Clinical trial results:
A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects With Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study)

Summary

EudraCT number	2013-000706-36
Trial protocol	IT GB DE
Global end of trial date	06 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	20120216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000427
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	06 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the rate of complete remission (CR)/complete remission with partial hematological recovery (CRh*) in adult subjects with relapsed/refractory Philadelphia chromosome (Ph)-positive B-precursor acute lymphoblastic leukemia (ALL).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and United States Food and Drug Administration regulations/guidelinese.
The study protocol and all amendments were reviewed by an independent ethics committee (IEC) or institutional review board (IRB).
Before a subject's participation in the clinical study, the investigator was responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	45
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	33
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 19 centers in 4 European countries and the United States: 3 centers in France, 3 in Germany, 5 in Italy, 1 in the United Kingdom, and 7 in the United States.
The first participant enrolled on 03 January 2014 and the last participant enrolled on 12 January 2015.

Pre-assignment

Screening details:

This was a single-arm, Simon 2-stage design, multicenter study that consisted of a 3-week screening and prephase period for the administration of dexamethasone to reduce both tumor burden and the incidence of tumor lysis syndrome, an induction phase of 2 cycles of blinatumomab, a consolidation phase, and a long-term follow-up phase.

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 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	MT103
Other name	AMG 103 Blincyto®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab is administered as a continuous intravenous infusion (CIV). A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab followed by a 2-week treatment-free interval.

Number of subjects in period 1	Blinatumomab
Started	45
Completed	8
Not completed	37
Death	37

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 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.

The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

Reporting group values	Overall Study	Total	
Number of subjects	45	45	
Age Categorical Units: Subjects			
18 to < 35 years	5	5	
35 to < 55 years	17	17	
55 to < 65 years	11	11	
≥ 65 years	12	12	
Age Continuous Units: years			
arithmetic mean	52.8		
standard deviation	± 15.0	-	
Gender Categorical Units: Subjects			
Female	21	21	
Male	24	24	
Ethnicity Units: Subjects			
Hispanic/Latino	2	2	
ot Hispanic/Latino	43	43	
Race Units: Subjects			
White	39	39	
Asian	1	1	
Black (or African American)	3	3	
Other	2	2	
Prior Tyrosine Kinase Inhibitor (TKI) Treatment Units: Subjects			
1 TKI	7	7	
2 TKIs	21	21	
3 TKIs	13	13	
4 TKIs	4	4	
Number of Prior Relapses Units: Subjects			
No relapses	3	3	
1 relapse	25	25	
2 relapses	13	13	

≥ 3 relapses	4	4	
Number of Prior Salvage Regimens Units: Subjects			
No prior regimens	14	14	
1 prior regimen	12	12	
2 prior regimens	11	11	
≥ 3 prior regimens	8	8	
Prior Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Units: Subjects			
Yes	20	20	
No	25	25	
Time From Initial Diagnosis Units: months			
arithmetic mean	27.3		
standard deviation	± 26.1	-	

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 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

Primary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery (CR/CRh*) During the First Two Treatment Cycles

End point title	Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery (CR/CRh*) During the First Two Treatment Cycles[1]

End point description:

Participants were evaluated for efficacy at the end of each treatment cycle via a central bone marrow aspiration and local peripheral blood counts.
Complete remission was defined as meeting all 3 of the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease
• full recovery of peripheral blood counts: platelets > 100,000/µl, and absolute neutrophil count (ANC) > 1000/µl.
Complete remission with partial hematological recovery (CRh*) was defined as meeting all 3 of the following criteria:
• less than or equal to 5% blasts in the bone marrow
• no evidence of disease
• partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.
The analysis was based on the full analysis set which included all participants who received an infusion of blinatumomab. Participants without a post-baseline disease assessment were considered non-responders.

End point type	Primary

End point timeframe:

Approximately 12 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: Statistical analyses were not performed in this single-arm study.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	35.6 (21.9 to 51.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Remission During the First 2 Cycles of Treatment

End point title	Percentage of Participants With Minimal Residual Disease (MRD) Remission During the First 2 Cycles of Treatment

End point description:

Bone marrow samples were evaluated for MRD remission by a central laboratory using bcr-abl fusion gene reverse transcription polymerase chain reaction (RT-PCR).
An MRD response was defined as MRD < 10^-4 measured by PCR.
The analysis was based on the full analysis set. Participants with no post-baseline MRD assessment were considered non-responders.

End point type	Secondary

End point timeframe:

Approximately 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	40.0 (25.7 to 55.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CR or CRh* Response

End point title	Duration of CR or CRh* Response

End point description:

Duration of response was measured for participants in remission (CR/CRh*), and was measured from the time the participant first achieved remission until first documented relapse or death from disease progression. Participants without a documented relapse (hematological or extramedullary) and who did not die were censored at the time of the last bone marrow assessment or the last survival follow-up visit to confirm remission. Participants who died without having reported hematological relapse or without showing any clinical sign of disease progression were censored on their date of death.
The analysis was based on the full analysis set with a CR or CRh* response during the first 2 treatment cycles. "99999" indicates data that could not be estimated.

End point type	Secondary

End point timeframe:

Up to the final analysis cut-off date; median observation time was 16.1 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: months				
median (confidence interval 95%)	6.8 (4.5 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission (CR) During the First Two Treatment Cycles

End point title	Percentage of Participants With Complete Remission (CR) During the First Two Treatment Cycles

End point description:

Participants were evaluated for efficacy at the end of each treatment cycle via a central bone marrow aspiration and local peripheral blood counts.
Complete remission was defined as meeting all 3 of the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease;
• full recovery of peripheral blood counts: platelets > 100,000/µl, and absolute neutrophil count (ANC) > 1000/µl.
The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

End point type	Secondary

End point timeframe:

Approximately 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	31.1 (18.2 to 46.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission With Partial Hematological Recovery (CRh*) During the First Two Treatment Cycles

End point title	Percentage of Participants With Complete Remission With Partial Hematological Recovery (CRh*) During the First Two Treatment Cycles

End point description:

Participants were evaluated for efficacy at the end of each treatment cycle via a central bone marrow aspiration and local peripheral blood counts.
Complete remission with partial hematological recovery (CRh*) was defined as meeting all 3 of the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease;

• partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.
The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

End point type	Secondary

End point timeframe:

Approximately 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	4.4 (0.5 to 15.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) During the First Two Treatment Cycles

End point title	Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) During the First Two Treatment Cycles

End point description:

Complete remission was defined as meeting the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease;
• full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1000/µl.
Complete remission with partial hematological recovery was defined as meeting the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease;
• partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.
Complete remission with incomplete hematologic recovery was defined as meeting all of the following criteria:
• less than or equal to 5% blasts in the bone marrow;
• no evidence of disease;
• incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000/µl.
The analysis was based on the full analysis set. Participants without a post-baseline disease assessment were considered non-responders.

End point type	Secondary

End point timeframe:

Approximately 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)	40.0 (25.7 to 55.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was assessed from the date the participant received the first infusion of blinatumomab until death from any cause or the date of the last follow-up.
Participants still alive at the data cut-off date were censored on the last documented visit date or the date of the last 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:

From first dose of blinatumomab until the final analysis data cut-off date; median observation time was 25.1 months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: months				
median (confidence interval 95%)	9.0 (5.7 to 13.5)			

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 achieved remission (CR/CRh*) during the first 2 cycles of treatment and received an allogeneic HSCT.

End point type	Secondary

End point timeframe:

Up to the final analysis data cut-off date; maximum duration on study was 26.1 months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percentage of participants				
number (confidence interval 95%)	43.8 (19.8 to 70.1)			

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 participants who received an allogeneic HSCT while in remission (CR/CRh*) after 2 cycles of blinatumomab treatment and did not receive any additional antileukemic treatment. 100-day mortality after allogeneic HSCT was calculated relative to the date of allogeneic HSCT.
The 100-day mortality rate after allogeneic HSCT was defined as the percentage of participants having died up to 100 days after allogeneic HSCT estimated using the estimated time to death in percent calculated by Kaplan-Meier methods. Participants 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.

End point type	Secondary

End point timeframe:

From the date of allogeneic HSCT until the final analysis data cut-off date; maximum observation time was 16.9 months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of participants				
number (confidence interval 95%)	25.0 (3.9 to 87.2)			

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

End point description:

Adverse events (AEs) were graded for severity according to the CTCAE version 4.0, where Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.
Treatment-related adverse events (TRAEs) were those assessed by the investigator as possibly related to blinatumomab based on response to the question: Is there a reasonable possibility that the event may have been caused by blinatumomab or other protocol-specified therapies/procedures?

End point type	Secondary

End point timeframe:

From the first dose of blinatumomab until 30 days after the last dose; the median duration of treatment was 53.8 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: participants				
Any adverse event	45			
AE grade ≥ 3	38			
AE grade ≥ 4	18			
Serious adverse events	28			
Leading to discontinuation of blinatumomab	3			
Leading to interruption of blinatumomab	17			
Fatal adverse events	5			
Treatment-related adverse events	41			
Treatment-related AE grade ≥ 3	20			
Treatment-related AE grade ≥ 4	7			
Treatment-related serious adverse events	12			
TRAE leading to discontinuation of blinatumomab	2			
TRAE leading to interruption of blinatumomab	12			
Treatment-related fatal adverse events	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Anti-blinatumomab Antibodies

End point title	Number of Participants Who Developed Anti-blinatumomab Antibodies

End point description:

Anti-blinatumomab binding antibodies were evaluated with a validated blinatumomab anti-drug antibody assay with the electrochemiluminescence detection technology.

End point type	Secondary

End point timeframe:

Day 29 of each treatment period and 30 days after the last dose

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	31[2]			
Units: participants				
number (not applicable)	0			

Notes:

[2] - Participants with available post-baseline antibody results

Statistical analyses

No statistical analyses for this end point

Secondary: Steady State Concentration of Blinatumomab

End point title	Steady State Concentration of Blinatumomab

End point description:

End point type	Secondary

End point timeframe:

Cycle 1, day 8, 6 to 8 hours after the dose step to 28 µg/day, and Cycle 2, day 1, 6 to 8 hours after blinatumomab infusion

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28[3]			
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	452 (± 122.0)			
Cycle 2 (N = 20)	598 (± 102.7)			

Notes:

[3] - Participants with available serum concentration data

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 the last dose; the median duration of treatment was 53.8 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 2 cycles. Participants who achieved a complete remission or complete remission with partial or incomplete hematologic recovery within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
The initial dose was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 and for all subsequent cycles of treatment.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 45 (62.22%)		
number of deaths (all causes)	37		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Product issues			
Device infusion issue			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device malfunction			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest X-ray abnormal			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Depressed level of consciousness				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	4 / 45 (8.89%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				

subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymph node pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoblastosis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders				
Arthritis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Catheter site infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Sepsis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Septic shock			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	7		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 8		
Chest pain subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5		
Chills subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4		
Fatigue subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 6		
Oedema peripheral subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 9		
Pain subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 9		
Pyrexia subjects affected / exposed occurrences (all)	26 / 45 (57.78%) 57		
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 8		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 8		
Epistaxis			

subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Insomnia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	10		
Blood bilirubin increased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Blood calcium decreased			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	7		
Tachycardia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	15 / 45 (33.33%)		
occurrences (all)	24		

Paraesthesia subjects affected / exposed occurrences (all)	6 / 45 (13.33%) 8		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 12 / 45 (26.67%) 24 15 / 45 (33.33%) 23 3 / 45 (6.67%) 5 10 / 45 (22.22%) 21		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 7 / 45 (15.56%) 7 3 / 45 (6.67%) 3 9 / 45 (20.00%) 9 3 / 45 (6.67%) 3 6 / 45 (13.33%) 10 5 / 45 (11.11%) 7		
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Hyperhidrosis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Petechiae			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	8		
Bone pain			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Staphylococcal infection			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Urinary tract infection			

subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	8		
Hypocalcaemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2013	Added an external independent data monitoring committee (DMC) to oversee the interim analysis and assess safety approximately every 6 months provided an adequate enrollment rate.
15 September 2014	- Clarified timing and scope of study procedures - Specified that tyrosine kinase inhibitor therapy within 2 weeks before start of blinatumomab was not exclusionary, but was to be completed before start of treatment - Provided updated information on packaging and presentation of blinatumomab investigational product - Replaced the term "CNS events" with the term "neurologic events" throughout to describe clinically relevant neurologic events associated with introduction to blinatumomab - Provided instructions on blinatumomab overdose reporting (> 10%) as a serious adverse event under the criterion of "other medically important serious event" - Clarified requirements for medical coverage and safety monitoring in the outpatient setting - Provided specific guidance for blinatumomab dose modifications from grade 3 infection events - Clarified criteria for discontinuation of blinatumomab and withdrawal of subjects - Clarified definitions for evaluation of treatment response - Clarified objectives, endpoints, and scope of statistical analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported