Clinical trial results:
An Open-label, Multicenter, Phase 2 Study to Evaluate Efficacy and Safety of the Bi-specific T cell Engager (BiTE®) Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2011-002257-61
Trial protocol	DE GB ES IT
Global end of trial date	03 January 2017

Results information

Result version number	v1 (current)
This version publication date	30 December 2017
First version publication date	30 December 2017

Trial information

Trial identification

Sponsor protocol code	MT103-211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01466179
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	03 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2017
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 antibody blinatumomab (MT103) is effective and safe in the treatment of patients with relapsed or refractory acute lymphoblastic leukemia (ALL).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
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) or Institutional Review Board (IRB), as appropriate, 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	06 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 122
Worldwide total number of subjects	238
EEA total number of subjects	116

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)	206
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 37 centers in Germany, Italy, Spain, France, the United Kingdom, and the United States from 06 December 2011 to 03 January 2017.

Pre-assignment

Screening details:

This study initially used a Simon 2-stage design, in which 66 subjects were enrolled. A third stage (extension) was introduced leading to the enrollment of 123 further patients. An additional 36 subjects were enrolled to evaluate central nervous system (CNS) symptoms. Furthermore, up to 13 patients were enrolled into the Open Enrollment Cohort.

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

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 seven days of treatment, escalated to 28 µg/day starting from Week 2 of treatment.

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. In the first cycle, the initial dose was 9 µg/day for 7 days, then 28 µg/day for the remaining 3 weeks. The target dose of 28 µg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose reduction was possible in the case of adverse events.

Number of subjects in period 1	Blinatumomab
Started	238
Completed	14
Not completed	224
Physician decision	63
Consent withdrawn by subject	11
Protocol violation	2
Adverse event, non-fatal	37
Other	4
Death	10

Disease relapse	30
Progressive disease	53
Lack of efficacy	14

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
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 seven days of treatment, escalated to 28 µg/day starting from Week 2 of treatment.	

Reporting group values	Overall Study	Total	
Number of subjects	238	238	
Age Categorical Units: Subjects			
Adults (18-64 years)	206	206	
From 65-84 years	32	32	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	41.4		
standard deviation	± 17.28	-	
Gender Categorical Units: Subjects			
Female	91	91	
Male	147	147	
Race			
Race was not recorded for any subjects from France and for 1 further subject due to privacy reasons.			
Units: Subjects			
White	183	183	
Asian	8	8	
Black/African American	7	7	
American Indian or Alaska Native	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
Other	13	13	
Not recorded	25	25	
Disease Stage Entry Criteria Met			
HSCT = hematopoietic stem cell transplantation			
Units: Subjects			
Primary refractory	22	22	
Relapse ≤ 12 months of allogeneic HSCT	44	44	
Entering first salvage; first remission ≤ 12 mo	29	29	
Entering second or greater salvage therapies	137	137	
No criteria met	6	6	
Number of Prior Relapses Units: Subjects			
None	22	22	
One	135	135	
Two	57	57	

More than two	24	24	
Prior Allogeneic HSCT and Prior Relapses			
alloHSCT = allogeneic hematopoietic stem cell transplantation			
Units: Subjects			
Prior allogeneic HSCT	75	75	
No prior alloHSCT, no prior relapse	22	22	
No prior alloHSCT, 1 prior relapse	108	108	
No prior alloHSCT, 2 prior relapses	29	29	
No prior alloHSCT, > 2 prior relapses	4	4	
Number of Prior Salvage Therapies			
Units: Subjects			
No prior salvage therapy	49	49	
1 prior salvage therapy	95	95	
2 prior salvage therapies	50	50	
> 2 prior salvage therapies	44	44	
Baseline Bone Marrow Blast Category			
Bone marrow blasts as assessed by the local laboratory			
Units: Subjects			
< 10%	8	8	
10% - < 50%	61	61	
≥ 50%	162	162	
Not recorded	7	7	
Time Since Initial Diagnosis			
Units: months			
median	16.66		
full range (min-max)	1.9 to 249.0	-	
Time Since Last Relapse			
Reported for 216 participants with a prior relapse (the other 22 participants were primary refractory with no prior relapses).			
Units: months			
median	1.38		
full range (min-max)	0.0 to 56.8	-	

End points

End points reporting groups

Reporting group title	Blinatumomab

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 seven days of treatment, escalated to 28 µg/day starting from Week 2 of treatment.

Subject analysis set title	Cycle 1: Blinatumomab 9 µg/Day
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving 9 µg/day blinatumomab by continuous intravenous (CIV) infusion during Cycle 1.

Subject analysis set title	Cycle 1: Blinatumomab 28 µg/Day
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving 28 µg/day blinatumomab by continuous intravenous (CIV) infusion during Cycle 1.

Subject analysis set title	Cycle 2: Blinatumomab 28 µg/Day
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receiving 28 µg/day blinatumomab by continuous intravenous (CIV) infusion during Cycle 2.

Primary: 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	Percentage of Participants With a Best Response of Complete Remission or Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment[1]

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):
- bone marrow blasts ≤ 5%
- no evidence of disease
- 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*):
- bone marrow blasts ≤ 5%
- no evidence of disease
- partial recovery of peripheral blood counts:
  - platelets > 50,000/µL, and
  - ANC > 500/µL.

The primary analysis was based on the primary analysis set (PAS), defined as participants from the first 3 stages of the study who received any infusion of blinatumomab.

End point type	Primary

End point timeframe:

Within the first 2 cycles of treatment, 12 weeks, up to the data cut-off date of 20 January 2017.

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; no statistical comparisons were conducted.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189			
Units: percentage of participants				
number (confidence interval 95%)	43.9 (36.7 to 51.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hematological Relapse (Duration of Response)

End point title	Time to Hematological Relapse (Duration of Response)

End point description:

Time to hematological relapse was measured for subjects in remission (CR or CRh*) during the core study (the time from the first infusion to 30 days after the last infusion), from the time the subject first achieved remission until first documented relapse or death due to disease progression. Subjects without documented relapse (hematological or extramedullary) and who did not die were censored at the time of their last bone marrow assessment or their last survival follow-up visit confirming remission. Subjects who died without having reported hematological relapse or without showing any clinical sign of disease progression were censored on their date of death.
Hematological relapse was defined as:
- proportion of blasts in bone marrow > 5% after documented CR/CRh* or
- blasts in peripheral blood after documented CR/CRh*

The analysis was based on the full analysis set, defined as all subjects who received any infusion of blinatumomab, including the additional evaluation cohort.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 20 January 2017; median observation time was 34.4 months, estimated using the reverse Kaplan-Meier method.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	101[2]			
Units: months				
median (confidence interval 95%)	10.0 (6.3 to 18.9)			

Notes:

[2] - All patients who reached CR or CRh* during the core study

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) During Blinatumomab Induced Remission

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.
The analysis was based on the full analysis set.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 20 January 2017; the maximum duration on study was 49.9 months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	99[3]			
Units: percentage of participants				
number (confidence interval 95%)	40.4 (30.7 to 50.7)			

Notes:

[3] - Subjects who reached CR or CRh* during the first two cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Response of Complete Remission Within 2 Cycles of Treatment

End point title	Percentage of Participants With a Best Response of Complete Remission Within 2 Cycles of Treatment

End point description:

Complete Remission was defined by the following criteria:
- bone marrow blasts ≤ 5%
- no evidence of disease
- full recovery of peripheral blood counts:
  - platelets > 100,000/µL, and
  - absolute neutrophil count (ANC) > 1,000/µL

The analysis was based on the primary analysis set.

End point type	Secondary

End point timeframe:

Within the first 2 cycles of treatment, 12 weeks, up to the data cut-off date of 20 January 2017.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189[4]			
Units: percentage of participants				
number (confidence interval 95%)	33.3 (26.7 to 40.5)			

Notes:

[4] - Primary analysis set

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With a Best Response of Complete Remission With Only Partial Hematological Recovery Within 2 Cycles of Treatment

End point description:

Complete Remission With Partial Hematological Recovery was defined by the following criteria:
- bone marrow blasts ≤ 5%
- no evidence of disease
- partial recovery of peripheral blood counts:
  - platelets > 50,000/µL, and
  - ANC > 500/µL.

The analysis was based on the primary analysis set.

End point type	Secondary

End point timeframe:

Within the first 2 cycles of treatment, 12 weeks, up to the data cut-off date of 20 January 2017.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189[5]			
Units: percentage of participants				
number (confidence interval 95%)	10.6 (6.6 to 15.9)			

Notes:

[5] - Primary analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Response of Partial Remission Within 2 Cycles of Treatment

End point title	Percentage of Participants With a Best Response of Partial Remission Within 2 Cycles of Treatment

End point description:

Partial Remission is defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.

The analysis was based on the primary analysis set.

End point type	Secondary

End point timeframe:

Within the first 2 cycles of treatment, 12 weeks, up to the data cut-off date of 20 January 2017.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189[6]			
Units: percentage of participants				
number (confidence interval 95%)	2.6 (0.9 to 6.1)			

Notes:

[6] - Primary analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free Survival

End point title	Relapse-free Survival

End point description:

Relapse-free survival was assessed for participants who achieved a complete remission or complete remission with partial hematological recovery during the core study and was measured from the time the participant first achieved remission until first documented relapse or death due to any cause. Participants without a documented relapse (hematological or extramedullary) or who did not die were censored at the time of their last bone marrow assessment or their last survival follow-up visit confirming remission.
The analysis was based on the full analysis set.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 20 January 2017; median observation time was 34.7 months, estimated using the reverse Kaplan-Meier method.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	101[7]			
Units: months				
median (confidence interval 95%)	7.4 (5.5 to 10.1)			

Notes:

[7] - Patients who reached CR or CRh* during the core study

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival

End point title	Event-free survival

End point description:

Event-free survival was calculated from the start date of blinatumomab infusion until the date of bone marrow aspiration at which hematological relapse was first detected, or the date of diagnosis on which the hematological or extramedullary relapse was documented or the date of start of any new therapy for ALL (excluding HSCT), or the date of death, whichever was earlier. Participants who did not achieve complete remission or complete remission with partial hematological recovery during the core study were evaluated as having an event on Day 1. Participants in remission who did not experience hematological relapse, did not receive a new therapy for ALL (excluding HSCT), and did not die were censored on the date of the last available bone marrow aspiration or on the last date of survival follow-up visit, whichever was later.

The analysis was based on the full analysis set.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 20 January 2017; median observation time was 35.8 months, estimated using the reverse Kaplan-Meier method.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	225[8]			
Units: months				
median (confidence interval 95%)	0.0 (0.0 to 2.0)			

Notes:

[8] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was measured for all participants from the time the participant received the first treatment of blinatumomab until death due to any cause or the date of the last follow-up. Participants who did not die 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 analysis was based on the full analysis set.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 20 January 2017; median observation time was 35.9 months, estimated using the reverse Kaplan-Meier method.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	225[9]			
Units: months				
median (confidence interval 95%)	6.5 (4.8 to 7.7)			

Notes:

[9] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events

End point title	Number of Participants With Treatment-emergent Adverse Events

End point description:

Adverse events (AEs) were evaluated for severity according to the 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, requires or prolongs inpatient hospitalization, results in persistent or significant incapacity or substantial disruption to conduct normal life functions, is a congenital anomaly or birth defect or is a medically important condition.
Progressive disease was not an adverse event, per the protocol, unless it was more severe than expected for the patient. Therefore, many deaths due to progressive disease were not counted as adverse events.

End point type	Secondary

End point timeframe:

From the start of the first infusion to 30 days after the end of the last infusion in the core study or from the start of the first retreatment cycle infusion to 30 days after the end of the last retreatment cycle, median treatment duration was 28.3 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: participants				
Any adverse event (AE)	237			
Adverse events of at least CTC grade 3	194			
Treatment-related adverse events	206			
Related adverse events of at least CTC grade 3	130			
Serious adverse events	153			
Serious adverse events of at least CTC grade 3	133			
Related serious adverse events	79			
AEs leading to interruption of blinatumomab	83			
AEs leading to discontinuation of blinatumomab	40			
Related AE leading to treatment discontinuation	21			
AEs leading to death	34			
Related AEs leading to death	4			

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

End point description:

The analysis of 100-day mortality after allogeneic HSCT was assessed for all participants who received an allogeneic HSCT while in remission (CR/CRh*) following treatment with blinatumomab. 100-day

mortality after allogeneic HSCT was calculated relative to the date of allogeneic HSCT.
Patients 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.

End point type	Secondary

End point timeframe:

From the date of allogeneic HSCT until the data cut-off date of 20 January 2017; median observation time was 32.2 months, estimated using the reverse Kaplan-Meier method.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	40[10]			
Units: percentage of participants				
number (confidence interval 95%)	12.5 (5.4 to 27.5)			

Notes:

[10] - Participants who received an allogeneic HSCT while in remission induced by blinatumomab treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Blinatumomab Concentration at Steady State

End point title	Serum Blinatumomab Concentration at Steady State

End point description:

The steady state concentration of blinatumomab was summarized as the observed concentrations collected at least 10 hours after the start of the IV infusion or dose step for cycle 1 and cycle 2, respectively. Serum concentrations of blinatumomab were measured using a validated bioassay. The lower limit of quantitation (LLOQ) = 50.0 pg/mL.
The pharmacokinetic data tet (PKS) was defined as all patients who received any infusion of blinatumomab and had at least one PK sample collected unless significant protocol deviations affected the data analysis or if key dosing, dosing interruption or sampling information was missing.

End point type	Secondary

End point timeframe:

Samples were taken before treatment start and on Days 3, 8, 10, 15, 22, and 29 after infusion start during Cycles 1 and 2.

End point values	Cycle 1: Blinatumomab 9 µg/Day	Cycle 1: Blinatumomab 28 µg/Day	Cycle 2: Blinatumomab 28 µg/Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	178	188	101	
Units: pg/mL				
arithmetic mean (standard deviation)	246 (± 305)	632 (± 510)	755 (± 433)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Cytokine Peak Levels

End point title	Serum Cytokine Peak Levels

End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor alpha(TNF-α) and interferon gamma (IFN-γ) using enzyme-linked immunosorbent assays or cytometric bead assays. The limit of detection of the assay (LOD) was 20 pg/mL and the limit of quantification (LOQ) was 125 pg/mL. Data below LOD were set to 10 pg/mL while data < LOQ and > LOD were reported as measured.
Serum IL-4 levels were below detection limit (< 20 pg/mL) at all time points in all participants studied.
The pharmacodynamic data set (PDS) included all participants who received any infusion of blinatumomab and had at least one pharmacodynamic sample collected. "N" indicates the number of participants with available data at each time point.

End point type	Secondary

End point timeframe:

Serum samples were collected on Days 1 and 8 at 2 hours and 6 hours after treatment start, and on Day 2 (24 hours) and Day 3 (48 hours) of each treatment cycle and on Days 9 and 10 after dose step.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	220			
Units: pg/mL				
arithmetic mean (standard deviation)				
IFN-: Cycle 1 Week 1 (N=220)	86.5 (± 376)			
IFN-: Cycle 1 Week 2 (N=208)	25.1 (± 76.4)			
IFN-: Cycle 2 Week 1 (N=113)	20.9 (± 42.3)			
IFN-: Cycle 3 Week 1 (N=50)	19.5 (± 25)			
IL-10: Cycle 1 Week 1 (N=220)	598 (± 801)			
IL-10: Cycle 1 Week 2 (N=208)	97.9 (± 149)			
IL-10: Cycle 2 Week 1 (N=113)	371 (± 607)			
IL-10: Cycle 3 Week 1 (N=50)	419 (± 863)			
IL-2: Cycle 1 Week 1 (N=220)	25.3 (± 44.3)			
IL-2: Cycle 1 Week 2 (N=208)	10.8 (± 5.01)			
IL-2: Cycle 2 Week 1 (N=113)	10.9 (± 4.76)			
IL-2: Cycle 3 Week 1 (N=50)	10.3 (± 1.84)			
IL-6: Cycle 1 Week 1 (N=220)	1005 (± 3358)			
IL-6: Cycle 1 Week 2 (N=208)	264 (± 746)			
IL-6: Cycle 2 Week 1 (N=113)	284 (± 883)			
IL-6: Cycle 3 Week 1 (N=50)	64.8 (± 104)			
TNF-α: Cycle 1 Week 1 (N=220)	32.5 (± 120)			
TNF-α: Cycle 1 Week 2 (N=208)	10.3 (± 3.16)			
TNF-α: Cycle 2 Week 1 (N=113)	12.0 (± 14.0)			
TNF-α: Cycle 3 Week 1 (N=50)	11.6 (± 7.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Response of Blast Free Hypoplastic or Aplastic Bone Marrow Within 2 Cycles of Treatment

End point title	Percentage of Participants With a Best Response of Blast Free Hypoplastic or Aplastic Bone Marrow Within 2 Cycles of Treatment

End point description:

Blast Free Hypoplastic or Aplastic Bone Marrow was defined as:
• bone marrow blasts ≤ 5%
• no evidence of disease
• insufficient recovery of peripheral counts: platelets ≤ 50,000/µL and/or absolute neutrophil count (ANC) ≤ 500/µL
The analysis was based on the primary analysis set.

End point type	Secondary

End point timeframe:

Within the first 2 cycles of treatment, 12 weeks, up to the data cut-off date of 20 January 2017.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189			
Units: percentage of participants				
number (confidence interval 95%)	7.9 (4.5 to 12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response During the Core Study

End point title	Best Response During the Core Study

End point description:

Complete Remission (CR):
• bone marrow blasts ≤ 5%
• no evidence of disease
• 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*):
• bone marrow blasts ≤ 5%
• no evidence of disease
• partial recovery of peripheral blood counts:
◦ platelets > 50,000/µL, and
◦ ANC > 500/µL

Blast Free Hypoplastic or Aplastic Bone Marrow:
• bone marrow blasts ≤ 5%
• no evidence of disease
• insufficient recovery of peripheral counts: platelets ≤ 50,000/µL and/or ANC ≤ 500/µL

Partial Remission:
• bone marrow blasts 6% to 25% with at least a 50% reduction from Baseline.

The analysis was based on the primary analysis set.

End point type	Secondary

End point timeframe:

From the first dose of blinatumomab until 30 days after the end of the last infusion during the core study, or until the data cut-off date of 20 January 2017; a maximum of 7.5 months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	189			
Units: percentage of participants				
number (confidence interval 95%)				
Remission (CR/CRh*)	44.4 (37.2 to 51.8)			
Complete remission	35.4 (28.6 to 42.7)			
Complete remission, partial hematological recovery	9.0 (5.3 to 14.0)			
Blast free hypoplastic or aplastic bone marrow	7.9 (4.5 to 12.8)			
Partial remission	2.6 (0.9 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of the first infusion to 30 days after the end of the last infusion in the core study or from the start of the first retreatment cycle infusion to 30 days after the end of the last retreatment cycle, median treatment duration was 28.3 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Blinatumomab

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 seven days of treatment, escalated to 28 µg/day starting from Week 2 of treatment.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	153 / 238 (64.29%)		
number of deaths (all causes)	193		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Acute lymphocytic leukaemia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
B precursor type acute leukaemia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chloroma				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoma				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Capillary leak syndrome				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypotension				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				

subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Central venous catheter removal			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Resuscitation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Complication associated with device			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	3 / 238 (1.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		

Fatigue				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Oedema peripheral				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	16 / 238 (6.72%)			
occurrences causally related to treatment / all	5 / 16			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Graft versus host disease				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				

subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	3 / 238 (1.26%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	5 / 238 (2.10%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Delirium febrile			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Restlessness				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device occlusion				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Blood bilirubin increased				
subjects affected / exposed	5 / 238 (2.10%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas test positive				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Accidental overdose			
subjects affected / exposed	4 / 238 (1.68%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	5 / 238 (2.10%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular access complication			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			

Aplasia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Aphasia				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cognitive disorder				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysaesthesia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	6 / 238 (2.52%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	1 / 1			
Headache				

subjects affected / exposed	5 / 238 (2.10%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorder				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological symptom				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neurotoxicity				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Poor quality sleep				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	5 / 238 (2.10%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Trigeminal nerve disorder				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cytopenia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	23 / 238 (9.66%)			
occurrences causally related to treatment / all	9 / 25			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	10 / 238 (4.20%)			
occurrences causally related to treatment / all	6 / 12			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Diplopia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Nausea				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Erythema multiforme				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperhidrosis				

subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash vesicular			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin lesion			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder perforation			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal failure			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Back pain			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	5 / 238 (2.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Myopathy			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspergillus infection			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
BK virus infection			

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cellulitis				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				

subjects affected / exposed	9 / 238 (3.78%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal bacteraemia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Enterococcal infection				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Enterococcal sepsis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				

subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Fungaemia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fungal infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fusarium infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Gastroenteritis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Kidney infection				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Leuconostoc infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Mucormycosis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pathogen resistance				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pilonidal cyst				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	12 / 238 (5.04%)			
occurrences causally related to treatment / all	5 / 15			
deaths causally related to treatment / all	0 / 3			
Pneumonia fungal				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia klebsiella				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal bacteraemia				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Rhinitis				

subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	10 / 238 (4.20%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	1 / 5			
Septic shock				
subjects affected / exposed	3 / 238 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Sinusitis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis fungal				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	4 / 238 (1.68%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				

subjects affected / exposed	2 / 238 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic candida				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella zoster virus infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral haemorrhagic cystitis				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 238 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 238 (0.84%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 238 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Blinatumomab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 238 (97.90%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 238 (7.14%)		
occurrences (all)	17		
Hypotension			
subjects affected / exposed	31 / 238 (13.03%)		
occurrences (all)	40		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	20 / 238 (8.40%) 23		
Chest pain subjects affected / exposed occurrences (all)	19 / 238 (7.98%) 19		
Chills subjects affected / exposed occurrences (all)	37 / 238 (15.55%) 43		
Fatigue subjects affected / exposed occurrences (all)	36 / 238 (15.13%) 41		
Oedema subjects affected / exposed occurrences (all)	13 / 238 (5.46%) 13		
Oedema peripheral subjects affected / exposed occurrences (all)	58 / 238 (24.37%) 67		
Pain subjects affected / exposed occurrences (all)	17 / 238 (7.14%) 17		
Pyrexia subjects affected / exposed occurrences (all)	135 / 238 (56.72%) 238		
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	28 / 238 (11.76%) 36		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	39 / 238 (16.39%) 41		
Dyspnoea subjects affected / exposed occurrences (all)	22 / 238 (9.24%) 26		
Epistaxis			

subjects affected / exposed occurrences (all)	14 / 238 (5.88%) 15		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 19 / 238 (7.98%) 19 14 / 238 (5.88%) 18 35 / 238 (14.71%) 42		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Immunoglobulins decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	 33 / 238 (13.87%) 36 31 / 238 (13.03%) 33 17 / 238 (7.14%) 18 20 / 238 (8.40%) 20 19 / 238 (7.98%) 22		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 14 / 238 (5.88%) 16 14 / 238 (5.88%) 17		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	30 / 238 (12.61%) 33		
Headache subjects affected / exposed occurrences (all)	76 / 238 (31.93%) 113		
Somnolence subjects affected / exposed occurrences (all)	12 / 238 (5.04%) 16		
Tremor subjects affected / exposed occurrences (all)	37 / 238 (15.55%) 47		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	48 / 238 (20.17%) 60		
Febrile neutropenia subjects affected / exposed occurrences (all)	49 / 238 (20.59%) 65		
Leukopenia subjects affected / exposed occurrences (all)	20 / 238 (8.40%) 33		
Neutropenia subjects affected / exposed occurrences (all)	32 / 238 (13.45%) 48		
Thrombocytopenia subjects affected / exposed occurrences (all)	27 / 238 (11.34%) 35		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	15 / 238 (6.30%) 18		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	37 / 238 (15.55%) 41		
Constipation			

subjects affected / exposed	45 / 238 (18.91%)		
occurrences (all)	55		
Diarrhoea			
subjects affected / exposed	46 / 238 (19.33%)		
occurrences (all)	58		
Nausea			
subjects affected / exposed	58 / 238 (24.37%)		
occurrences (all)	70		
Vomiting			
subjects affected / exposed	32 / 238 (13.45%)		
occurrences (all)	39		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	12 / 238 (5.04%)		
occurrences (all)	13		
Rash			
subjects affected / exposed	27 / 238 (11.34%)		
occurrences (all)	32		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 238 (9.66%)		
occurrences (all)	29		
Back pain			
subjects affected / exposed	31 / 238 (13.03%)		
occurrences (all)	37		
Bone pain			
subjects affected / exposed	19 / 238 (7.98%)		
occurrences (all)	23		
Muscular weakness			
subjects affected / exposed	15 / 238 (6.30%)		
occurrences (all)	19		
Myalgia			
subjects affected / exposed	18 / 238 (7.56%)		
occurrences (all)	21		
Pain in extremity			

subjects affected / exposed occurrences (all)	24 / 238 (10.08%) 31		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 13 / 238 (5.46%) 16		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 25 / 238 (10.50%) 27 56 / 238 (23.53%) 70 26 / 238 (10.92%) 32 18 / 238 (7.56%) 21 32 / 238 (13.45%) 35		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2012	- To implement urgent safety measures regarding neurologic events. - Adaptation of subject information and ICF: the safety section was updated in accordance with the Investigator's Brochure, version 13.0.
22 June 2012	- To increase the sample size (add third stage [extension]). - To harmonize the study protocol between Germany and other centers in the European and the United States and clarify/adapt protocol mandated assessments. - Adaptation of study endpoints: the names and definition of endpoints related to response duration were updated for consistency with other blinatumomab studies (MT103-206) and International Working Group endpoint definitions. - To document the acquisition of Micromet by Amgen. - Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol.
29 October 2012	- To increase the sample size: from approximately 140 to 150 subjects to approximately 170 to 190 subjects. - To clarify/adapt protocol mandated assessments based on current experience: total dose of dexamethasone, bone marrow biopsy in the case of progressive disease does not need to be performed; some laboratory tests were considered routine and do not need to be repeated for study screening if conducted within a certain time before ICF signature; treatment of foreign subjects. - Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol
18 June 2013	- To add an additional evaluation cohort of approximately 30 subjects: to understand CNS symptoms and predictive factors; PAS was added; mandatory MRIs for baseline and after neurologic events of ≥ grade 3. - 13 additional subjects were enrolled in the open-enrollment cohort. - To clarify treatment interruptions after adverse events. - Update the safety section: to clarify the serious adverse events reporting per European guidelines; to clarify duration of adverse events recording in for early end of core study visit; align adverse events/serious adverse events recording instruction in the protocol. - To describe additional DMC meetings and document policies with respect to conflicts of interest of DMC members. - Adaptation of subject information and ICF: the informed consent was updated based on changes in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported