

[30] - 99999=not applicable (n=1); 999999=not applicable (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Tumor Necrosis Factor-Alpha (TNFα) Concentration

End point title	Phase 1b and Phase 2: Tumor Necrosis Factor-Alpha (TNFα) Concentration
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End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon gamma (IFN-γ) using multiplex cytometric bead assays. The lower limit of quantification (LLOQ) was 125 pg/mL and the limit of detection (LOD) was 20 pg/mL. For calculations of mean cytokine concentrations at every time point across all participants, samples with concentrations below LLOQ were included in the calculation as ½ LLOQ (= 62.5 pg/mL); samples with values below LOD were included as ½ LOD (= 10 pg/mL).

Analysis Population Description: Phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected, with available data at each time point.

End point type	Secondary
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End point timeframe:

Adults: cycle 1, day 1: 2, 6, 10, 24 hrs after infusion start; day 8: 2, 6, 10 hrs after dose step. Cycles 2-5, day 1: 6 hrs after infusion start. Pediatric: cycle 1, day 1: 6, 10, 24 hrs after infusion start; Cycles 2-5, day 1: 6 hrs after infusion start

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m²/day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[31]	9 ^[32]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 day 1, 2 hrs after infusion start; n=26,0	37.3 (± 61.8)	999999 (± 999999)		
Cycle 1 day 1, 6 hrs after infusion start; n=26,9	24.1 (± 23.7)	15.8 (± 17.5)		
Cycle 1 day 1, 10 hrs after infusion start; n=26,9	20.1 (± 21.1)	15.8 (± 17.5)		
Cycle 1 day 1, 24 hrs after infusion start; n=26,9	10.0 (± 0.0)	15.8 (± 17.5)		

Cycle 1 day 8, 2 hrs after infusion start; n=25,0	16.6 (± 32.8)	999999 (± 999999)		
Cycle 1 day 8, 6 hrs after infusion start; n=25,0	10.0 (± 0.0)	999999 (± 999999)		
Cycle 1 day 8, 10 hrs after infusion start; n=25,0	10.0 (± 0.0)	999999 (± 999999)		
Cycle 2 day 1, 6 hrs after infusion start; n=20,7	12.6 (± 11.7)	17.5 (± 19.8)		
Cycle 3 day 1, 6 hrs after infusion start; n=8,2	16.6 (± 18.6)	10.0 (± 0.0)		
Cycle 4 day 1, 6 hrs after infusion start; n=3,1	10.0 (± 0.0)	10.0 (± 99999)		
Cycle 5 day 1, 6 hrs after infusion start; n=2,1	10.0 (± 0.0)	10.0 (± 99999)		

Notes:

[31] - n= participants with an assessment at given time point

[32] - 999999=not applicable (n=1); 999999=not applicable (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Interferon Gamma (IFN-γ) Concentration

End point title	Phase 1b and Phase 2: Interferon Gamma (IFN-γ) Concentration
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End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)-α and interferon gamma (IFN-γ) using multiplex cytometric bead assays. The lower limit of quantification (LLOQ) was 125 pg/mL and the limit of detection (LOD) was 20 pg/mL. For calculations of mean cytokine concentrations at every time point across all participants, samples with concentrations below LLOQ were included in the calculation as ½ LLOQ (= 62.5 pg/mL); samples with values below LOD were included as ½ LOD (= 10 pg/mL).

Analysis Population Description: Phase 1b and phase 2 participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected, with available data at each time point.

End point type	Secondary
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End point timeframe:

Adults: cycle 1, day 1: 2, 6, 10, 24 hrs after infusion start; day 8: 2, 6, 10 hrs after dose step. Cycles 2-5, day 1: 6 hrs after infusion start. Pediatric: cycle 1, day 1: 6, 10, 24 hrs after infusion start; Cycles 2-5, day 1: 6 hrs after infusion start

End point values	Blinatumomab 9/28 µg/day (Phase 1b and Phase 2 Adults)	Blinatumomab 5/15 µg/m ² /day (Phase 1b and Phase 2 Pediatric)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 ^[33]	9 ^[34]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 day 1, 2 hrs after infusion start; n=26,0	26.2 (± 24.7)	999999 (± 999999)		

Cycle 1 day 1, 6 hrs after infusion start; n=26,9	52.3 (± 56.2)	41.2 (± 42.8)		
Cycle 1 day 1, 10 hrs after infusion start; n=26,9	65.8 (± 71.6)	64.5 (± 107)		
Cycle 1 day 1, 24 hrs after infusion start; n=26,9	42.1 (± 51.8)	129 (± 176)		
Cycle 1 day 8, 2 hrs after infusion start; n=25,0	16.3 (± 17.4)	999999 (± 999999)		
Cycle 1 day 8, 6 hrs after infusion start; n=25,0	14.2 (± 14.5)	999999 (± 999999)		
Cycle 1 day 8, 10 hrs after infusion start; n=25,0	14.2 (± 14.5)	999999 (± 999999)		
Cycle 2 day 1, 6 hrs after infusion start; n=20,7	17.9 (± 19.2)	40.0 (± 28.1)		
Cycle 3 day 1, 6 hrs after infusion start; n=8,2	35.8 (± 55.0)	10.0 (± 0.0)		
Cycle 4 day 1, 6 hrs after infusion start; n=3,1	10.0 (± 0.0)	10.0 (± 99999)		
Cycle 5 day 1, 6 hrs after infusion start; n=2,1	10.0 (± 0.0)	10.0 (± 99999)		

Notes:

[33] - n=participants with an assessment at given time point

[34] - 99999=not applicable (n=1); 999999=not applicable (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Cohort Adult: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment

End point title	Expansion Cohort Adult: Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment ^[35]
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End point description:

Hematological assessments were performed from bone marrow biopsy samples. All hematological assessments of bone marrow were reviewed in a central reference laboratory. Hematological remissions were defined by the following criteria: - Complete Remission (CR) is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/μl and absolute neutrophil count (ANC) > 1,000/μl. - Complete Remission With Partial Hematological Recovery (CRh*) is defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/μl and ANC > 500/μl.

Analysis Population Description: Expansion Cohort adult participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Within the first 2 cycles of treatment, 12 weeks

Notes:

[35] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Expansion Cohort: Blinatumomab 9/28 µg/day (Adults)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of participants				
number (confidence interval 95%)	78.6 (49.2 to 95.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion Cohort Pediatric: Percentage of Participants with M1 Remission Within 2 Cycles of Treatment

End point title	Expansion Cohort Pediatric: Percentage of Participants with M1 Remission Within 2 Cycles of Treatment ^[36]
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End point description:

M1 remission for pediatric participants was defined as ≤ 5% blasts (M1 bone marrow) in the bone marrow and no evidence of disease.

Analysis Population Description: Expansion Cohort pediatric participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

Within the first 2 cycles of treatment, 12 weeks

Notes:

[36] - 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: Unique endpoints were planned for each Phase, per protocol.

End point values	Expansion Cohort: Blinatumomab 5/15 µg/m ² /day (Pediatric)			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (confidence interval 95%)	29.4 (10.3 to 56.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The median treatment duration for Blinatumomab is 108 days for Adult Phase 1b Cohort, 56 days for Pediatric Phase 1b Cohort, 56 days for Adult Phase 2 Cohort, 55.6 days for Adult Expansion Cohort and 28 days for Pediatric Expansion Cohort

Adverse event reporting additional description:

A Phase 1b/2 Study of Blinatumomab in Japanese Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (Horai Study)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Blinatumomab 9-28 ug/day Phase 1b Adult Population
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Reporting group description: -

Reporting group title	Blinatumomab 5-15 ug/m ² /day Phase 1b Pediatric Population
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Reporting group description: -

Reporting group title	Blinatumomab 9-28 ug/day Phase 2 Adult Population
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Reporting group description: -

Reporting group title	Blinatumomab 9-28 ug/day Adult Expansion Population
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Reporting group description: -

Reporting group title	Blinatumomab 5-15 ug/m ² /day Pediatric Expansion Population
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Reporting group description: -

Serious adverse events	Blinatumomab 9-28 ug/day Phase 1b Adult Population	Blinatumomab 5-15 ug/m ² /day Phase 1b Pediatric Population	Blinatumomab 9-28 ug/day Phase 2 Adult Population
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	7 / 21 (33.33%)
number of deaths (all causes)	5	7	15
number of deaths resulting from adverse events			
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (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	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (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
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (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
Infections and infestations			
Bacteraemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	Blinatumomab 9-28 ug/day Adult Expansion Population	Blinatumomab 5-15 ug/m ² /day Pediatric Expansion Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	3 / 17 (17.65%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			

subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Blinatumomab 9-28 ug/day Phase 1b Adult Population	Blinatumomab 5-15 ug/m ² /day Phase 1b Pediatric Population	Blinatumomab 9-28 ug/day Phase 2 Adult Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	9 / 9 (100.00%)	21 / 21 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Central nervous system leukaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Leukaemic infiltration extramedullary subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	4 / 9 (44.44%) 10	0 / 21 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	1 / 9 (11.11%) 1	1 / 21 (4.76%) 1
Hot flush subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	1 / 21 (4.76%) 1
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	2 / 21 (9.52%) 2
Fatigue subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 5	2 / 9 (22.22%) 3	0 / 21 (0.00%) 0
Localised oedema subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 9 (11.11%) 2	6 / 21 (28.57%) 8
Oedema subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 9 (22.22%) 8	0 / 21 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	7 / 9 (77.78%) 21	15 / 21 (71.43%) 21
Catheter site pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Infusion site extravasation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cytokine release syndrome			
subjects affected / exposed	4 / 5 (80.00%)	5 / 9 (55.56%)	8 / 21 (38.10%)
occurrences (all)	9	9	12
Hypogammaglobulinaemia			
subjects affected / exposed	2 / 5 (40.00%)	2 / 9 (22.22%)	2 / 21 (9.52%)
occurrences (all)	2	2	2
Engraftment syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Graft versus host disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Hypersensitivity subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Reproductive system and breast disorders			
Balanoposthitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Metrorrhagia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 2	0 / 21 (0.00%) 0
Pelvic pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	1 / 21 (4.76%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 9 (22.22%) 4	1 / 21 (4.76%) 1
Hiccups subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 9 (0.00%) 0	1 / 21 (4.76%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Hypoxia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Laryngeal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	5	0
Delirium			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	3 / 21 (14.29%)
occurrences (all)	0	2	3
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hallucination			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	3 / 9 (33.33%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	5 / 9 (55.56%)	4 / 21 (19.05%)
occurrences (all)	1	17	6
Amylase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	1 / 21 (4.76%)
occurrences (all)	0	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	4 / 9 (44.44%)	3 / 21 (14.29%)
occurrences (all)	1	9	3
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 9 (33.33%)	1 / 21 (4.76%)
occurrences (all)	0	4	2
Blood glucose decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood uric acid increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	4 / 9 (44.44%)	1 / 21 (4.76%)
occurrences (all)	0	7	1
Glucose urine present			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Immunoglobulins decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
International normalised ratio increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	1 / 21 (4.76%)
occurrences (all)	0	4	1
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	6	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	3 / 21 (14.29%)
occurrences (all)	13	0	3
Neutrophil count decreased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	5 / 21 (23.81%)
occurrences (all)	0	1	6
Oxygen saturation decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 9 (11.11%)	5 / 21 (23.81%)
occurrences (all)	4	1	8
Prothrombin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Serum ferritin increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 9 (22.22%)	1 / 21 (4.76%)
occurrences (all)	1	7	1
White blood cell count decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 9 (11.11%)	4 / 21 (19.05%)
occurrences (all)	11	1	5
Antithrombin III decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blast cell count increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Blood fibrinogen decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	1 / 21 (4.76%) 1
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	1 / 9 (11.11%) 2	0 / 21 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Cardiac disorders			
Cardiac failure subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	1 / 21 (4.76%) 1
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	2 / 21 (9.52%) 3
Arrhythmia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Ventricular tachycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Nervous system disorders			
Altered state of consciousness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Aphasia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Facial paralysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	3 / 5 (60.00%)	4 / 9 (44.44%)	6 / 21 (28.57%)
occurrences (all)	3	6	7
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Intention tremor			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	2 / 5 (40.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Movement disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Posterior reversible encephalopathy			

syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Wernicke's encephalopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	4 / 9 (44.44%)	7 / 21 (33.33%)
occurrences (all)	1	18	10
Bone marrow failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	7 / 21 (33.33%)
occurrences (all)	0	0	7
Febrile neutropenia			
subjects affected / exposed	2 / 5 (40.00%)	5 / 9 (55.56%)	10 / 21 (47.62%)
occurrences (all)	3	6	15
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 9 (44.44%)	3 / 21 (14.29%)
occurrences (all)	0	17	6
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 9 (44.44%)	2 / 21 (9.52%)
occurrences (all)	0	19	2
Neutropenia			
subjects affected / exposed	2 / 5 (40.00%)	5 / 9 (55.56%)	5 / 21 (23.81%)
occurrences (all)	13	12	8
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 9 (33.33%)	5 / 21 (23.81%)
occurrences (all)	0	7	8
Hypoglobulinaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pancytopenia			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Thrombotic microangiopathy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Eye disorders			
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	1 / 21 (4.76%) 1
Photophobia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Vitreous floaters subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Glaucoma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 3	0 / 21 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 9 (33.33%) 5	0 / 21 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Constipation			

subjects affected / exposed	1 / 5 (20.00%)	3 / 9 (33.33%)	0 / 21 (0.00%)
occurrences (all)	1	3	0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	3 / 9 (33.33%)	8 / 21 (38.10%)
occurrences (all)	0	6	9
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	2 / 9 (22.22%)	9 / 21 (42.86%)
occurrences (all)	4	3	12
Oral pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Proctitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 9 (22.22%)	7 / 21 (33.33%)
occurrences (all)	1	2	7
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	5 / 9 (55.56%)	3 / 21 (14.29%)
occurrences (all)	2	8	7
Dental caries			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			

subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Lip pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oral disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Salivary gland pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Liver disorder			
subjects affected / exposed	1 / 5 (20.00%)	1 / 9 (11.11%)	4 / 21 (19.05%)
occurrences (all)	1	1	6
Liver injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Drug-induced liver injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hepatic function abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Hepatic pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Asteatosis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	2 / 21 (9.52%) 2
Dry skin subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	3 / 21 (14.29%) 3
Erythema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	3 / 21 (14.29%) 3
Ingrowing nail subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 9 (22.22%) 2	3 / 21 (14.29%) 3
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Urticaria			

subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Dermatitis diaper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Renal disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cystitis noninfective			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Steroid withdrawal syndrome			

subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Myopathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pain in jaw			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Back pain			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	1 / 21 (4.76%) 1
Infections and infestations			
Bronchopulmonary aspergillosis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	2 / 21 (9.52%) 2
Cystitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Cytomegalovirus infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	2 / 21 (9.52%) 3
Device related infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Gingivitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Hepatitis B subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 9 (0.00%) 0	0 / 21 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0
Infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 9 (0.00%) 0	2 / 21 (9.52%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	2 / 21 (9.52%) 2
Otitis media subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 9 (11.11%) 1	0 / 21 (0.00%) 0

Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Staphylococcal sepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Sialoadenitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Skin candida			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	3 / 9 (33.33%)	3 / 21 (14.29%)
occurrences (all)	3	4	3
Fluid retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Hypercalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Hyperkalaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 5 (20.00%)	5 / 9 (55.56%)	2 / 21 (9.52%)
occurrences (all)	2	15	3
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	6 / 21 (28.57%)
occurrences (all)	0	2	7
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 9 (22.22%)	3 / 21 (14.29%)
occurrences (all)	0	2	3
Hyponatraemia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Hypernatraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Blinatumomab 9-28 ug/day Adult Expansion Population	Blinatumomab 5-15 ug/m ² /day Pediatric Expansion Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	16 / 17 (94.12%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Central nervous system leukaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Leukaemic infiltration extramedullary			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	2 / 17 (11.76%)	
occurrences (all)	1	3	
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	

Hot flush			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	9	
Localised oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	3 / 14 (21.43%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Oedema			
subjects affected / exposed	3 / 14 (21.43%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	4 / 14 (28.57%)	15 / 17 (88.24%)	
occurrences (all)	10	34	
Catheter site pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Chills			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Disease progression			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Face oedema			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 17 (5.88%) 1	
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Immune system disorders Acute graft versus host disease subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Cytokine release syndrome subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 7	6 / 17 (35.29%) 6	
Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 6	0 / 17 (0.00%) 0	
Engraftment syndrome subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Graft versus host disease subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Reproductive system and breast disorders Balanoposthitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Metrorrhagia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Pelvic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hiccups			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hypoxia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Laryngeal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Delirium			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	3 / 14 (21.43%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Sleep disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Disorientation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	6 / 17 (35.29%)	
occurrences (all)	2	10	
Amylase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	6 / 17 (35.29%)	
occurrences (all)	0	15	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Blood glucose decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Blood uric acid increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)	
occurrences (all)	1	4	
Glucose urine present			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Immunoglobulins decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	1 / 14 (7.14%)	2 / 17 (11.76%)	
occurrences (all)	1	3	
Lipase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 14 (7.14%)	2 / 17 (11.76%)	
occurrences (all)	6	5	
Neutrophil count decreased			
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)	
occurrences (all)	4	7	
Oxygen saturation decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			

subjects affected / exposed	1 / 14 (7.14%)	5 / 17 (29.41%)	
occurrences (all)	3	10	
Prothrombin time prolonged			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Serum ferritin increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	2 / 14 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	2	4	
White blood cell count decreased			
subjects affected / exposed	2 / 14 (14.29%)	4 / 17 (23.53%)	
occurrences (all)	7	11	
Antithrombin III decreased			
subjects affected / exposed	0 / 14 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	4	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blast cell count increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood cholesterol increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Blood fibrinogen decreased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Infusion related reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Wrist fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Arthropod bite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Sinus bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Arrhythmia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Aphasia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Facial paralysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Headache			

subjects affected / exposed	3 / 14 (21.43%)	4 / 17 (23.53%)
occurrences (all)	5	9
Hypoaesthesia		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Intention tremor		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Lethargy		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Peripheral sensory neuropathy		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Seizure		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Somnolence		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Tremor		
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)
occurrences (all)	1	3
Haemorrhage intracranial		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Movement disorder		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Posterior reversible encephalopathy syndrome		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Wernicke's encephalopathy		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 14 (28.57%)	6 / 17 (35.29%)	
occurrences (all)	7	11	
Bone marrow failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 14 (14.29%)	3 / 17 (17.65%)	
occurrences (all)	2	3	
Febrile neutropenia			
subjects affected / exposed	7 / 14 (50.00%)	4 / 17 (23.53%)	
occurrences (all)	8	5	
Leukopenia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Lymphopenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	6 / 14 (42.86%)	0 / 17 (0.00%)	
occurrences (all)	10	0	
Thrombocytopenia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Hypoglobulinaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Dry eye subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Photophobia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Vitreous floaters subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Glaucoma subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 3	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 4	2 / 17 (11.76%) 2	
Dyspepsia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Gastritis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Gingival swelling		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Nausea		
subjects affected / exposed	8 / 14 (57.14%)	2 / 17 (11.76%)
occurrences (all)	14	2
Oral pain		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Pancreatitis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Proctitis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Stomatitis		
subjects affected / exposed	5 / 14 (35.71%)	2 / 17 (11.76%)
occurrences (all)	5	2
Vomiting		
subjects affected / exposed	4 / 14 (28.57%)	6 / 17 (35.29%)
occurrences (all)	6	7
Dental caries		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorder		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Haemorrhoids		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Lip pain		

subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Oral disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Salivary gland pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Liver disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Liver injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Cholecystitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Drug-induced liver injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Hepatic function abnormal			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hepatic pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Alopecia		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Asteatosis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Dermatitis contact		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Dry skin		
subjects affected / exposed	2 / 14 (14.29%)	1 / 17 (5.88%)
occurrences (all)	2	1
Erythema		
subjects affected / exposed	3 / 14 (21.43%)	0 / 17 (0.00%)
occurrences (all)	5	0
Ingrowing nail		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Rash		
subjects affected / exposed	2 / 14 (14.29%)	1 / 17 (5.88%)
occurrences (all)	2	1
Rash maculo-papular		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Urticaria		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Dermatitis acneiform		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0

Dermatitis diaper subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Dermatitis exfoliative generalised subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 17 (11.76%) 2	
Pruritus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Renal and urinary disorders Cystitis haemorrhagic subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Renal disorder subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Cystitis noninfective subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Pollakiuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 17 (0.00%) 0	
Urinary retention subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 17 (5.88%) 1	
Endocrine disorders Steroid withdrawal syndrome subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 17 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	2 / 17 (11.76%) 3	

Arthritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Myopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)	
occurrences (all)	1	4	
Pain in jaw			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Spinal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	2 / 14 (14.29%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Cystitis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Cytomegalovirus infection		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Device related infection		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Gingivitis		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Hepatitis B		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Herpes zoster		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Infection		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Otitis media		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Pneumonia		
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)
occurrences (all)	1	0
Sepsis		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Staphylococcal sepsis		

subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)	
occurrences (all)	0	0	
Bacteraemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 14 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Paronychia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Sialoadenitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin candida			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 14 (21.43%)	5 / 17 (29.41%)	
occurrences (all)	5	9	
Fluid retention			
subjects affected / exposed	1 / 14 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

Hypercalcaemia		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Hyperglycaemia		
subjects affected / exposed	2 / 14 (14.29%)	1 / 17 (5.88%)
occurrences (all)	2	5
Hyperkalaemia		
subjects affected / exposed	1 / 14 (7.14%)	2 / 17 (11.76%)
occurrences (all)	1	2
Hyperlipidaemia		
subjects affected / exposed	0 / 14 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0
Hyperuricaemia		
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	1
Hypoalbuminaemia		
subjects affected / exposed	0 / 14 (0.00%)	4 / 17 (23.53%)
occurrences (all)	0	10
Hypocalcaemia		
subjects affected / exposed	1 / 14 (7.14%)	3 / 17 (17.65%)
occurrences (all)	1	4
Hypokalaemia		
subjects affected / exposed	4 / 14 (28.57%)	1 / 17 (5.88%)
occurrences (all)	5	4
Hypomagnesaemia		
subjects affected / exposed	2 / 14 (14.29%)	0 / 17 (0.00%)
occurrences (all)	2	0
Hyponatraemia		
subjects affected / exposed	1 / 14 (7.14%)	4 / 17 (23.53%)
occurrences (all)	2	9
Hypophosphataemia		
subjects affected / exposed	2 / 14 (14.29%)	1 / 17 (5.88%)
occurrences (all)	3	1
Hypernatraemia		
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)
occurrences (all)	1	1

Hypertriglyceridaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hypoglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2015	<ul style="list-style-type: none">Added pediatric cohorts (dose de-escalation design) in phase 1b to be able to file in Japan in a pediatric setting
07 March 2016	<ul style="list-style-type: none">Updated and clarified the dexamethasone premedication dosingUpdated Appendix H to reflect the latest investigator's brochureUpdated inclusion and exclusion criteriaUpdated contraception and pregnancy languageUpdated secondary endpoints to align with the current blinatumomab programAdded an additional subgroup covariateClarified time-sensitive pharmacokinetic samplesUpdated Appendix B, Appendix C, Appendix D, and Appendix KClarified dose modifications in Table 5Updated Section 10.3.1 to clarify stage 1 and stage 2 of the protocol
23 May 2016	<ul style="list-style-type: none">Updated and clarified the dexamethasone premedication dosingUpdated pediatric inclusion criteriaUpdated contraception and pregnancy languageRemoved the capture of disease-related events: no case report forms or statistical analysis plan were updated when they were added, so these documents were not required to be updatedRemoved definition of complete remission with incomplete hematological recoveryCorrected covariates for subgroup and ageUpdated protocol to align with current protocol templateCorrected Appendix C and Appendix D
23 June 2017	<ul style="list-style-type: none">Updated and clarified the dexamethasone premedication dosingUpdated pediatric inclusion criteriaUpdated contraception and pregnancy languageRemoved the capture of disease-related events: no case report forms or statistical analysis plan were updated when they were added, so these documents were not required to be updatedRemoved definition of complete remission with incomplete hematological recoveryCorrected covariates for subgroup and ageUpdated protocol to align with current protocol templateCorrected Appendix C and Appendix D
12 July 2018	<ul style="list-style-type: none">Identified and fixed a typo in Section 6.5.2 clarifying that appropriate prophylactic anticonvulsant treatment would be administered during the next treatment round if the event was a \geq grade 2 seizure
20 March 2019	<ul style="list-style-type: none">Updated the primary completion and end of study language to reflect end of evaluation in the expansion cohort instead of phase 1b/2 part of studyRevised the analysis to include expansion cohortAligned that the final analysis occurred when the last subject in the expansion cohort completed safety follow up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported