Clinical trial results:
A Randomized, Open-label, Controlled Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Subjects With High-risk First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2014-002476-92
Trial protocol	DE CZ BE IT SE PT DK AT GB PL ES FR NL Outside EU/EEA GR NO HU RO
Global end of trial date	05 December 2022
Results information	
Result version number	v1
This version publication date	19 May 2023
First version publication date	19 May 2023

Trial information

Trial identification	
Sponsor protocol code	20120215
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02393859
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.com
Scientific contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000574-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate event-free survival (EFS) after blinatumomab when compared to standard of care (SOC) chemotherapy.

Protection of trial subjects:

The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice and applicable national or regional regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 7
Worldwide total number of subjects	111
EEA total number of subjects	97

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)	3
Children (2-11 years)	88
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 48 centers across 13 countries (Europe, Australia, Israel). The first participant was enrolled on 10 November 2015. The last participant enrolled on 30 August 2019. The primary completion date was 17 July 2019 and the study completion date was 05 December 2022.

Pre-assignment

Screening details:

After a 3-week screening period, participants were enrolled and randomized 1:1 into 1 of 2 treatment groups: High Risk Consolidation 3 (HC3) chemotherapy or blinatumomab. Randomization was stratified by age and bone marrow/minimal residual disease (MRD) status.

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	HC3 Chemotherapy

Arm description:

One week of treatment with HC3 followed by 3 weeks of no treatment. The standard intensive consolidation chemotherapy course HC3 includes dexamethasone (10 mg/m^2/day intravenous [IV] on Days 1-6), vincrisitne (1.5 mg/m^2/day IV on Days 1 and 6), daunorubicin (30 mg/m^2 IV over 24 hours on Day 5), methotrexate (1 g/m^2 IV over 36 hours on Day 1), ifosfamide (800 mg/m^2 IV for 1 hour on Days 2-4), and pegylated [PEG]-asparaginase (1000 U/m^2 IV for 2 hours or intramuscularly [IM] on Day 6) or, if allergic, erwinia-asparaginase (20,000 units/m^2 IV or IM every 48 hours for a total of 6 doses).

Arm type	Active comparator
Investigational medicinal product name	SOC chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Intramuscular use

Dosage and administration details:

The standard intensive consolidation chemotherapy course HC3 included dexamethasone (10 mg/m^2/day IV on Days 1-6), vincrisitne (1.5 mg/m^2/day IV on Days 1 and 6), daunorubicin (30 mg/m^2 IV over 24 hours on Day 5), methotrexate (1 g/m^2 IV over 36 hours on Day 1), ifosfamide (800 mg/m^2 IV for 1 hour on Days 2-4), and PEG-asparaginase (1000 U/m^2 IV for 2 hours or IM on Day 6) or, if allergic, erwinia-asparaginase (20,000 units/m^2 IV or IM every 48 hours for a total of 6 doses).

Arm title	Blinatumomab

Arm description:

One 4-week cycle of blinatumomab
15 µg/m^2/day as a continuous intravenous infusion (CIVI).

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab was administered as CIVI at a constant daily flow rate of 15 µg/m^2/day over 4 weeks

(1 cycle).

Number of subjects in period 1	HC3 Chemotherapy	Blinatumomab
Started	57	54
Participants Treated	52	54
Primary analysis population	54	54
Final analysis population	57	54
Completed	16	33
Not completed	41	21
Adverse event, serious fatal	27	10
Consent withdrawn by subject	11	6
Decision by Sponsor	2	4
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	HC3 Chemotherapy
Reporting group description:	
One week of treatment with HC3 followed by 3 weeks of no treatment. The standard intensive consolidation chemotherapy course HC3 includes dexamethasone (10 mg/m^2/day intravenous [IV] on Days 1-6), vincrisitne (1.5 mg/m^2/day IV on Days 1 and 6), daunorubicin (30 mg/m^2 IV over 24 hours on Day 5), methotrexate (1 g/m^2 IV over 36 hours on Day 1), ifosfamide (800 mg/m^2 IV for 1 hour on Days 2-4), and pegylated [PEG]-asparaginase (1000 U/m^2 IV for 2 hours or intramuscularly [IM] on Day 6) or, if allergic, erwinia-asparaginase (20,000 units/m^2 IV or IM every 48 hours for a total of 6 doses).	
Reporting group title	Blinatumomab
Reporting group description:	
One 4-week cycle of blinatumomab 15 µg/m^2/day as a continuous intravenous infusion (CIVI).	

Reporting group values	HC3 Chemotherapy	Blinatumomab	Total
Number of subjects	57	54	111
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	6.6	7.3	
standard deviation	± 4.3	± 4.4	-
Gender Categorical Units: Subjects			
Female	34	24	58
Male	23	30	53
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	54	53	107
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	46	50	96
Other, Not Specified	5	3	8
Asian	3	1	4
Black or African American	3	0	3
Stratification Factor: Marrow/Minimal Residual Disease (MRD)			
M1: representative bone marrow aspirate or biopsy with blasts < 5%, with satisfactory cellularity and with regenerating hematopoiesis; M2: Representative bone marrow aspirate or biopsy with ≥ 5% and < 25% blasts; MRD=minimal residual disease levels ≥ 10^-3 or < 10^-3, by polymerase chain reaction (PCR) or flow cytometry.			
Units: Subjects			
M1 Marrow + MRD level ≥ 10^-3	17	15	32
M1 Marrow + MRD level < 10^-3	36	35	71
M2 Marrow	4	4	8
Stratification Factor: Age Category			

Units: Subjects			
1 to 9 years	41	39	80
Other (< 1 year and > 9 years)	16	15	31

End points

End points reporting groups

Reporting group title	HC3 Chemotherapy

Reporting group description:

One week of treatment with HC3 followed by 3 weeks of no treatment. The standard intensive consolidation chemotherapy course HC3 includes dexamethasone (10 mg/m^2/day intravenous [IV] on Days 1-6), vincrisitne (1.5 mg/m^2/day IV on Days 1 and 6), daunorubicin (30 mg/m^2 IV over 24 hours on Day 5), methotrexate (1 g/m^2 IV over 36 hours on Day 1), ifosfamide (800 mg/m^2 IV for 1 hour on Days 2-4), and pegylated [PEG]-asparaginase (1000 U/m^2 IV for 2 hours or intramuscularly [IM] on Day 6) or, if allergic, erwinia-asparaginase (20,000 units/m^2 IV or IM every 48 hours for a total of 6 doses).

Reporting group title	Blinatumomab

Reporting group description:

One 4-week cycle of blinatumomab
15 µg/m^2/day as a continuous intravenous infusion (CIVI).

Subject analysis set title	HC3 Chemotherapy (Primary Analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the full analysis set at the primary completion date randomized to HC3 chemotherapy. The standard intensive consolidation chemotherapy course HC3 includes dexamethasone (10 mg/m^2/day intravenous [IV] on Days 1-6), vincrisitne (1.5 mg/m^2/day IV on Days 1 and 6), daunorubicin (30 mg/m^2 IV over 24 hours on Day 5), methotrexate (1 g/m^2 IV over 36 hours on Day 1), ifosfamide (800 mg/m^2 IV for 1 hour on Days 2-4), and pegylated [PEG]-asparaginase (1000 U/m^2 IV for 2 hours or intramuscularly [IM] on Day 6) or, if allergic, erwinia-asparaginase (20,000 units/m^2 IV or IM every 48 hours for a total of 6 doses).

Subject analysis set title	Blinatumomab (Primary Analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants in the full analysis set at the primary completion date randomized to blinatumomab

Primary: Kaplan Meier Estimate: EFS (Primary Analysis)

End point title	Kaplan Meier Estimate: EFS (Primary Analysis)

End point description:

EFS is calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a complete remission (CR), failure to achieve a CR at the end of treatment, second malignancy, or death due to any cause, whichever occurs first. Participants who failed to achieve a CR following treatment with investigational product (IP) or who died before the disease assessment at the end of treatment were considered treatment failures and assigned an EFS duration of 1 day. Participants still alive and event-free were censored on their last disease assessment date. Participants were said to be in CR when they had the following: M1 marrow, peripheral blood without blasts, absence of extramedullary leukemic involvement. Full analysis set (FAS): randomized participants analyzed according to their randomized treatment assignment, regardless of the treatment received (primary analysis population).
99999 = data was not estimable.

End point type	Primary

End point timeframe:

As of the primary analysis data cutoff date (17 July 2019), overall median follow-up time for EFS was 22.4 months.

End point values	HC3 Chemotherapy (Primary Analysis)	Blinatumomab (Primary Analysis)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	54		
Units: months				
median (confidence interval 95%)	7.4 (4.5 to 12.7)	99999 (12.0 to 99999)		

Statistical analyses

Statistical analysis title	Stratified log-rank test
Comparison groups	HC3 Chemotherapy (Primary Analysis) v Blinatumomab (Primary Analysis)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Stratified log-rank test

Notes:

[1] - Normal score = -11.54 (A normal score < 0 indicates fewer than expected events for blinatumomab relative to HC3 and therefore a longer event-free survival time.)
[2] - Stratification factors were: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^-3 vs M1 with MRD level ≥ 10^-3 vs M2).

Statistical analysis title	Unstratified log-rank test
Comparison groups	HC3 Chemotherapy (Primary Analysis) v Blinatumomab (Primary Analysis)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.001
Method	Unstratified log-rank test

Notes:

[3] - Normal score: -11.16. (A normal score < 0 indicates fewer than expected events for blinatumomab relative to HC3 and therefore a longer event-free survival time.)

Statistical analysis title	Stratified hazard ratio (HR)

Statistical analysis description:

Cox proportional hazard model. Stratification factors were: age and marrow/MRD status. (HR < 1.0 indicates a lower average event rate and a longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy (Primary Analysis) v Blinatumomab (Primary Analysis)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.66

Statistical analysis title	Unstratified HR

Statistical analysis description:

Cox proportional hazard model. (HR < 1.0 indicates a lower average event rate and a longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy (Primary Analysis) v Blinatumomab (Primary Analysis)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Unstratified HR
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.7

Statistical analysis title	Stratified HR with time-dependent covariate

Statistical analysis description:

Cox proportional hazard model including time from randomization to allogeneic hematopoietic stem cell transplant. Stratification factors: age and marrow/MRD status. (HR <1.0=lower average event rate and longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy (Primary Analysis) v Blinatumomab (Primary Analysis)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.64

Primary: Kaplan Meier Estimate: EFS (Final Analysis)

End point title	Kaplan Meier Estimate: EFS (Final Analysis)

End point description:

EFS is calculated from the time of randomization until the date of relapse or M2 marrow after having achieved a CR, failure to achieve a CR at the end of treatment, second malignancy, or death due to any

cause, whichever occurs first. Participants who failed to achieve a CR following treatment with IP or who died before the disease assessment at the end of treatment were considered treatment failures and assigned an EFS duration of 1 day. Participants still alive and event-free were censored on their last disease assessment date. Participants were said to be in CR when they had the following: M1 marrow, peripheral blood without blasts, absence of extramedullary leukemic involvement. FAS: randomized participants analyzed according to their randomized treatment assignment, regardless of the treatment received (final analysis population).
99999 = data was not estimable.

End point type	Primary

End point timeframe:

At final analysis, overall median follow-up time for EFS was 51.9 months.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: months				
median (confidence interval 95%)	7.8 (5.8 to 13.4)	99999 (24.8 to 99999)		

Statistical analyses

Statistical analysis title	Stratified log-rank test
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001 [5]
Method	Stratified log-rank test

Notes:

[4] - Normal score: -13.90 (A normal score < 0 indicates fewer than expected events for blinatumomab relative to HC3 and therefore a longer event-free survival time.)
[5] - Stratification factors were: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^-3 vs M1 with MRD level ≥ 10^-3 vs M2).

Statistical analysis title	Unstratified log-rank test
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	Unstratified log-rank test

Notes:

[6] - Normal score: -13.61 (A normal score < 0 indicates fewer than expected events for Blinatumomab relative to HC3 and therefore a longer event free survival time.)

Statistical analysis title	Stratified HR with time-dependent covariate

Statistical analysis description:

Cox proportional hazard model including time from randomization to allogeneic hematopoietic stem cell transplant. Stratification factors: age and marrow/MRD status. (HR <1.0=lower average event rate and longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.59

Statistical analysis title	Unstratified HR

Statistical analysis description:

Cox proportional hazard model. (HR < 1.0 indicates a lower average event rate and a longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Unstratified HR
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.65

Statistical analysis title	Stratified HR

Statistical analysis description:

Cox proportional hazard model. Stratification factors were: age and marrow/MRD status. (HR < 1.0 indicates a lower average event rate and a longer EFS for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.61

Secondary: Kaplan Meier Estimate: Overall Survival (OS)

End point title	Kaplan Meier Estimate: Overall Survival (OS)

End point description:

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.
FAS: randomized participants analyzed according to their randomized treatment assignment, regardless of the treatment received.
99999 = data was not estimable.

End point type	Secondary

End point timeframe:

At final analysis, overall median follow-up time for OS was 55.2 months.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: months				
median (confidence interval 95%)	25.6 (17.5 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Stratified log-rank test
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.001 [8]
Method	Stratified log-rank test

Notes:

[7] - Normal score: -10.14 (A normal score < 0 indicates fewer than expected events for blinatumomab relative to HC3 and therefore a longer event-free survival time.)
[8] - Stratification factors were: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^-3 vs M1 with MRD level ≥ 10^-3 vs M2).

Statistical analysis title	Unstratified HR

Statistical analysis description:

Cox proportional hazard model. (HR < 1.0 indicates a lower average event rate and a longer survival for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Unstratified HR
Point estimate	0.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.65

Statistical analysis title	Stratified HR

Statistical analysis description:

Cox proportional hazard model. Stratification factors were: age and marrow/MRD status. (HR < 1.0 indicates a lower average event rate and a longer survival for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.66

Statistical analysis title	Unstratified log-rank test
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001
Method	Unstratified log-rank test

Notes:

[9] - Normal score: -10.32 (A normal score < 0 indicates fewer than expected events for blinatumomab relative to HC3 and therefore a longer event-free survival time.)

Secondary: Percentage of Participants With an MRD Response Within 29 Days of Treatment Initiation

End point title	Percentage of Participants With an MRD Response Within 29 Days of Treatment Initiation

End point description:

At the end of the first treatment cycle (Day 29) a bone marrow aspiration/biopsy was performed and evaluated by the central MRD laboratory. MRD response was defined as MRD level < 10^-4, by polymerase chain reaction (PCR) or flow cytometry, at the end of treatment (Cycle 1 Day 29) with study drug. Participants who were part of the MRD Evaluable Set and were missing the end of treatment (Cycle 1 Day 29) assessment for a respective MRD assessment method were considered not to have achieved a response. MRD Evaluable Set: participants for whom an evaluable baseline MRD marker can be found with either of the MRD assessment methods of PCR or flow cytometry.

End point type	Secondary

End point timeframe:

Up to End of Treatment (Cycle 1, Day 29)

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	54		
Units: percentage of participants				
number (confidence interval 95%)				
MRD Response by PCR (N=49; 49)	53.1 (38.3 to 67.5)	93.9 (83.1 to 98.7)		
MRD Response by Flow Cytometry (N=55; 54)	60.0 (45.9 to 73.0)	92.6 (82.1 to 97.9)		

Statistical analyses

Statistical analysis title	MRD response by flow cytometry
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10-3 vs M1 with MRD level ≥ 10-3 vs M2).

Statistical analysis title	MRD response by PCR
Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[11] - Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (1 to 9 years vs other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level < 10^-3 vs M1 with MRD level ≥ 10^-3 vs M2).

Secondary: Cumulative Incidence of Relapse (CIR)

End point title	Cumulative Incidence of Relapse (CIR)

End point description:

CIR estimate, presented as median months to relapse, calculated from date of achievement of first CR, using the cumulative incidence method (Fine JP, Gray RJ:1999). Deaths prior to relapse not considered related to an otherwise undocumented relapse were treated as a competing risk. Participants still alive without a date of relapse were censored at the time of last follow-up. Relapse=presence of ≥1 of the following: isolated bone marrow relapse (M3 marrow [representative bone marrow aspirate or biopsy with ≥25% blasts] in the absence of extramedullary involvement), combined bone marrow relapse (M2 or M3 marrow and ≥1 extramedullary manifestation of acute lymphoblastic leukemia), central nervous system extramedullary relapse, testicular extramedullary relapse, extramedullary relapse at other sites. FAS: randomized participants analyzed according to their randomized treatment assignment, regardless of the treatment received. 99999 = data was not estimable.

End point type	Secondary

End point timeframe:

At final analysis, the overall maximum follow-up time was 82.0 months.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: months				
median (confidence interval 95%)	7.9 (5.8 to 18.6)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Stratified HR

Statistical analysis description:

The subdistribution HR estimates are obtained from the subdistribution Cox model. (HR < 1.0 indicates a lower average event rate and a longer relapse-free time for blinatumomab relative to HC3.)
Stratification factors are age and marrow/MRD status.

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Stratified HR
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.48

Statistical analysis title	HR

Statistical analysis description:

The subdistribution HR estimates are obtained from the subdistribution Cox model. (HR < 1.0 indicates a lower average event rate and a longer relapse-free time for blinatumomab relative to HC3.)

Comparison groups	HC3 Chemotherapy v Blinatumomab
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.52

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs)

End point description:

Adverse event (AE): any untoward medical occurrence. Serious AE: an AE meeting at least 1 of the following serious criteria: fatal; life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; other medically important serious event. Severity was graded according to the Common Terminology Criteria for AEs (CTCAE) version 4.03: 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death. Investigational product (IP) in the HC3 arm refers to dexamethasone, methotrexate, daunorubicin, erwinase, ifosfamide, asparaginase, and vincristine, and in the blinatumomab arm refers to blinatumomab. Treatment-related refers to the assessment of a relationship between IP and the event.
Safety Analysis Set: participants who received protocol-specified therapy analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

From first dose of IP through the last dose of IP (up to Day 29) plus 30 days.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
TEAEs	50	54		
TEAEs Grade ≥ 3	43	33		
Serious TEAEs	24	15		
Fatal TEAEs	0	0		
TEAEs Leading to Discontinuation of IP	0	2		
TEAEs Leading to Interruption of IP	2	6		
TRAEs	41	45		
TRAEs Grade ≥ 3	33	9		
Serious TRAEs	15	9		
Fatal TRAEs	0	0		
TRAEs Leading to Discontinuation of IP	0	2		
TRAEs Leading to Interruption of IP	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With TEAEs of Interest

End point title	Number of Participants With TEAEs of Interest

End point description:

TEAEs of interest included capillary leak syndrome (CLS), cytokine release syndrome (CRS), decreased immunoglobulins (DI), elevated liver enzymes (ELE), embolic and thrombotic events (ETE), infections (INF), infusion reactions without considering duration (IRWCD), medication errors (ME), neurologic events (NE), neutropenia and febrile neutropenia (NFN), pancreatitis (PNC), tumor lysis syndrome, leukoencephalopathy, immunogenicity. Severity was graded according to the CTCAE version 4.03: 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death.
Safety Analysis Set: participants who received protocol-specified therapy analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

From first dose of IP through the last dose of IP (up to Day 29) plus 30 days.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
CLS Events	1	0		
CLS Events Grade ≥ 3	1	0		
Serious CLS Events	1	0		
Fatal CLS Events	0	0		
CLS Events Leading to Discontinuation of IP	0	0		
CLS Events Leading to Interruption of IP	0	0		
CRS Events	1	2		
CRS Events Grade ≥ 3	0	0		
Serious CRS Events	0	0		
Fatal CRS Events	0	0		
CRS Events Leading to Discontinuation of IP	0	0		
CRS Events Leading to Interruption of IP	0	0		
DI Events	6	9		
DI Events Grade ≥ 3	1	1		
Serious DI Events	0	1		
Fatal DI Events	0	0		
DI Events Leading to Discontinuation of IP	0	0		
DI Events Leading to Interruption of IP	0	0		
ELE Events	15	7		
ELE Events Grade ≥ 3	9	3		
Serious ELE Events	1	0		
Fatal ELE Events	0	0		
ELE Events Leading to Discontinuation of IP	0	0		
ELE Events Leading to Interruption of IP	0	0		
ETE Events	0	4		
ETE Events Grade ≥ 3	0	2		
Serious ETE Events	0	0		
Fatal ETE Events	0	0		
ETE Events Leading to Discontinuation of IP	0	0		
ETE Events Leading to Interruption of IP	0	0		

INF Events	18	25		
INF Events Grade ≥ 3	6	11		
Serious INF events	6	4		
Fatal INF Events	0	0		
IFN Events Leading to Discontinuation of IP	0	0		
IFN Events Leading to Interruption of IP	0	0		
IRWCD Events	4	37		
IRWCD Events Grade ≥ 3	0	2		
Serious IRWCD Events	0	1		
Fatal IRWCD Events	0	0		
IRWCD Events Leading to Discontinuation of IP	0	0		
IRWCD Events Leading to Interruption of IP	0	0		
ME Events	0	1		
ME Events Grade ≥ 3	0	0		
Serious ME Events	0	1		
Fatal ME Events	0	0		
ME Events Leading to Discontinuation of IP	0	0		
ME Events Leading to Interruption of IP	0	1		
NE Events	15	26		
NE Events Grade ≥ 3	1	3		
Serious NE Events	1	5		
Fatal NE Events	0	0		
NE Events Leading to Discontinuation of IP	0	2		
NE Events Leading to Interruption of IP	1	3		
NFN events	28	12		
NFN Events Grade ≥ 3	27	11		
Serious NFN Events	12	0		
Fatal NFN Events	0	0		
NFN Events Leading to Discontinuation of IP	0	0		
NFN Events Leading to Interruption of IP	0	0		
PNC Events	1	0		
PNC Events Grade ≥ 3	1	0		
Serious PNC Events	1	0		
Fatal PNC Events	0	0		
PNC Events Leading to Discontinuation of IP	0	0		
PNC Events Leading to Interruption of IP	0	0		
Tumour Lysis Syndrome Events	0	0		
Leukoencephalopathy Events	0	0		
Immunogenicity Events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline Grade 0 or 1 to Worst Postbaseline Grade 3 or 4 Clinical Chemistry and Hematology Values

End point title	Number of Participants With Shifts From Baseline Grade 0 or 1 to Worst Postbaseline Grade 3 or 4 Clinical Chemistry and Hematology Values

End point description:

Severity was graded according to the CTCAE version 4.03: 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death. Increases () or decreases () in laboratory value grades (Gr) from baseline (BL) to worst postbaseline (PB) grade are presented. NA=not available.
Safety Analysis Set: who received protocol-specified therapy analyzed according to the treatment they received.

End point type	Secondary

End point timeframe:

Up to Day 29 (± 2 days)

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: participants				
Potassium BL Gr 0 PB Gr 3	0	1		
Potassium BL Gr 0 PB Gr 3	4	5		
Potassium BL Gr 0 PB Gr 4	1	1		
Albumin BL Gr 0 PB Gr 3	0	1		
Calcium BL Gr 0 PB Gr 4	1	1		
Alanine Aminotransferase BL Gr 0 PB Gr 3	1	0		
Alanine Aminotransferase BL Gr 1 PB Gr 3	9	5		
Aspartate Aminotransferase BL Gr NA PB Gr 3	1	0		
Aspartate Aminotransferase BL Gr 0 PB Gr 3	2	0		
Aspartate Aminotransferase BL Gr 1 PB Gr 3	5	1		
Aspartate Aminotransferase BL Gr 1 PB Gr 4	1	0		
Gamma-Glutamyl Transferase BL Gr NA PB Gr 3	0	1		
Gamma-Glutamyl Transferase BL Gr 0 PB Gr 3	3	4		
Gamma-Glutamyl Transferase BL Gr 1 PB Gr 3	6	2		
Gamma-Glutamyl Transferase BL Gr 1 PB Gr 4	0	3		
Amylase BL Gr 0 PB Gr 3	1	1		
Amylase BL Gr 0 PB Gr 4	1	0		
Amylase BL Gr 1 PB Gr 3	0	1		
Lipase BL Gr 0 PB Gr 3	3	2		
Lipase BL Gr 0 PB Gr 4	1	2		
Bilirubin BL Gr 0 PB Gr 3	2	1		
Bilirubin BL Gr 0 PB Gr 4	1	0		
Creatinine BL Gr NA PB Gr 3	0	2		
Hemoglobin BL Gr 0 PB Gr 3	1	0		

Hemoglobin BL Gr 1 PB Gr 3	4	1		
Platelets BL Gr 0 PB Gr 3	7	6		
Platelets BL Gr 0 PB Gr 4	13	6		
Platelets BL Gr 1 PB Gr 3	1	2		
Platelets BL Gr 1 PB Gr 4	8	2		
Leukocytes BL Gr 0 PB Gr 3	2	0		
Leukocytes BL Gr 0 PB Gr 4	4	0		
Leukocytes BL Gr 1 PB Gr 3	4	4		
Leukocytes BL Gr 1 PB Gr 4	7	1		
Neutrophils BL Gr 0 PB Gr 3	4	11		
Neutrophils BL Gr 0 PB Gr 4	23	3		
Lymphocytes BL Gr 0 PB Gr 3	0	1		
Lymphocytes BL Gr 0 PB Gr 3	1	3		
Lymphocytes BL Gr 0 PB Gr 4	1	1		
Lymphocytes BL Gr 1 PB Gr 3	0	1		
Lymphocytes BL Gr 1 PB Gr 4	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of 100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

End point title	Kaplan-Meier Estimate of 100-Day Mortality After Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT)

End point description:

The analysis of 100-day mortality after alloHSCT was assessed for participants who received an alloHSCT while in remission and did not receive any additional anti-leukemic treatment. 100-day mortality after alloHSCT was calculated relative to the date of alloHSCT. The 100-day mortality rate after alloHSCT was defined as the percentage of participants having died up to 100 days after alloHSCT, estimated using the estimated time to death in percent calculated by Kaplan-Meier methods. Participants still alive were censored at the date they were last known to be alive.
HSCT Analysis Set: participants who underwent an HSCT while in remission without any other anti-leukemic therapy.

End point type	Secondary

End point timeframe:

From the date of alloHSCT until death/censor date; median follow up time was 1742.0 days for blinatumomab and 1619.0 days for HC3.

End point values	HC3 Chemotherapy	Blinatumomab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	51		
Units: percentage of participants				
number (confidence interval 95%)	5.1 (1.3 to 19.0)	3.9 (1.0 to 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Clearance (CL) of Blinatumomab (Blinatumomab arm only)

End point title	Pharmacokinetics: Clearance (CL) of Blinatumomab (Blinatumomab arm only)[12]

End point description:

PK Analysis Set: participants who received any infusion of blinatumomab and had at least one PK sample collected

End point type	Secondary

End point timeframe:

Day 1: at least 10 hours after infusion start and up to 24 hours; Day 15

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint assessed blinatumomab pharmacokinetics in participants assigned to the blinatumomab arm only.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: L/hr/m^2				
arithmetic mean (standard deviation)	1.14 (± 0.836)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Concentration of Blinatumomab at Steady State (Css) (Blinatumomab arm only)

End point title	Pharmacokinetics: Concentration of Blinatumomab at Steady State (Css) (Blinatumomab arm only)[13]

End point description:

Pharmacokinetic (PK) Analysis Set: participants who received any infusion of blinatumomab and had at least one PK sample collected.

End point type	Secondary

End point timeframe:

Day 1: at least 10 hours after infusion start and up to 24 hours; Day 15

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The secondary endpoint assessed blinatumomab pharmacokinetics in participants assigned to the blinatumomab arm only.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: pg/mL				
arithmetic mean (standard deviation)	884 (± 969)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Blinatumomab Antibodies Postbaseline (Blinatumomab Arm Only)

End point title	Number of Participants With Anti-Blinatumomab Antibodies Postbaseline (Blinatumomab Arm Only)[14]

End point description:

Participants receiving blinatumomab had blood samples analyzed for binding antibodies. Samples testing positive for binding antibodies were also tested for neutralizing antibodies. Participants who were binding antibody-positive or neutralizing antibody-positive post-baseline with a negative or no result at baseline are presented.
Safety Analysis Set: participants who received protocol-specified therapy analyzed according to the treatment they received. Participants in the blinatumumab arm with a post-baseline result.

End point type	Secondary

End point timeframe:

Day 1 to Day 29

Notes:

[14] - 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: The secondary endpoint assessed anti-blinatumomab antibodies in participants assigned to the blinatumomab arm only.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: participants				
Binding Antibody Positive	0			
Neutralizing Antibody Positive	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from randomization through the end of study; the median overall follow-up time was 55.2 months. Treatment-emergent adverse events are reported from first dose of IP through the last dose of IP (up to Day 29) plus 30 days.

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled/randomized in the study. Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Blinatumomab

Reporting group description:

One 4-week cycle of blinatumomab 15 µg/m^2/day as a continuous intravenous infusion (CIVI).

Reporting group title	HC3 Chemotherapy

Reporting group description:

One week of treatment with HC3 followed by 3 weeks of no treatment.

Serious adverse events	Blinatumomab	HC3 Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 54 (27.78%)	24 / 52 (46.15%)	
number of deaths (all causes)	11	27	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B precursor type acute leukaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			

subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Engraftment syndrome			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neurological examination abnormal			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			

subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pneumothorax traumatic			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 54 (3.70%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	2 / 54 (3.70%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 54 (0.00%)	9 / 52 (17.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 54 (0.00%)	3 / 52 (5.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			

subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal cellulitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngotracheitis obstructive			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Herpes virus infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Blinatumomab	HC3 Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)	48 / 52 (92.31%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 54 (11.11%)	4 / 52 (7.69%)	
occurrences (all)	6	5	
Hypertension			
subjects affected / exposed	7 / 54 (12.96%)	4 / 52 (7.69%)	
occurrences (all)	9	4	
Haematoma			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	9 / 54 (16.67%)	4 / 52 (7.69%)	
occurrences (all)	10	4	
Pain			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	43 / 54 (79.63%)	10 / 52 (19.23%)	
occurrences (all)	69	12	
Fatigue			
subjects affected / exposed	3 / 54 (5.56%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	6 / 54 (11.11%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
Immunodeficiency			
subjects affected / exposed	4 / 54 (7.41%)	0 / 52 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	5	1	
Epistaxis			
subjects affected / exposed	5 / 54 (9.26%)	7 / 52 (13.46%)	
occurrences (all)	6	8	
Oropharyngeal pain			
subjects affected / exposed	2 / 54 (3.70%)	3 / 52 (5.77%)	
occurrences (all)	2	4	
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	5	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 54 (7.41%)	7 / 52 (13.46%)	
occurrences (all)	6	19	
Platelet count decreased			
subjects affected / exposed	7 / 54 (12.96%)	8 / 52 (15.38%)	
occurrences (all)	9	17	
Neutrophil count decreased			
subjects affected / exposed	5 / 54 (9.26%)	2 / 52 (3.85%)	
occurrences (all)	8	4	
Fluid balance positive			
subjects affected / exposed	2 / 54 (3.70%)	3 / 52 (5.77%)	
occurrences (all)	4	4	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 54 (3.70%)	5 / 52 (9.62%)	
occurrences (all)	3	11	
Antithrombin III decreased			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	2	6	
White blood cell count decreased			
subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	7	4	
Congenital, familial and genetic disorders			

Aplasia			
subjects affected / exposed	2 / 54 (3.70%)	4 / 52 (7.69%)	
occurrences (all)	2	4	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 54 (37.04%)	8 / 52 (15.38%)	
occurrences (all)	28	13	
Tremor			
subjects affected / exposed	5 / 54 (9.26%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 54 (5.56%)	4 / 52 (7.69%)	
occurrences (all)	3	5	
Anaemia			
subjects affected / exposed	13 / 54 (24.07%)	24 / 52 (46.15%)	
occurrences (all)	16	46	
Thrombocytopenia			
subjects affected / exposed	4 / 54 (7.41%)	11 / 52 (21.15%)	
occurrences (all)	9	18	
Neutropenia			
subjects affected / exposed	5 / 54 (9.26%)	13 / 52 (25.00%)	
occurrences (all)	8	18	
Leukopenia			
subjects affected / exposed	0 / 54 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 54 (7.41%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Abdominal pain			
subjects affected / exposed	7 / 54 (12.96%)	11 / 52 (21.15%)	
occurrences (all)	9	16	
Vomiting			
subjects affected / exposed	17 / 54 (31.48%)	11 / 52 (21.15%)	
occurrences (all)	27	16	
Stomatitis			

subjects affected / exposed	11 / 54 (20.37%)	27 / 52 (51.92%)	
occurrences (all)	11	44	
Oral pain			
subjects affected / exposed	1 / 54 (1.85%)	3 / 52 (5.77%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	23 / 54 (42.59%)	9 / 52 (17.31%)	
occurrences (all)	37	9	
Diarrhoea			
subjects affected / exposed	12 / 54 (22.22%)	9 / 52 (17.31%)	
occurrences (all)	17	11	
Constipation			
subjects affected / exposed	5 / 54 (9.26%)	7 / 52 (13.46%)	
occurrences (all)	9	9	
Anal inflammation			
subjects affected / exposed	4 / 54 (7.41%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 54 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Hypertransaminasaemia			
subjects affected / exposed	1 / 54 (1.85%)	4 / 52 (7.69%)	
occurrences (all)	1	7	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	6 / 54 (11.11%)	2 / 52 (3.85%)	
occurrences (all)	6	2	
Petechiae			
subjects affected / exposed	4 / 54 (7.41%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Pruritus			
subjects affected / exposed	6 / 54 (11.11%)	5 / 52 (9.62%)	
occurrences (all)	7	5	
Urticaria			

subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Rash maculo-papular			
subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	7 / 54 (12.96%)	5 / 52 (9.62%)	
occurrences (all)	9	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 54 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Back pain			
subjects affected / exposed	3 / 54 (5.56%)	5 / 52 (9.62%)	
occurrences (all)	3	5	
Pain in extremity			
subjects affected / exposed	2 / 54 (3.70%)	5 / 52 (9.62%)	
occurrences (all)	2	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 54 (5.56%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Paronychia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Rhinitis			
subjects affected / exposed	1 / 54 (1.85%)	5 / 52 (9.62%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	4 / 54 (7.41%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	6 / 54 (11.11%)	5 / 52 (9.62%)	
occurrences (all)	6	6	
Decreased appetite			

subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3	1 / 52 (1.92%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	- modified exclusion criteria to clarify that participants with abnormal serum creatinine were to be excluded from the study - added measures to prevent and/or minimize pain and discomfort during blood draws - added measures to minimize the blood volumes drawn during the study
29 September 2015	- added prophylactic intrathecal hydrocortisone as an alternative to prednisolone to allow the United Kingdom and Australia to participate in the study - changed distribution of sites participating in the study (New Zealand was removed) - changed the time period for administration of intrathecal prophylaxis to align with best medical practice for the standard of care arm - added "cumulative incidence of relapse" to secondary endpoints - clarified that MRD aliquots for PCR and/or flow cytometry that were to be collected at screening, Day 15 (blinatumomab arm only), and at Day 29 were to be analyzed at a central lab defined by the sponsor - updated pregnancy, contraception, and lactation requirements to align with current risk and discomforts language
19 April 2016	- added "population PK analysis" as a secondary endpoint - corrected the time frame for administration of intrathecal prophylaxis as premedication in the HC3 arm - changed treatment-free interval from 2 weeks to 1 week when defining a cycle in the adaptive design - updated the number of sites from 60 to 75 - in inclusion criteria, added a requirement for historical samples for central analysis of MRD - updated exclusion criteria to clarify that for participants with total bilirubin < 1.5 mg/dL, measurement of direct bilirubin was not required, and to remove exclusion of other investigational procedures during study contact - clarified that maximum daily dose of blinatumomab was not to exceed 28 µg/day - clarified criteria for discontinuation of blinatumomab - updated laboratory analyte listing - updated language for pregnancy and lactation reporting

11 July 2017	- added text to "evaluate PK of blinatumomab" to the secondary objectives. Previously, this was an endpoint that was not listed as an objective - secondary endpoints for population PK analysis were clarified - clarified that not all participants were to proceed to transplant if M1 marrow occurred after consolidation (reasons not to proceed to transplant may include issues such as donor not available, infection, organ function issues) - updated number of study centers from 75 to 82 - updated the definition of primary completion to include the premature conclusion of the study - updated inclusion criteria to remove definition of M2 marrow and to exclude central nervous system relapse participants from having to supply material requested for central lab MRD analysis - updated exclusion criteria to change direct bilirubin values to total bilirubin and increased the acceptable level of total bilirubin for study entry, to indicate that other exclusion criteria do not have to resolve to ≤ grade 2 for study participation and to clarify that asparaginase reactions were not an exclusion criterion - clarified that the screening period could be extended by up to 7 days for bone marrow count recovery and/or scheduling of bone marrow collection only - clarified that anticonvulsant treatment needed to be started before resumption of the cycle after a seizure had interrupted the blinatumomab infusion - clarified that blinatumomab should only be discontinued in case of blinatumomab-related relevant neurologic events - added allergic reactions as a complication that occurs with asparaginase - clarified the concomitant medications that needed to be collected - clarified the timing of intrathecal chemotherapy and that it could have been administered before signing consent as long as it was administered within 7 days prior to treatment start
05 December 2017	- adaptation was removed from the protocol to align with the Pediatric Investigation Plan amendment - inclusion criterion updated to clarify what cases were exempt from supplying material from relapse for PCR central lab analysis - the section on excluded treatments and/or procedures during the study period was updated to exclude participants who received additional cycles of the study drugs (HC3 or blinatumomab) after the treatment cycle was completed until an event occurred - long-term follow-up for participants was changed from 36 months after alloHSCT to until the last participant enrolled on the study was 36 months after alloHSCT to allow longer follow-up data on the participants to be collected while the study was open - primary completion and end of study language was updated
01 November 2019	- added an exploratory endpoint - updated the number of study centers from 82 to 113 - updated adverse event guidance
23 December 2021	- clarified that adverse events associated with key safety parameter should be reported for the duration of the study with the exception of those related to other anti-cancer therapies occurring post blinatumomab treatment could be excluded - updated language to clarify that serious adverse events suspected to be related to blinatumomab that the investigator became aware of were to be reported to Amgen within 24 hours of awareness during the long-term follow-up phase - changed the contraception period, avoidance of pregnancy, breast feeding, and sperm donation period from 6 months to 48 hours - updated the language for reporting procedures for adverse events and serious adverse events - clarified that only adverse events and serious adverse events were to be reported if there was harm from overdose - updated the serious adverse event reporting, pregnancy, and lactation form in the appendices
01 August 2022	- updated contraception duration - clarified that where there was a potential overlap of contraceptive duration requirements due to different treatments, the most conservative contraceptive duration requirement was to be followed - overdose language was updated to inform that for HC3 chemotherapy or concomitant medications, overdose was not to be reported as an adverse event/serious adverse event unless it was an intentional overdose

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported