



Clinical trial results:

A Confirmatory Multicenter, Single-arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab in Adult Patients With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (BLAST)

Summary

EudraCT number	2010-018314-75
Trial protocol	DE BE GB AT ES CZ FR PL IT NL
Global end of trial date	07 January 2019

Results information

Result version number	v1 (current)
This version publication date	02 January 2020
First version publication date	02 January 2020

Trial information

Trial identification

Sponsor protocol code	MT103-203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01207388
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to confirm whether the bispecific T cell engager blinatumomab (MT103) is effective, safe and tolerable in the treatment of ALL patients with minimal residual disease.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the GCPs applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki.

The study protocol and all amendments, the informed consent form, and any accompanying materials provided to subjects were reviewed and approved by an Independent Ethics Committee (IEC), at each center/country.

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	30 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	116
EEA total number of subjects	114

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 46 centers in Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Romania, Russia, Spain, and the United Kingdom.

Pre-assignment

Screening details:

This study enrolled adults with a diagnosis of minimal residual disease (MRD; $\geq 10^{-3}$ leukemic cells) - positive B-precursor acute lymphoblastic leukemia (ALL) who were in complete hematologic remission. A total of 211 subjects were screened; 116 subjects received at least 1 infusion of blinatumomab and were included in the full analysis set (FAS).

Period 1

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

Arms

Arm title	Blinatumomab
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Arm description:

Participants received blinatumomab as a continuous intravenous infusion at a constant flow rate of 15 $\mu\text{g}/\text{m}^2/\text{day}$ over 28 days followed by an infusion-free period of 14 days for up to 4 cycles of treatment. Participants suitable for allogeneic hematopoietic stem cell transplant (HSCT) after treatment with at least 1 cycle of blinatumomab may have undergone allogeneic HSCT instead of receiving further cycles with blinatumomab.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	MT103
Other name	BLINCYTO™
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by continuous intravenous infusion at a constant flow rate of 15 $\mu\text{g}/\text{m}^2/\text{day}$ over 28 days.

Number of subjects in period 1	Blinatumomab
Started	116
Completed	48
Not completed	68
Consent withdrawn by subject	1
Death	67

Baseline characteristics

Reporting groups

Reporting group title	Blinatumomab
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Reporting group description:

Participants received blinatumomab as a continuous intravenous infusion at a constant flow rate of 15 µg/m²/day over 28 days followed by an infusion-free period of 14 days for up to 4 cycles of treatment. Participants suitable for allogeneic hematopoietic stem cell transplant (HSCT) after treatment with at least 1 cycle of blinatumomab may have undergone allogeneic HSCT instead of receiving further cycles with blinatumomab.

Reporting group values	Blinatumomab	Total	
Number of subjects	116	116	
Age categorical			
Units: Subjects			
≥ 18 and <35 years	36	36	
≥ 35 and < 55 years	41	41	
≥ 55 and < 65 years	24	24	
≥ 65 years	15	15	
Age continuous			
Units: years			
arithmetic mean	44.6		
standard deviation	± 16.4	-	
Gender categorical			
Units: Subjects			
Female	48	48	
Male	68	68	
Race			
Race was not permitted to be collected in France.			
Units: Subjects			
White	102	102	
Asian	1	1	
Mixed	1	1	
Unknown	12	12	
Philadelphia Chromosome Disease Status			
Units: Subjects			
Positive	5	5	
Negative	111	111	
MRD Level at Baseline by Central Laboratory			
Measured by polymerase chain reaction (PCR) performed on bone marrow and assessed by the central laboratory; Lower limit of quantification was at least 10 ⁻⁴ leukemic cells.			
Units: Subjects			
≥ 10 ⁻¹ and < 1	9	9	
≥ 10 ⁻² and < 10 ⁻¹	45	45	
≥ 10 ⁻³ and < 10 ⁻²	52	52	
< 10 ⁻³	3	3	
Below Lower Limit of Quantification	5	5	
Unknown	2	2	

Confirmed t(4;11) Translocation / MLL-AF4+ ALL			
t(4;11)(q21;q23) translocation, resulting in the fusion of the mixed lineage leukemia (MLL) gene on chromosome 11 and the AF4 gene on chromosome 4			
Units: Subjects			
Yes	5	5	
No	88	88	
Unknown	23	23	
White Blood Cells at First Diagnosis			
Units: Subjects			
≤ 30,000/mL	78	78	
> 30,000/mL	18	18	
Unknown	20	20	

End points

End points reporting groups

Reporting group title	Blinatumomab
Reporting group description: Participants received blinatumomab as a continuous intravenous infusion at a constant flow rate of 15 µg/m ² /day over 28 days followed by an infusion-free period of 14 days for up to 4 cycles of treatment. Participants suitable for allogeneic hematopoietic stem cell transplant (HSCT) after treatment with at least 1 cycle of blinatumomab may have undergone allogeneic HSCT instead of receiving further cycles with blinatumomab.	
Subject analysis set title	Cycle 1 MRD 10 ⁻⁵
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with an MRD level 10 ⁻⁵ at the end of cycle 1.	
Subject analysis set title	Cycle 1 MRD 10 ⁻⁴
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with an MRD level 10 ⁻⁴ at the end of cycle 1.	
Subject analysis set title	Cycle 1 MRD 10 ⁻³
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with an MRD level 10 ⁻³ at the end of cycle 1.	
Subject analysis set title	Cycle 1 MRD 10 ⁻¹
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with an MRD level 10 ⁻¹ at the end of cycle 1.	
Subject analysis set title	Cycle 1 MRD Unknown
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with an unknown MRD level at the end of cycle 1.	

Primary: Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First Treatment Cycle

End point title	Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First Treatment Cycle ^[1]
End point description: At the end of the first treatment cycle (Day 29) a bone marrow aspiration/biopsy was performed and evaluated by the central MRD laboratory. Complete MRD response is defined as no polymerase chain reaction (PCR) amplification of individual rearrangements of immunoglobulin (Ig)- or T-cell receptor (TCR)-genes detected after completion of the first cycle. The analysis was conducted using the primary endpoint full analysis set (Prim EP FAS), which included all participants with an Ig TCR PCR MRD assay with the minimum required sensitivity of 1 x 10 ⁻⁴ at central lab established at Baseline.	
End point type	Primary
End point timeframe: During the first cycle (6 weeks)	

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: This was a single-arm study.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: percentage of participants				
number (confidence interval 95%)	77.0 (68.1 to 84.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological Relapse-free Survival (RFS)

End point title	Hematological Relapse-free Survival (RFS)
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End point description:

Hematological RFS was measured from first dose of blinatumomab until the first assessment of documented relapse (either hematological or extramedullary), secondary leukemia, or death due to any cause. Participants without documented relapse or death were censored at the time of their last hematological assessment. Participants who received chemotherapy for relapsed or persistent MRD or for any other reason, or HSCT after blinatumomab treatment, before relapse or death occurred, were censored at the start of chemotherapy or HSCT, respectively.

Hematological relapse was defined as unequivocal detection of > 5% leukemia cells in bone marrow as measured by cytological, microscopic assessment, presence of circulating leukemia blasts, or extramedullary leukemia, whichever occurred first. The 18-month Kaplan-Meier estimate of hematological RFS is reported.

Analysis is based on FAS participants in hematological complete remission at treatment start, excluding Philadelphia-positive subjects.

End point type	Secondary
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End point timeframe:

18 months, up to the data cut-off date of 05 August 2015

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: percentage of participants				
number (confidence interval 95%)	54 (33 to 70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival was measured from the first treatment with blinatumomab until death due to any cause. Participants who did not die were censored at their last contact date.

The analysis was conducted in the FAS. "99999" indicates data not estimable at the time of analysis due to the low number of events.

End point type	Secondary
End point timeframe:	
Until the data cut-off date of 05 August 2015; median time on study was 18.3 months.	

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: months				
median (confidence interval 95%)	36.5 (19.2 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplant

End point title	100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplant
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End point description:

The mortality rate within 100 days after allogeneic HSCT was defined as the Kaplan-Meier estimate of the percentage of participants dying within 100 days after the day of the first allogeneic HSCT. The analysis was based on FAS participants who underwent HSCT prior to relapse (hematological or extramedullary) excluding Philadelphia-positive participants.

End point type	Secondary
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End point timeframe:

100 days after HSCT, as of the data cut-off date of 05 August 2015

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percentage of participants				
number (confidence interval 95%)	7 (3 to 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hematological Relapse

End point title	Time to Hematological Relapse
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End point description:

Time to hematological relapse was measured from the start of treatment with blinatumomab until hematological or extramedullary relapse. Participants who died or received HSCT or post-blinatumomab

chemotherapy after treatment with blinatumomab were censored at their last hematological assessment prior to death or HSCT or post-blinatumomab chemotherapy (whichever occurred first).

The analysis was based on FAS participants who were in hematological complete remission at treatment start, excluding Philadelphia-positive participants. "99999" indicates data not estimable due to the low number of events.

End point type	Secondary
End point timeframe:	
Until the data cut-off date of 05 August 2015; median time on study was 18.3 months.	

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: months				
median (confidence interval 95%)	99999 (7.1 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete MRD Response

End point title	Duration of Complete MRD Response
End point description:	
Duration of MRD response was analyzed as the time from onset of MRD negativity until MRD or hematological relapse or date of last confirmation of negative MRD status. Participants who received chemotherapy or HSCT after treatment with blinatumomab before hematological or extramedullary relapse were censored at the start of chemotherapy or HSCT, respectively. MRD relapse is defined as the reappearance of individual rearrangements of Ig- or TCR-genes $\geq$ lower limit of quantification (LLOQ) for at least 1 individual marker measured by an assay with a sensitivity of minimum 10^{-4} . Hematological relapse is defined as the unequivocal detection of $> 5\%$ leukemia cells in bone marrow as measured by cytological or microscopic assessment, presence of circulating leukemia blasts, or extramedullary leukemia. The analysis was based on FAS participants in hematological complete remission at treatment start, excluding Philadelphia-positive participants, who had an MRD complete response at cycle 1.	
End point type	Secondary
End point timeframe:	
Until the data cut-off date of 05 August 2015; median time on study was 18.3 months.	

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: months				
median (confidence interval 95%)	45.0 (6.5 to 45.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MRD Level From Baseline to End of Cycle 1 in Non-MRD Responders

End point title	Change in MRD Level From Baseline to End of Cycle 1 in Non-MRD Responders
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End point description:

MRD level was measured by polymerase chain reaction (PCR) performed on bone marrow and assessed by the central laboratory. An MRD level of 10^{-n} corresponds to residual leukemia cells at a frequency of 1 per 10^n bone marrow cells.

The analysis was conducted in FAS participants who were in hematological complete remission at treatment start, with no MRD Response in the first treatment cycle, excluding Philadelphia-positive participants.

End point type	Secondary
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End point timeframe:

Baseline and end of cycle 1 (6 weeks)

End point values	Cycle 1 MRD 10^{-5}	Cycle 1 MRD 10^{-4}	Cycle 1 MRD 10^{-3}	Cycle 1 MRD 10^{-1}
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	13	4	2
Units: participants				
Baseline MRD Unknown	0	1	0	0
Baseline MRD 10^{-5}	0	0	0	0
Baseline MRD 10^{-4}	0	1	0	0
Baseline MRD 10^{-3}	1	6	2	1
Baseline MRD 10^{-2}	0	5	2	1
Baseline MRD 10^{-1}	1	0	0	0

End point values	Cycle 1 MRD Unknown			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: participants				
Baseline MRD Unknown	0			
Baseline MRD 10^{-5}	0			
Baseline MRD 10^{-4}	0			
Baseline MRD 10^{-3}	0			
Baseline MRD 10^{-2}	0			
Baseline MRD 10^{-1}	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events
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End point description:

Adverse events (AEs) were evaluated for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4, 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.

An AE was considered "serious" if it resulted in death, was life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant incapacity or substantial disruption to conduct normal life functions, was a congenital anomaly or birth defect or was a medically important condition.

Safety analyses were conducted in all participants who received any infusion of blinatumomab.

End point type	Secondary
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End point timeframe:

From the first dose of blinatumomab until 30 days after last dose; the median treatment duration was 55 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: participants				
Any adverse event	116			
Serious adverse events	73			
Adverse events $\geq$ CTC grade 3	71			
Adverse events $\geq$ CTC grade 4	33			
Fatal adverse events	2			
AEs leading to discontinuation of blinatumomab	20			
AEs leading to interruption of blinatumomab	36			
Treatment-related adverse events	112			
Treatment-related serious adverse events	60			
Treatment-related adverse events $\geq$ CTC grade 3	60			
Treatment-related adverse events $\geq$ CTC grade 4	26			
Treatment-related fatal adverse events	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in EORTC-QLQ-C30 Scales in Cycles 1 to 4

End point title	Maximum Change From Baseline in EORTC-QLQ-C30 Scales in Cycles 1 to 4
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End point description:

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Impact).

For each of these scales, scores range from 0 to 100. For the GHS and 5 functional scales a high score indicates better global health status/functioning and a positive change from baseline indicates improvement. For the 9 symptom scales, a high score indicates a higher level of symptoms, and a negative change from Baseline indicates an improvement in symptoms.

The maximum changes from baseline to cycles 1 through 4 in each domain are reported, in the full analysis set (FAS).

End point type	Secondary
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End point timeframe:

Baseline and day 29 of treatment cycles 1 - 4

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	111 ^[2]			
Units: units on a scale				
arithmetic mean (standard error)				
Global Health Status (n=26)	9.0 (± 4.2)			
Physical Functioning (n=26)	2.6 (± 2.3)			
Role Functioning (n=15)	12.2 (± 8.5)			
Emotional Functioning (n=26)	6.5 (± 4.9)			
Cognitive Functioning (n=15)	-3.3 (± 5.2)			
Social Functioning (n=15)	12.2 (± 8.5)			
Fatigue Symptom (n=15)	-5.9 (± 5.5)			
Nausea and Vomiting Symptom (n=26)	-4.5 (± 4.7)			
Pain Symptom (n=26)	3.8 (± 3.6)			
Dyspnea Symptom (n = 26)	-9.0 (± 4.7)			
Insomnia Symptom (n=26)	-2.6 (± 3.2)			
Appetite Loss Symptom (n=15)	-17.8 (± 6.4)			
Constipation Symptom (n=26)	-5.1 (± 3.6)			
Diarrhea Symptom (n=26)	5.1 (± 5.5)			
Financial Difficulties Symptom (n=26)	-5.1 (± 4.8)			

Notes:

[2] - n = subjects included in the calculation of each scale at the time point of maximum change.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC-QLQ-C30 Scales at the End of the Core Study

End point title	Change From Baseline in EORTC-QLQ-C30 Scales at the End of the Core Study
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End point description:

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, Financial Impact).

For each of these scales, scores range from 0 to 100. For the GHS and 5 functional scales a high score indicates better global health status/functioning and a positive change from baseline indicates improvement. For the 9 symptom scales, a high score indicates a higher level of symptoms, and a negative change from Baseline indicates an improvement in symptoms.

End point type	Secondary
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End point timeframe:

Baseline and 30 days after end of the last infusion (end of the core study, a maximum of 26 weeks).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	74 ^[3]			
Units: units on a scale				
arithmetic mean (standard error)				
Global Health Status (n=74)	3.9 (± 2.4)			
Physical Functioning (n=74)	2.2 (± 1.9)			
Role Functioning (n=72)	1.4 (± 3.5)			
Emotional Functioning (n=74)	5.3 (± 2.7)			
Cognitive Functioning (n=74)	-2.3 (± 2.5)			
Social Functioning (n=74)	14.9 (± 3.8)			
Fatigue Symptom (n=74)	-5.4 (± 2.4)			
Nausea and Vomiting Symptom (n=73)	-2.3 (± 2.0)			
Pain Symptom (n=74)	-1.4 (± 2.7)			
Dyspnea Symptom (n=74)	-0.9 (± 2.9)			
Insomnia Symptom (n=73)	3.7 (± 3.5)			
Appetite Loss Symptom (n=73)	-9.1 (± 3.4)			
Constipation Symptom (n=74)	0.0 (± 2.2)			
Diarrhea Symptom (n=74)	0.0 (± 2.3)			
Financial Difficulties Symptom (n=72)	-0.9 (± 2.9)			

Notes:

[3] - Full analysis set with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in EuroQoL 5-Dimension (EQ-5D) Scales During Cycles 1 to 4

End point title	Maximum Change From Baseline in EuroQoL 5-Dimension (EQ-5D) Scales During Cycles 1 to 4
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End point description:

The EQ-5D is a self-administered questionnaire which captures 3 basic types of information: a descriptive profile (health state index) and the overall health rating using a visual analog scale. The health state index measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression on scales from no problems (score = 1), some problems (score = 2), to extreme problems (score = 3). For each dimension the mean change from baseline was calculated at the end of each treatment cycle and at the end of the core study. The maximum observed change from baseline during cycles 1 to 4 are reported for each dimension in the FAS.

End point type	Secondary
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End point timeframe:

Baseline and day 29 of treatment cycles 1 - 4

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	112 ^[4]			
Units: units on a scale				
arithmetic mean (standard error)				
Mobility (n=14)	-0.2 (± 0.1)			
Self-care (n=13)	-0.1 (± 0.1)			
Usual Activities (n=27)	-0.1 (± 0.1)			
Pain/Discomfort (n=14)	-0.2 (± 0.2)			
Anxiety/Depression (n=56)	-0.2 (± 0.1)			

Notes:

[4] - n = subjects included in the calculation of each scale at the time point of maximum change

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5-Dimension (EQ-5D) Scales at the End of the Core Study

End point title	Change From Baseline in EuroQoL 5-Dimension (EQ-5D) Scales at the End of the Core Study
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End point description:

The EQ-5D is a self-administered questionnaire which captures 3 basic types of information: a descriptive profile (health state index) and the overall health rating using a visual analog scale. The health state index measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression

on scales from no problems (score = 1), some problems (score = 2), to extreme problems (score = 3). For each dimension the mean change from baseline was calculated at the end of each treatment cycle and at the end of the core study.

End point type	Secondary
End point timeframe:	
Baseline and 30 days after end of the last infusion (end of the core study, a maximum of 26 weeks).	

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	75 ^[5]			
Units: units on a scale				
arithmetic mean (standard error)				
Mobility (n=75)	0.0 (± 0.1)			
Self-care (n=73)	0.0 (± 0.0)			
Usual Activities (n=75)	-0.1 (± 0.1)			
Pain/Discomfort (n=75)	-0.1 (± 0.1)			
Anxiety/Depression (n=75)	-0.1 (± 0.1)			

Notes:

[5] - Full analysis set with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Utilization: Number of Participants Reporting Use of Transfusion of Blood Products

End point title	Resource Utilization: Number of Participants Reporting Use of Transfusion of Blood Products
End point description:	
Resource utilization was analyzed in all participants in the FAS.	
End point type	Secondary
End point timeframe:	
From first dose of study drug through the end of follow-up; median (minimum, maximum) time on study was 33.8 (1, 62) months	

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: participants				
Overall	14			
Cycle 1	5			
Cycle 2	8			
Cycle 3	0			
Cycle 4	1			
Follow-up Period	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Resource Utilization: Duration of Hospitalization

End point title	Resource Utilization: Duration of Hospitalization
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End point description:

Resource utilization was analyzed in all participants in the FAS.

End point type	Secondary
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End point timeframe:

From first dose of study drug through the end of follow-up; median (minimum, maximum) time on study was 33.8 (1, 62) months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	116			
Units: days				
median (full range (min-max))	14.0 (3 to 63)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of blinatumomab until 30 days after last dose; the median treatment duration was 55 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Blinatumomab [15 ug/m2/d]
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Reporting group description:

Participants received blinatumomab as a continuous intravenous infusion at a constant flow rate of 15 µg/m²/day over 28 days followed by an infusion-free period of 14 days for up to 4 cycles of treatment.

Serious adverse events	Blinatumomab [15 ug/m2/d]		
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 116 (62.93%)		
number of deaths (all causes)	67		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Kaposi's sarcoma			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leukaemia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device issue			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device malfunction			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site extravasation			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Puncture site pain			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product contamination microbial			

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	17 / 116 (14.66%)		
occurrences causally related to treatment / all	19 / 19		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine aminotransferase increased subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Body temperature increased subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased subjects affected / exposed	4 / 116 (3.45%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Prothrombin time prolonged subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Accidental overdose			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Incision site haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	5 / 116 (4.31%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Spinal fracture			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Sinus bradycardia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Intention tremor			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Motor dysfunction			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leukoencephalopathy			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	3 / 116 (2.59%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	8 / 116 (6.90%)		
occurrences causally related to treatment / all	14 / 14		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 116 (1.72%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	5 / 116 (4.31%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Hepatotoxicity			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cystitis klebsiella				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	3 / 116 (2.59%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	2 / 116 (1.72%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 116 (0.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	3 / 116 (2.59%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection staphylococcal				

subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Blinatumomab [15 ug/m2/d]		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 116 (95.69%)		
Investigations			
Weight increased			
subjects affected / exposed	7 / 116 (6.03%)		
occurrences (all)	7		
C-reactive protein increased			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences (all)	7		
Blood immunoglobulin G decreased			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences (all)	6		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 116 (6.03%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	13 / 116 (11.21%)		
occurrences (all)	17		
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 116 (37.93%)		
occurrences (all)	61		
Dizziness			
subjects affected / exposed	9 / 116 (7.76%)		
occurrences (all)	10		
Aphasia			
subjects affected / exposed	9 / 116 (7.76%)		
occurrences (all)	10		

Paraesthesia subjects affected / exposed occurrences (all)	6 / 116 (5.17%) 6		
Tremor subjects affected / exposed occurrences (all)	28 / 116 (24.14%) 34		
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	14 / 116 (12.07%) 18		
Leukopenia subjects affected / exposed occurrences (all)	7 / 116 (6.03%) 8		
Anaemia subjects affected / exposed occurrences (all)	6 / 116 (5.17%) 8		
General disorders and administration site conditions			
Chills subjects affected / exposed occurrences (all)	30 / 116 (25.86%) 35		
Pyrexia subjects affected / exposed occurrences (all)	99 / 116 (85.34%) 177		
Fatigue subjects affected / exposed occurrences (all)	27 / 116 (23.28%) 29		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	13 / 116 (11.21%) 16		
Diarrhoea subjects affected / exposed occurrences (all)	22 / 116 (18.97%) 27		
Nausea subjects affected / exposed occurrences (all)	27 / 116 (23.28%) 33		

Vomiting subjects affected / exposed occurrences (all)	26 / 116 (22.41%) 32		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	15 / 116 (12.93%) 20		
Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	7 / 116 (6.03%) 7 11 / 116 (9.48%) 12		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	17 / 116 (14.66%) 18		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	10 / 116 (8.62%) 16 15 / 116 (12.93%) 18 8 / 116 (6.90%) 9		
Infections and infestations Device related infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 116 (5.17%) 6 8 / 116 (6.90%) 10		
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	18 / 116 (15.52%)		
occurrences (all)	21		
Hypomagnesaemia			
subjects affected / exposed	6 / 116 (5.17%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2011	- Update storage and stability information - Update to labeling information
04 July 2011	- Add collection of blinatumomab immunogenicity sample - Update known and potential benefits and risks - Implement prescreening for early detection of MRD - Update MRD assay requirements - Update inclusion criteria #4 (diagnosis of ALL) - Update labeling information - Update storage and stability information - Update preparation of drug product - Update safety follow-up for subjects who undergo HSCT - Update early termination - Update definitions in drug safety - Add information regarding legal and ethical requirements and protocol amendments - Clarify the following: duration of subject participation, intense chemotherapy, informed consent, writing test, examination of CSF, selected sites for ECG and PK assessments - Implement minor administrative changes and update references and contacts
17 February 2012	- Add a provision to implement additional urgent safety measures in case of neurologic-related adverse events - Change contact details for drug safety department and safe reporting - Adapt patient information and informed consent form
11 July 2012	- Update assessment schedule - Update list of contacts - Update known and potential benefits and risks - Add a provision to restart drug at a lower dose in the case of neurologic-related adverse events - Add C-reactive Protein testing - Clarify the following: retreatment cycles, efficacy assessments, hospitalization, discontinuation criteria, use of premedication, MRD sample requirements, assessment for neurologic-related adverse events, reporting periods for adverse events, safety reporting procedures
06 March 2014	- Amend the key secondary objective/endpoint
13 June 2014	- Harmonize the description of the blinatumomab and its preparation with the Investigator's Brochure and other clinical trials within the blinatumomab clinical development program

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29358182>