Clinical trial results:
A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

Summary

EudraCT number	2013-000536-10
Trial protocol	IT CZ DE BE IE AT GB ES FR GR PL BG
Global end of trial date	14 March 2017

Results information

Result version number	v1 (current)
This version publication date	09 March 2018
First version publication date	09 March 2018

Trial information

Trial identification

Sponsor protocol code	00103311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02013167
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	14 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of blinatumomab on overall survival when compared to standard of care (SOC) chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The regulations or guidelines were applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. All study centers complied with local regulations.
The study and all amendments were reviewed by an independent ethics committee (IEC)/institutional review board (IRB) at each center.

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	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Turkey: 28
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Korea, Republic of: 15

Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Austria: 7
Worldwide total number of subjects	405
EEA total number of subjects	227

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)	357
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 101 centers in 21 countries in Asia, Australia, Europe, and Latin and North America.
The first participant was enrolled on 03 January 2014 and was treated on 06 January 2014. The last participant enrolled on 25 September 2015.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to either blinatumomab or standard of care (SOC) chemotherapy regimens. Randomization was stratified by age (< 35 years vs ≥ 35 years), prior salvage therapy (yes vs no), and prior allogeneic hematopoietic stem cell transplantation (HSCT) (yes vs no) as assessed at the time of consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care Chemotherapy

Arm description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy. Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

Arm type	Active comparator
Investigational medicinal product name	Standard of Care Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

• FLAG (fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor) ± anthracycline-based regimen (e.g. idarubicin 10 mg/m² days 1 & 3; fludarabine 30 mg/m² days 1-5; cytarabine arabinoside 2 g/m² days 1-5). Patients > 60 years: Idarubicin 5 mg/m² day 1 & 3; fludarabine 20 mg/m² day 1-5; cytarabine arabinoside 1 g/m² day 1-5
• HiDAC (high-dose cytarabine arabinoside) - based regimen ≥1 g/m²/day ± anthracycline and/or in combination with other drugs such as native Escherichia coli asparaginase, polyethylene glycol linked to asparaginase (PEG-asparaginase), vinca alkaloids, steroids, etoposide or alkylating agents
• High-dose methotrexate-based regimen (HDMTX; 500 mg/m² to 3 g/m² infused up to 24 hours) in combination with native E. coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.
• Clofarabine as a single agent as recommended in the prescribing information or clofarabine-based regimens with 20 mg/m²/day for up to 5 days.

Arm title	Blinatumomab

Arm description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have

a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	MT103
Other name	Blincyto® AMG 103 MT103
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).

Number of subjects in period 1	Standard of Care Chemotherapy	Blinatumomab
Started	134	271
Received Treatment	109	267
Completed	0	0
Not completed	134	271
Consent withdrawn by subject	15	15
Death	88	178
Lost to follow-up	-	1
Decision by sponsor	31	77

Baseline characteristics

Reporting groups	
Reporting group title	Standard of Care Chemotherapy

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

Reporting group title	Blinatumomab

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

Reporting group values	Standard of Care Chemotherapy	Blinatumomab	Total
Number of subjects	134	271	405
Age Categorical Units: Subjects			
< 35 years	60	124	184
35 to 54 years	33	80	113
55 to 64 years	26	34	60
≥ 65 years	15	33	48
Age Continuous Units: years			
arithmetic mean	41.1	40.8	
standard deviation	± 17.3	± 17.1	-
Gender Categorical Units: Subjects			
Female	57	109	166
Male	77	162	239
Ethnicity Units: Subjects			
Hispanic or Latino	11	26	37
Not Hispanic or Latino	122	243	365
Unknown	1	2	3
Race Units: Subjects			
American Indian or Alaska Native	1	4	5
Asian	9	19	28
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	3	5	8

White	112	228	340
Multiple	0	2	2
Other	8	12	20
Age Stratification at Randomization Units: Subjects			
< 35 years	60	123	183
≥ 35 years	74	148	222
Prior Salvage Therapy Stratification at Randomization Units: Subjects			
Yes	80	164	244
No	54	107	161
Prior Allogeneic Hematopoietic Stem Cell Transplant (HCST) Units: Subjects			
Yes	46	94	140
No	88	177	265
Standard of Care Chemotherapy Regimen Received			
FLAG = fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC = high-dose cytarabine arabinoside			
Units: Subjects			
FLAG ± anthracycline	56	0	56
High-dose methotrexate	30	0	30
Clofarabine	26	0	26
HIDAC	22	0	22
Not applicable	0	271	271

End points

End points reporting groups

Reporting group title	Standard of Care Chemotherapy

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

Reporting group title	Blinatumomab

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

Primary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was calculated from time of randomization until death due to any cause. Participants still alive were censored at the date they were last known to be alive.

End point type	Primary

End point timeframe:

From randomization until end of study (14 March 2017); median observation time was 13.6 months in the SOC group and 15.7 months in the blinatumomab group.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: months				
median (confidence interval 95%)	4.0 (2.9 to 5.5)	7.7 (5.6 to 9.6)		

Statistical analyses

Statistical analysis title	Primary Analysis of Overall Survival

Statistical analysis description:

A 2-sided stratified log-rank test, stratified by the randomization factors, was used to determine if overall survival was superior in the blinatumomab arm compared to SOC chemotherapy arm. A hazard

ratio with a 95% CI was estimated from a stratified Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average event rate and longer survival time for blinatumomab relative to SOC chemotherapy.

Comparison groups	Standard of Care Chemotherapy v Blinatumomab
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052 [1]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1

Notes:

[1] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

Secondary: Percentage of Participants With Complete Remission Within 12 Weeks of Treatment Initiation

End point title	Percentage of Participants With Complete Remission Within 12 Weeks of Treatment Initiation

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 (CR) was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and absolute neutrophil count (ANC) > 1,000/µl. CR must have occurred within 12 weeks of the first dose of therapy.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of participants				
number (confidence interval 95%)	15.7 (10.0 to 23.0)	33.6 (28.0 to 39.5)		

Statistical analyses

Statistical analysis title	PrimaryAnalysis of Complete Remission
Comparison groups	Standard of Care Chemotherapy v Blinatumomab

Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	17.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	26.2

Notes:

[2] - Adjusted for the stratification factors: age (< 35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

Secondary: Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) Within 12 Weeks of Treatment Initiation

End point title	Percentage of Participants With Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi) Within 12 Weeks of Treatment Initiation

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 having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl.
Complete Remission with partial hematological recovery (CRh*) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl.
Complete remission with incomplete hematological recovery (CRi) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000 (but not both).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of participants				
number (confidence interval 95%)	24.6 (17.6 to 32.8)	43.9 (37.9 to 50.0)		

Statistical analyses

Statistical analysis title	Primary Analysis of CR/CRh*/CRi
Comparison groups	Standard of Care Chemotherapy v Blinatumomab
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	28.7

Notes:

[3] - Adjusted for the stratification factors: age (< 35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

Secondary: Event Free Survival (EFS) Rate at 6 Months

End point title	Event Free Survival (EFS) Rate at 6 Months

End point description:

Event free survival was defined as the time from randomization until a documented relapse after achieving CR/CRh*/CRi or death, whichever occurred first. Participants who failed to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation were considered as non-responders and assigned an EFS duration of 1 day. Participants still alive and relapse-free were censored on their last disease assessment date.
A relapse event was any one of the following:
• Hematological relapse: proportion of blasts in bone marrow >5% or blasts in peripheral blood after documented CR or CRh* or CRi
• Progressive disease: An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5,000 cells/µL in the number of circulating leukemia cells
• Extramedullary relapse: extramedullary lesion that is new or increased by 50% from nadir as assessed by Cheson criteria.

The Kaplan-Meier estimate of EFS at 6 months is reported.

End point type	Secondary

End point timeframe:

6 months

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of participants				
number (confidence interval 95%)	13.3 (8.0 to 19.9)	31.4 (25.8 to 37.1)		

Statistical analyses

Statistical analysis title	Primary Analysis of Event-free Survival

Statistical analysis description:

The hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer survival for Blinatumomab relative to SOC Chemotherapy.

Comparison groups	Standard of Care Chemotherapy v Blinatumomab
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.73

Notes:

[4] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

Secondary: Duration of Complete Remission

End point title	Duration of Complete Remission

End point description:

Duration of complete remission, calculated only for participants who achieved a CR, was calculated from the date a CR was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first. Participants who did not have a relapse event were censored on their last disease assessment date.

End point type	Secondary

End point timeframe:

Up to the end of study (14 March 2017); median observation time was 10.8 months in the SOC group and 15.3 months in the blinatumomab group.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[5]	91[6]		
Units: months				
median (confidence interval 95%)	7.8 (2.2 to 19.0)	8.9 (6.0 to 10.7)		

Notes:

[5] - Participants with a best response of complete remission within 12 weeks of treatment initiation.

[6] - Participants with a best response of complete remission within 12 weeks of treatment initiation.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological

Recovery (CR/CRh*/CRi)

End point title	Duration of Complete Remission/Complete Remission With Partial Hematological Recovery/Complete Remission With Incomplete Hematological Recovery (CR/CRh*/CRi)

End point description:

Duration of CR/CRh*/CRi, calculated only for participants who achieved a CR/CRh*/CRi, was calculated from the date a CR/CRh*/CRi was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first. Participants who did not have a relapse event were censored on their last disease assessment date.

End point type	Secondary

End point timeframe:

Up to the end of study (14 March 2017); median observation time was 10.8 months in the SOC group and 15.3 months in the blinatumomab group.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[7]	119[8]		
Units: months				
median (confidence interval 95%)	5.4 (1.8 to 19.0)	8.8 (6.0 to 10.2)		

Notes:

[7] - Participants with a best response of CR/CRh*/CRi within 12 weeks of treatment initiation.

[8] - Participants with a best response of CR/CRh*/CRi within 12 weeks of treatment initiation.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Minimal Residual Disease (MRD) Within 12 Weeks of Treatment Initiation

End point title	Percentage of Participants With Minimal Residual Disease (MRD) Within 12 Weeks of Treatment Initiation

End point description:

Bone marrow samples were evaluated for MRD remission by a central laboratory. MRD remission was defined as the occurrence of an MRD level below 10^-4 measured by quantitative reverse transcription polymerase chain reaction (PCR) or flow cytometry.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of participants				
number (confidence interval 95%)	14.2 (8.8 to 21.3)	29.9 (24.5 to 35.7)		

Statistical analyses

Statistical analysis title	Primary Analysis of MRD Response
Comparison groups	Standard of Care Chemotherapy v Blinatumomab
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	23.7

Notes:

[9] - Stratified by age (<35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)

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

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

End point description:

End point type	Secondary

End point timeframe:

Up to the end of study; maximum time on study was 26 months.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	271		
Units: percentage of participants				
number (confidence interval 95%)	23.9 (16.9 to 32.0)	24.7 (19.7 to 30.3)		

Statistical analyses

Statistical analysis title	Analysis of Postbaseline alloHSCT
Comparison groups	Standard of Care Chemotherapy v Blinatumomab
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	9.7

Notes:

[10] - Stratified by age (< 35 years; ≥ 35 years), prior salvage therapy (yes vs. no), and prior allogeneic HSCT (yes vs. no).

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 first dose of protocol-specified therapy until 30 days after the last dose; median duration of treatment was 5 days in the SOC group and 70 days in the blinatumomab group.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[11]	267[12]		
Units: participants				
Any adverse event	108	263		
AE grade ≥ 2	106	256		
AE grade ≥ 3	100	231		
AE grade ≥ 4	67	135		
Serious adverse events	49	168		
AEs leading to interruption of study drug	6	72		
AEs leading to discontinuation of study drug	10	42		
Life-threatening adverse events	27	56		
Fatal adverse events	20	52		

Treatment-related adverse events	92	214		
Treatment-related AE grade ≥ 2	89	195		
Treatment-related AE grade ≥ 3	78	144		
Treatment-related AE grade ≥ 4	51	59		
Serious treatment-related adverse events	34	76		
TRAEs leading to interruption of study drug	6	55		
TRAEs leading to discontinuation of study drug	8	23		
Treatment-related life-threatening adverse events	17	21		
Treatment-related fatal adverse events	8	8		

Notes:

[11] - Partipants who received protocol-specified therapy

[12] - Partipants who received protocol-specified therapy

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 achieved a best response of CR/CRh*CTi within 12 weeks of treatment initiation, who received an allogeneic HSCT and did not receive any additional anticancer treatment before the transplant. 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.
"99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

100 days, from the date of allogeneic HSCT until the end of study

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[13]	42[14]		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (-99999 to 99999)	12.3 (5.3 to 27.1)		

Notes:

[13] - Subjects with CR/CRh*/CRi within 12 weeks of treatment & no other anticancer therapy before alloHSCT

[14] - Subjects with CR/CRh*/CRi within 12 weeks of treatment & no other anticancer therapy before alloHSCT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-blinatumomab Antibodies

End point title	Number of Participants With Anti-blinatumomab Antibodies[15]

End point description:

Anti-blinatumomab binding antibodies were evaluated using a validated electrochemiluminescence (ECL)-based assay (binding assay). Samples positive for binding were analyzed using a cell-based bioassay to determine if the detected antibodies had neutralizing properties (neutralizing assay).

End point type	Secondary

End point timeframe:

Samples were collected on day 29 at the end of cycle 2 and 30 days after the last dose of blinatumomab (median duration of treatment was 70 days).

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was only conducted in participants who received blinatumomab.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	171[16]			
Units: participants				
Binding antibody positive	5			
Neutralizing antibody positive	3			

Notes:

[16] - Participants who received blinatumomab with available post-baseline antibody data.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to a 10-point Decrease From Baseline in Global Health Status and Quality of Life or Death

End point title	Time to a 10-point Decrease From Baseline in Global Health Status and Quality of Life or Death

End point description:

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is a 30-item questionnaire that assesses the health related quality of life of cancer patients. The EORTC QLQ-C30 consists of a global health status/quality of life (QoL) scale, 5 functional scales, 3 symptom scales, and 6 single items.
The global health/QoL scale consists of 2 questions that ask participants to rate their overall health and overall quality of life durig the past week on a scale from 1 (very poor) to 7 (excellent). The scale score was derived as the sum of each score and transformed to a scale from 0 to 100 where higher scores represent a high QoL.
Time to a ≥10-point decrease from baseline GHS/QoL or death, whichever came first, was calculated from baseline. Participants still alive and without a 10-point decrease in GHS/QoL EORTC QLQ-C30 were censored on their last EORTC QLQ-C30 assessment date.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 04 January 2016; EORTC QLQ-C30 was assessed on day 1, 8, 15, and 29 during cycle 1; days 1, 15, and 29 in cycle 2 and each consolidation cycle, and 30-days following the last dose of drug treatment.

End point values	Standard of Care Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95[17]	247[18]		
Units: months				
median (confidence interval 95%)	1.0 (0.5 to 1.5)	1.7 (1.1 to 3.6)		

Notes:

[17] - Subjects with non-missing baseline and at least 1 postbaseline result of any QLQ-C30 scales/item

[18] - Subjects with non-missing baseline and at least 1 postbaseline result of any QLQ-C30 scales/item

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of protocol-specified therapy until 30 days after the last dose; median duration of treatment was 5 days in the SOC group and 70 days in the blinatumomab group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Standard of Care Chemotherapy

Reporting group description:

Participants received one of four prespecified, investigator-chosen chemotherapy regimens for 2 induction cycles. Participants who achieved a bone marrow response, CR/CRh*/CRi within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of SOC chemotherapy.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive SOC therapy for an additional 12 months.

Reporting group title	Blinatumomab

Reporting group description:

Participants received blinatumomab by continuous intravenous infusion (CIVI) over 4 weeks followed by a 2 week treatment-free interval for 2 induction cycles. Participants who achieved a bone marrow response, complete remission, or complete remission with partial or incomplete hematologic recovery (CR/CRh*/CRi) within 2 induction cycles of treatment could receive up to 3 additional consolidation cycles of blinatumomab.
Participants who received 2 induction and up to 3 consolidation cycles of therapy and continued to have a bone marrow response or CR/CRh*/CRi could continue to receive blinatumomab for an additional 12 months (4 cycles), where 1 cycle consisted of 4 weeks of CIVI followed by an 8-week treatment-free period.
The initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment, increased to 28 µg/day starting on day 8 through day 29 and for all subsequent cycles.

Serious adverse events	Standard of Care Chemotherapy	Blinatumomab	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 109 (44.95%)	168 / 267 (62.92%)	
number of deaths (all causes)	78	180	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chloroma			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemic infiltration extramedullary			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukaemic infiltration pulmonary			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic occlusion			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 109 (1.83%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Discomfort			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperthermia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 109 (0.92%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Oedema peripheral			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 109 (0.92%)	16 / 267 (5.99%)	
occurrences causally related to treatment / all	1 / 1	6 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 109 (0.00%)	7 / 267 (2.62%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Dyspnoea			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			

subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 109 (0.92%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 109 (1.83%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	1 / 1	
Stridor			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mental status changes			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CSF cell count abnormal			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 109 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle fracture			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 109 (0.00%)	8 / 267 (3.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pericardial effusion			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Aphasia			
subjects affected / exposed	0 / 109 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 109 (0.00%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 109 (1.83%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemianopia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intention tremor			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	12 / 109 (11.01%)	24 / 267 (8.99%)	
occurrences causally related to treatment / all	11 / 12	12 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	0 / 109 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperleukocytosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukocytosis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 109 (1.83%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 109 (0.92%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 109 (1.83%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Hydronephrosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 109 (0.00%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess fungal			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 109 (2.75%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bacterial sepsis			
subjects affected / exposed	2 / 109 (1.83%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	2 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Brain abscess			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 109 (0.92%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
Catheter site infection			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system abscess			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter sepsis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 109 (0.92%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	2 / 109 (1.83%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis enteroviral			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			

subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fusarium infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatosplenic candidiasis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection in an immunocompromised host			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection fungal			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mastoiditis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Muscle abscess			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 109 (0.92%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Osteomyelitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 109 (1.83%)	10 / 267 (3.75%)	
occurrences causally related to treatment / all	1 / 2	3 / 10	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	2 / 109 (1.83%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 109 (0.92%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			

subjects affected / exposed	1 / 109 (0.92%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary mycosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 109 (6.42%)	13 / 267 (4.87%)	
occurrences causally related to treatment / all	5 / 9	3 / 13	
deaths causally related to treatment / all	2 / 4	2 / 8	
Sepsis syndrome			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	3 / 109 (2.75%)	8 / 267 (3.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 6	
Sinusitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 109 (0.92%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			

subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	0 / 109 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 109 (0.92%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 109 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard of Care Chemotherapy	Blinatumomab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 109 (97.25%)	251 / 267 (94.01%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 109 (8.26%)	18 / 267 (6.74%)	
occurrences (all)	9	20	
Hypotension			
subjects affected / exposed	11 / 109 (10.09%)	33 / 267 (12.36%)	
occurrences (all)	16	38	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 109 (10.09%)	20 / 267 (7.49%)	
occurrences (all)	15	32	
Chest pain			

subjects affected / exposed	6 / 109 (5.50%)	6 / 267 (2.25%)	
occurrences (all)	6	7	
Chills			
subjects affected / exposed	12 / 109 (11.01%)	20 / 267 (7.49%)	
occurrences (all)	16	24	
Fatigue			
subjects affected / exposed	14 / 109 (12.84%)	36 / 267 (13.48%)	
occurrences (all)	15	52	
Mucosal inflammation			
subjects affected / exposed	14 / 109 (12.84%)	9 / 267 (3.37%)	
occurrences (all)	15	10	
Oedema peripheral			
subjects affected / exposed	16 / 109 (14.68%)	39 / 267 (14.61%)	
occurrences (all)	20	52	
Pain			
subjects affected / exposed	6 / 109 (5.50%)	16 / 267 (5.99%)	
occurrences (all)	6	20	
Pyrexia			
subjects affected / exposed	48 / 109 (44.04%)	153 / 267 (57.30%)	
occurrences (all)	73	326	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 109 (0.00%)	35 / 267 (13.11%)	
occurrences (all)	0	42	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 109 (0.92%)	19 / 267 (7.12%)	
occurrences (all)	1	31	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 109 (5.50%)	42 / 267 (15.73%)	
occurrences (all)	7	52	
Dyspnoea			
subjects affected / exposed	8 / 109 (7.34%)	16 / 267 (5.99%)	
occurrences (all)	9	17	
Epistaxis			

subjects affected / exposed	9 / 109 (8.26%)	16 / 267 (5.99%)	
occurrences (all)	10	17	
Oropharyngeal pain			
subjects affected / exposed	7 / 109 (6.42%)	15 / 267 (5.62%)	
occurrences (all)	8	16	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 109 (5.50%)	14 / 267 (5.24%)	
occurrences (all)	6	14	
Insomnia			
subjects affected / exposed	10 / 109 (9.17%)	31 / 267 (11.61%)	
occurrences (all)	12	44	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 109 (10.09%)	24 / 267 (8.99%)	
occurrences (all)	35	47	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 109 (9.17%)	15 / 267 (5.62%)	
occurrences (all)	24	31	
Blood bilirubin increased			
subjects affected / exposed	9 / 109 (8.26%)	10 / 267 (3.75%)	
occurrences (all)	23	19	
Platelet count decreased			
subjects affected / exposed	13 / 109 (11.93%)	18 / 267 (6.74%)	
occurrences (all)	72	60	
Neutrophil count decreased			
subjects affected / exposed	11 / 109 (10.09%)	10 / 267 (3.75%)	
occurrences (all)	28	23	
White blood cell count decreased			
subjects affected / exposed	6 / 109 (5.50%)	14 / 267 (5.24%)	
occurrences (all)	12	38	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	6 / 109 (5.50%)	15 / 267 (5.62%)	
occurrences (all)	8	19	
Tachycardia			

subjects affected / exposed	10 / 109 (9.17%)	18 / 267 (6.74%)	
occurrences (all)	10	30	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 109 (7.34%)	18 / 267 (6.74%)	
occurrences (all)	8	20	
Headache			
subjects affected / exposed	32 / 109 (29.36%)	79 / 267 (29.59%)	
occurrences (all)	39	106	
Somnolence			
subjects affected / exposed	1 / 109 (0.92%)	14 / 267 (5.24%)	
occurrences (all)	1	20	
Tremor			
subjects affected / exposed	0 / 109 (0.00%)	26 / 267 (9.74%)	
occurrences (all)	0	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	46 / 109 (42.20%)	68 / 267 (25.47%)	
occurrences (all)	144	222	
Febrile neutropenia			
subjects affected / exposed	36 / 109 (33.03%)	48 / 267 (17.98%)	
occurrences (all)	42	55	
Neutropenia			
subjects affected / exposed	31 / 109 (28.44%)	51 / 267 (19.10%)	
occurrences (all)	50	108	
Thrombocytopenia			
subjects affected / exposed	32 / 109 (29.36%)	48 / 267 (17.98%)	
occurrences (all)	108	114	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 109 (17.43%)	16 / 267 (5.99%)	
occurrences (all)	25	19	
Constipation			
subjects affected / exposed	28 / 109 (25.69%)	35 / 267 (13.11%)	
occurrences (all)	34	46	
Diarrhoea			

subjects affected / exposed	38 / 109 (34.86%)	59 / 267 (22.10%)	
occurrences (all)	49	75	
Dyspepsia			
subjects affected / exposed	7 / 109 (6.42%)	10 / 267 (3.75%)	
occurrences (all)	7	11	
Haemorrhoids			
subjects affected / exposed	7 / 109 (6.42%)	7 / 267 (2.62%)	
occurrences (all)	7	7	
Nausea			
subjects affected / exposed	46 / 109 (42.20%)	51 / 267 (19.10%)	
occurrences (all)	69	73	
Proctalgia			
subjects affected / exposed	7 / 109 (6.42%)	2 / 267 (0.75%)	
occurrences (all)	8	2	
Stomatitis			
subjects affected / exposed	14 / 109 (12.84%)	17 / 267 (6.37%)	
occurrences (all)	16	18	
Vomiting			
subjects affected / exposed	26 / 109 (23.85%)	33 / 267 (12.36%)	
occurrences (all)	40	37	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	6 / 109 (5.50%)	7 / 267 (2.62%)	
occurrences (all)	6	7	
Rash			
subjects affected / exposed	13 / 109 (11.93%)	20 / 267 (7.49%)	
occurrences (all)	15	24	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 109 (5.50%)	8 / 267 (3.00%)	
occurrences (all)	8	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 109 (4.59%)	17 / 267 (6.37%)	
occurrences (all)	5	20	
Back pain			

subjects affected / exposed	10 / 109 (9.17%)	34 / 267 (12.73%)	
occurrences (all)	14	40	
Myalgia			
subjects affected / exposed	6 / 109 (5.50%)	19 / 267 (7.12%)	
occurrences (all)	7	21	
Bone pain			
subjects affected / exposed	8 / 109 (7.34%)	29 / 267 (10.86%)	
occurrences (all)	9	42	
Pain in extremity			
subjects affected / exposed	8 / 109 (7.34%)	25 / 267 (9.36%)	
occurrences (all)	8	39	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	6 / 109 (5.50%)	3 / 267 (1.12%)	
occurrences (all)	7	4	
Device related infection			
subjects affected / exposed	5 / 109 (4.59%)	14 / 267 (5.24%)	
occurrences (all)	5	17	
Oral herpes			
subjects affected / exposed	9 / 109 (8.26%)	15 / 267 (5.62%)	
occurrences (all)	10	16	
Pneumonia			
subjects affected / exposed	14 / 109 (12.84%)	7 / 267 (2.62%)	
occurrences (all)	16	7	
Sinusitis			
subjects affected / exposed	6 / 109 (5.50%)	6 / 267 (2.25%)	
occurrences (all)	6	7	
Upper respiratory tract infection			
subjects affected / exposed	1 / 109 (0.92%)	20 / 267 (7.49%)	
occurrences (all)	1	29	
Urinary tract infection			
subjects affected / exposed	2 / 109 (1.83%)	15 / 267 (5.62%)	
occurrences (all)	2	20	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 109 (0.00%)	15 / 267 (5.62%)	
occurrences (all)	0	17	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 109 (13.76%)	20 / 267 (7.49%)	
occurrences (all)	15	24	
Hyperglycaemia			
subjects affected / exposed	9 / 109 (8.26%)	21 / 267 (7.87%)	
occurrences (all)	15	29	
Hypoalbuminaemia			
subjects affected / exposed	11 / 109 (10.09%)	14 / 267 (5.24%)	
occurrences (all)	14	27	
Hypomagnesaemia			
subjects affected / exposed	18 / 109 (16.51%)	28 / 267 (10.49%)	
occurrences (all)	20	37	
Hypokalaemia			
subjects affected / exposed	30 / 109 (27.52%)	46 / 267 (17.23%)	
occurrences (all)	43	78	
Hypocalcaemia			
subjects affected / exposed	10 / 109 (9.17%)	12 / 267 (4.49%)	
occurrences (all)	14	14	
Hypophosphataemia			
subjects affected / exposed	6 / 109 (5.50%)	12 / 267 (4.49%)	
occurrences (all)	6	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2014	- Clarify timing, scope, and applicability of study procedures to treatment arms - Clarify criteria for discontinuation and withdrawal of blinatumomab-treated subjects, clarify terms and definitions used in protocol, clarify secondary endpoints and analyses, clarify study participation, clarify requirements for medical coverage and safety monitoring in an outpatient setting Increase the number of study centers globally - Provide updated information on packaging, presentation, dose modifications, and overdose (> 10%) of blinatumomab - Provide dose modification guidance for SOC chemotherapy regimen - Update Amgen publication policy guidelines and team contact information to facilitate the enrollment of subjects, entry criteria were modified to allow for the screening of serum for potential drugs of abuse in subjects receiving hemodialysis with no urine output and to remove the requirement of "no detectable viral RNA" for subjects known to have had hepatitis C
10 March 2015	- Clarify protocol-required procedures - Updates made to align with current Amgen protocol templates
09 September 2015	- Update pregnancy, lactation, and contraception requirements to align with blinatumomab core risk and discomfort language - Provide clarification on study design, and procedures for bone marrow aspirates, vital signs, and long-term follow-up
20 April 2016	- Update contraception timeframes to align with blinatumomab core risk and discomfort language - Update sponsor contact information and definition of adverse events to align with current protocol template language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported