Clinical trial results:
A Phase 2 Open-label Study Investigating the Safety and Efficacy of Blinatumomab After Frontline R-Chemotherapy in Adult Subjects With Newly Diagnosed High-risk Diffuse Large B-cell Lymphoma (DLBCL)

Summary

EudraCT number	2016-002190-35
Trial protocol	ES DE FR GB
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information

Trial identification

Sponsor protocol code	20150288

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03023878
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	28 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The safety profile of blinatumomab after frontline R-chemotherapy, consisting of either R-CHOP (14 or 21) or R-DA-EPOCH or R-CHOEP, will be determined.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures. The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	47
EEA total number of subjects	23

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)	26
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 12 centers in the European Union (France, Germany, Spain, and the United Kingdom), the United States, and Canada. Of the 54 subjects screened, 47 subjects were enrolled.

Pre-assignment

Screening details:

The study consisted of a standard of care rituximab-chemotherapy run-in period of approximately 21 weeks, a 12- to 16-week blinatumomab treatment period, a 30-day safety follow-up, and a long-term follow-up period up to 1 year from the first dose of blinatumomab, or until participant death, whichever occurred first.

Pre-assignment period milestones

Number of subjects started	47
Number of subjects completed	28

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol-specified criteria: 13
Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 5

Period 1

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

Arms

Arm title	Blinatumomab

Arm description:

Blinatumomab was administered as a continuous intravenous (IV) infusion. Cycle 1 was 12 weeks (84 days) in duration with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, 112 µg/day for 6 weeks, followed by a 4-week treatment free time.
An optional 4-week Cycle 2 of blinatumomab was available for participants whose disease did not progress, with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, and 112 µg/day for 14 days. There was a safety follow-up for 30 days. And a long-term follow-up of up to 8 months for a maximum of 1 year from first dose of blinatumomab or until participant death.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	
Other name	AMG103 BlinCyto
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Blinatumomab monotherapy was supplied in single-use sterile glass injection vials and administered as an IV infusion.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	corticosteroid
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 mg intravenous within 1 hour prior to start of treatment in each treatment cycle, and within 1 hour prior to dose-step (increase).

Number of subjects in period 1[1]	Blinatumomab
Started	28
Started Cycle 1	28
Started Cycle 2	11 [2]
Completed	25
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Disease Progression	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subject reported in the baseline period reflects the number of participants who completed the run-in period and who started the blinatumomab treatment period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants received Cycle 2 treatment at the Investigator's discretion.

Baseline characteristics

Reporting groups	
Reporting group title	Blinatumomab

Reporting group description:

Blinatumomab was administered as a continuous intravenous (IV) infusion. Cycle 1 was 12 weeks (84 days) in duration with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, 112 µg/day for 6 weeks, followed by a 4-week treatment free time.
An optional 4-week Cycle 2 of blinatumomab was available for participants whose disease did not progress, with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, and 112 µg/day for 14 days.
There was a safety follow-up for 30 days. And a long-term follow-up of up to 8 months for a maximum of 1 year from first dose of blinatumomab or until participant death.

Reporting group values	Blinatumomab	Total	
Number of subjects	28	28	
Age Categorical			
Note the overlapping age groups			
Units:			
< 65 years	18	18	
>=65 years	10	10	
Age Continuous			
Units: years			
arithmetic mean	60.2		
standard deviation	± 11.1	-	
Sex: Female, Male			
Units:			
Female	18	18	
Male	10	10	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7	7	
Not Hispanic or Latino	21	21	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized			
Units: Subjects			
Asian	1	1	
Black and African American	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
White	21	21	
Other	4	4	
Disease Stage at Time of Diagnosis			
•Stage I – Only one lymph node region is involved, only one lymph structure is involved •Stage IE - Only one extranodal site (IE) is involved. •Stage II – Two or more lymph node regions or lymph node structures on the same side of the diaphragm are involved. •Stage III – Lymph node regions or structures on both sides of the diaphragm are involved. •Stage IV – There is widespread involvement of a number of organs or tissues other than lymph node regions or structures, such as the liver, lung, or bone marrow.			
Units: Subjects			
Stage I	0	0	
Stage IE	1	1	

Stage II	0	0	
Stage III	5	5	
Stage IV	22	22	
International Prognostic Index Score at Diagnosis			
IPI score is an aid in predicting the prognosis of patients • Low risk (0-1 points) - 5-year survival of 73% • Low-intermediate risk (2 points) - 5-year survival of 51% • High-intermediate risk (3 points) - 5-year survival of 43% • High risk (4-5 points) - 5-year survival of 26%			
Units: Subjects			
Score 2	2	2	
Score 3	17	17	
Score 4	7	7	
Score 5	2	2	

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Blinatumomab was administered as a continuous intravenous (IV) infusion. Cycle 1 was 12 weeks (84 days) in duration with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, 112 µg/day for 6 weeks, followed by a 4-week treatment free time.
An optional 4-week Cycle 2 of blinatumomab was available for participants whose disease did not progress, with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, and 112 µg/day for 14 days.
There was a safety follow-up for 30 days. And a long-term follow-up of up to 8 months for a maximum of 1 year from first dose of blinatumomab or until participant death.

Primary: Participants with Treatment-Emergent (Blinatumomab) Adverse Events

End point title	Participants with Treatment-Emergent (Blinatumomab) Adverse Events[1]

End point description:

Overall incidence and severity of treatment-emergent adverse events occurring during the blinatumomab investigative product (IP) treatment period graded by investigators according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and based on the scale: Grade 1 = Mild - transient or mild discomfort; Grade 2 = Moderate - mild to moderate limitation in activity, assistance may be needed; minimal medical intervention required; Grade 3 = Severe - marked limitation in activity, assistance usually required; medical intervention required, hospitalization is possible; Grade 4 = Life threatening - extreme limitation in activity, assistance required; medical intervention, hospitalization or hospice care probable; Grade 5 = death.

End point type	Primary

End point timeframe:

From the start of first infusion of IP to 30 days after the end of last infusion of IP; median (min, max) treatment duration was 56 (16, 84) days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting of safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: participants				
TEAE	28			
TEAE severity grade >=3	11			
TEAE severity grade >=4	5			
Serious TEAE	7			
TEAE leading to interruption of IP	3			
Serious TEAE leading to interruption of IP	2			
TEAE leading to discontinuation of IP	2			
Serious TEAE leading to discontinuation of IP	1			
Fatal TEAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Participants with Treatment-Emergent Adverse Events Related to Blinatumomab Treatment

End point title	Participants with Treatment-Emergent Adverse Events Related to Blinatumomab Treatment[2]

End point description:

Overall incidence and severity of treatment-emergent adverse events deemed by investigators to be related to blinatumomab treatment. Severity was graded by investigators according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and based on the scale: Grade 1 = Mild - transient or mild discomfort; Grade 2 = Moderate - mild to moderate limitation in activity, assistance may be needed; minimal medical intervention required; Grade 3 = Severe - marked limitation in activity, assistance usually required; medical intervention required, hospitalization is possible; Grade 4 = Life threatening - extreme limitation in activity, assistance required; medical intervention, hospitalization or hospice care probable; Grade 5 = death.

End point type	Primary

End point timeframe:

From the start of first infusion of IP to 30 days after the end of last infusion of IP; median (min, max) treatment duration was 56 (16, 84) days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical reporting of safety outcomes was entirely descriptive, with no formal statistical testing performed.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: participants				
Treatment-related TEAE	23			
Related TEAE severity grade >=3	9			
Related TEAE severity grade >=4	3			
Related Serious TEAE	5			
Related TEAE leading to interruption of IP	3			
Related Serious TEAE leading to interruption of IP	2			
Related TEAE leading to discontinuation of IP	2			
Related Serious TEAE leading to discon of IP	1			
Related and Fatal TEAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Objective Response Rate (ORR) Expressed as the Percentage of Participants Achieving Complete Metabolic Response (CMR) and Partial Metabolic Response (PMR) Using Lugano 2014 Criteria During Cycle 1 and During Treatment Period

End point title	Overall Objective Response Rate (ORR) Expressed as the Percentage of Participants Achieving Complete Metabolic

	Response (CMR) and Partial Metabolic Response (PMR) Using Lugano 2014 Criteria During Cycle 1 and During Treatment Period

End point description:

Tumor response assessment was performed by a central reader according to modified Lugano classification using PET/CT scan. Overall objective response rate (ORR) is the percentage of participants with a best overall response of complete metabolic response (CMR) or partial metabolic response (PMR). CMR: a score of 1 (no uptake above background), 2 (uptake </=mediastinum), or 3 (uptake <mediastinum but </=liver) with/without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow; and normal/IHC-negative bone marrow morphology. PMR: a score 4 (uptake moderately greater than [>] liver) or 5 (uptake markedly >liver and/or new lesions) with reduced uptake compared with baseline and residual mass(es) of any size on PET 5-PS for lymph nodes and extralymphatic sites; no new lesions; and reduced residual uptake in bone marrow compared with baseline.

End point type	Secondary

End point timeframe:

Cycle 1: Day 78 (3 weeks following end of Cycle 1 IP treatment) Treatment Period: Either the Cycle 1 timeframe or approximately Day 128 (3 weeks after Cycle 2 ended) for participants who completed Cycle 2

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 1	89.3 (71.8 to 97.7)			
Entire Treatment Period	92.9 (76.5 to 99.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Duration of Response (DOR)

End point title	Kaplan-Meier Estimates for Duration of Response (DOR)

End point description:

DOR was calculated only for responders during cycle 1. For participants who had CR or PR on the PET/CT scan at the end of the run-in period, response was measured from the start of blinatumomab treatment. For participants who had SD at the end of the run-in period, duration was calculated from documentation of the first assessment of either PR or CR on blinatumomab.
Progression was defined as the first diagnosis of progressive metabolic response/progressive disease based on PET/CT scan per central or investigator review during the treatment period or relapse based on clinical tumor assessment during the long-term follow up. Duration was calculated until the start of new anti-tumor treatment (excluding any stem cell transplantation), PD, or death, whichever was the earliest event. Participants who did not have new anti-tumor treatment (excluding stem cell transplantation), PD, or death were censored at the last tumor assessment date.
9999=not estimable due to low number of events

End point type	Secondary

End point timeframe:

The median (range) follow-up time was 11.5 (8.2, 14.5) months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	25[3]			
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Notes:

[3] - Responder Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate Expressed as the Percentage of Participants Achieving Complete Metabolic Response (CMR) Using Lugano 2014 Criteria During Cycle 1 and During Treatment Period

End point title	Complete Response Rate Expressed as the Percentage of Participants Achieving Complete Metabolic Response (CMR) Using Lugano 2014 Criteria During Cycle 1 and During Treatment Period

End point description:

Tumor response assessment was performed by a central reader according to modified Lugano classification using PET/CT scan. CMR: a score of 1 (no uptake above background), 2 (uptake </=mediastinum), or 3 (uptake <mediastinum but </=liver) with/without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow; and normal/IHC-negative bone marrow morphology.

End point type	Secondary

End point timeframe:

Cycle 1: Day 78 (3 weeks following end of Cycle 1 IP treatment) Treatment Period: Either the Cycle 1 timeframe or approximately Day 128 (3 weeks after Cycle 2 ended) for participants who completed Cycle 2

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 1	85.7 (67.3 to 96.0)			
Entire Treatment Period	89.3 (71.8 to 97.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Overall Survival (OS) from First Dose of Blinatumomab

End point title	Kaplan-Meier Estimates for Overall Survival (OS) from First Dose of Blinatumomab

End point description:

OS was calculated as the time from the date of first IP infusion until death due to any cause. Participants who are alive at the date that triggers the analysis were censored at the date last known to be alive. Months were calculated as days from the first dose date of blinatumomab to death/censor date, divided by 30.5. 9999=not estimable due to low number of events

End point type	Secondary

End point timeframe:

The median (range) follow-up time was 12.0 (10.7, 14.5) months.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Progression Free Survival (PFS) from First Dose of Blinatumomab

End point title	Kaplan-Meier Estimates for Progression Free Survival (PFS) from First Dose of Blinatumomab

End point description:

PFS was calculated as the time from the date of first IP infusion until the date of diagnosis of progression of DLBCL or the date of death, whichever was the earliest. The diagnosis of progression of DLBCL was defined as the first diagnosis of progressive metabolic response/progressive disease based on PET/CT scan per central or investigator review during the treatment period or relapse based on clinical tumor assessment during the long-term follow up period. Participants who were alive and did not have progression were censored at the last evaluable non-missing tumor assessment date prior to the analysis trigger date. 9999=not estimable due to low number of events.

End point type	Secondary

End point timeframe:

The median (range) follow-up time was 12.0 (8.2, 14.5)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Had Hematopoietic Stem Cell Transplantation (HSCT)

End point title	Percentage of Participants Who Had Hematopoietic Stem Cell Transplantation (HSCT)

End point description:

Percentage of participants who had HSCT during the Long Term Follow-Up Period.

End point type	Secondary

End point timeframe:

Day 1 up to 14.5 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percentage of participants				
number (confidence interval 95%)	3.6 (0.1 to 18.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Results for Blinatumomab: Steady-State Concentrations at Week 1, Week 2 and Week 3 for Cycle 1

End point title	Pharmacokinetics (PK) Results for Blinatumomab: Steady-State Concentrations at Week 1, Week 2 and Week 3 for Cycle 1

End point description:

The steady-state serum concentration (Css), summarized as the observed concentrations collected after at least 10 hours after the start of continuous IV infusion. PK blood samples were analyzed in a central lab.

End point type	Secondary

End point timeframe:

Day 2 at least 24 hours after blinatumomab was started and on Day 9 and Day 16 at least 24 hours after blinatumomab dose was increased in the cycle

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: pg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Week 1: 9 mcg/day (N=26)	288 (± 289)			
Cycle 1 Week 2: 28 mcg/day (N=28)	795 (± 280)			
Cycle 1 Week 3: 112 mcg/day (N=26)	3160 (± 782)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Results for Blinatumomab: Clearance for Cycle 1

End point title	Pharmacokinetics (PK) Results for Blinatumomab: Clearance for Cycle 1

End point description:

PK blood samples were analyzed in a central lab.

End point type	Secondary

End point timeframe:

Day 2 at least 24 hours after blinatumomab was started and on Day 9 and Day 16 at least 24 hours after blinatumomab dose was increased in the cycle

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: L/hour				
arithmetic mean (standard deviation)	1.61 (± 0.496)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of blinatumomab to 30 days after last dose; median duration of treatment was 56 days. Serious adverse events related to blinatumomab and deaths were collected during the long-term follow-up period, median time on follow-up was 12 months.

Adverse event reporting additional description:

Adverse events are reported for all participants who received at least one dose of blinatumomab in the Treatment Period. One participant died during the run-in period and is not reflected in the tables below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Blinatumomab was administered as a continuous intravenous (IV) infusion. Cycle 1 was 12 weeks (84 days) in duration with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, 112 µg/day for 6 weeks, followed by a 4-week treatment free time.
An optional 4-week Cycle 2 of blinatumomab was available for participants whose disease did not progress, with step dosing of 9 µg/day for 7 days, 28 µg/day for 7 days, and 112 µg/day for 14 days.
There was a safety follow-up for 30 days. And a long-term follow-up of up to 8 months for a maximum of 1 year from first dose of blinatumomab or until participant death.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 28 (25.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neurotoxicity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Blinatumomab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 28 (92.86%)		
Vascular disorders			
Flushing			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	21		
Hypotension			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	6		
General disorders and administration			

site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2 3 / 28 (10.71%) 4 8 / 28 (28.57%) 10 10 / 28 (35.71%) 15		
Immune system disorders Cytokine release syndrome subjects affected / exposed occurrences (all)	 5 / 28 (17.86%) 10		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 8 / 28 (28.57%) 8 2 / 28 (7.14%) 3 3 / 28 (10.71%) 3 3 / 28 (10.71%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 4 / 28 (14.29%) 6		
Investigations			

Lymphocyte count decreased subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 6		
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3		
Platelet count decreased subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 6		
White blood cell count decreased subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 7		
Nervous system disorders Ataxia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 4		
Dizziness subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3		
Headache subjects affected / exposed occurrences (all)	7 / 28 (25.00%) 9		
Paraesthesia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Tremor subjects affected / exposed occurrences (all)	10 / 28 (35.71%) 13		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 4		
Neutropenia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 8		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 6		
Dry mouth subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Nausea subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 7		
Vomiting subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3		
Skin and subcutaneous tissue disorders			
Erythema subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Pruritus subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 5		
Rash subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5		
Back pain subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 7		
Flank pain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3		
Muscular weakness			

subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3 3 / 28 (10.71%) 3 4 / 28 (14.29%) 4 3 / 28 (10.71%) 3 5 / 28 (17.86%) 9		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Metabolism and nutrition disorders Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2017	This amendment was not submitted to the regulatory agency.
11 May 2017	This amendment reflects changes made to the original protocol in Amendments 1 and 2. The protocol was aligned to changes made in the other diffuse large B-cell lymphoma protocols (Studies 20150292 and 20140286) with respect to safety assessments and dose interruptions and stopping criteria. Sample size was reduced to support consideration of the study as a pilot study. The following points were clarified: -Run-in period treatment -Timing and frequency for evaluation of tumor response -Subjects with progressive disease are not eligible for treatment with blinatumomab -Toxicity monitoring and management and permanent discontinuation criteria -All grades 3 and 4 laboratory abnormalities were to be recorded as adverse events The Schedule of Assessments was updated to clarify for procedures during the screening and run-in phase and to provide clear guidance for cycle 1 and cycle 2 periods. The list of disease-related events was updated. The assessment of blinatumomab pharmacokinetics was changed from an exploratory objective and endpoint to a secondary objective and endpoint. The assessment of overall survival was added in the clinical hypothesis and as a secondary endpoint. Typographical and formatting changes were made throughout the protocol.
03 June 2018	The following points were clarified: -Grade 4 hematologic toxicity and grade 4 laboratory abnormalities lasting ≥ 7 days exclude lymphopenia -Subjects would be excluded from receiving blinatumomab if there was evidence of central nervous system involvement with diffuse large B-cell lymphoma at evaluation before starting blinatumomab -When vital signs would be obtained for hospitalized subjects versus subjects in the outpatient clinic -What assessments in the Schedule of Assessments should be obtained after restart of continuous intravenous infusion of blinatumomab after interruption requiring dose modification. Administration, typographical, and formatting changes were made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported