Clinical trial results:
A Phase 2/3 Multicenter Study to Evaluate the Safety and Efficacy of Blinatumomab in Subjects With Relapsed/Refractory Aggressive B-cell Non Hodgkin Lymphoma

Summary

EudraCT number	2016-002044-16
Trial protocol	GB BE ES IT
Global end of trial date	12 March 2020

Results information

Result version number	v1 (current)
This version publication date	10 March 2021
First version publication date	10 March 2021

Trial information

Trial identification

Sponsor protocol code	20150292

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02910063
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	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@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	12 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to estimate the complete metabolic response (CMR) rate after blinatumomab monotherapy administered in the second salvage treatment of transplant-eligible participants with relapsed/refractory (R/R) aggressive B cell non Hodgkin lymphoma who have not achieved CMR after standard platinum based first salvage chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and other regulations/guidelines as applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 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	Belgium: 3
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Australia: 14
Worldwide total number of subjects	41
EEA total number of subjects	13

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)	33
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 19 research centers in Australia, Belgium, Italy, Spain, the United Kingdom, and the United States from 23 January 2017 to 15 January 2018.

Pre-assignment

Screening details:

Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Period 1

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

Arms

Arm title	Blinatumomab

Arm description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (µg)/day, 7 days at 28 µg/day, and 42 days at 112 µg/day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.
Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doses ranging from 9 µg/day to 112 µg/day. Blinatumomab was administered as an intravenous (IV) infusion.

Number of subjects in period 1	Blinatumomab
Started	41
Started Phase 2	41
Started Cycle 1	41
Started Optional Cycle 2	4 [1]
Started Phase 3	0 [2]
Completed	13
Not completed	28
Adverse event, serious fatal	24
Consent withdrawn by subject	3

Lost to follow-up	1

Notes:

[1] - 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: Cycle 2 was an optional cycle that participants did not need to complete to complete the overall study. Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

[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: Cycle 2 was an optional cycle that participants did not need to complete to complete the overall study. Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	33	33	
From 65-84 years	8	8	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	54.7		
standard deviation	± 12.4	-	
Sex: Female, Male Units:			
Female	13	13	
Male	28	28	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	35	35	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	38	38	
More than one race	0	0	
Unknown or Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (µg)/day, 7 days at 28 µg/day, and 42 days at 112 µg/day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.
Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

Subject analysis set title	Phase 2: Blinatumomab 9 µg/day
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received blinatumomab 9 µg/day continuous infusion which was administered for 7 days of in Week 1 of Cycle 1 (Cycle 1 was 70 days in length).

Subject analysis set title	Phase 2: Blinatumomab 28 µg/day
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received blinatumomab 28 µg/day continuous infusion which was administered for 7 days in Week 2 of Cycle 1 (Cycle 1 was 70 days in length).

Subject analysis set title	Phase 2: Blinatumomab 112 µg/day
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received blinatumomab 112 µg/day continuous infusion which was administered for 7 days in Week 3 of Cycle 1 (Cycle 1 was 70 days in length).

Primary: Phase 2: Percentage of Participants who Achieved Complete Metabolic Response (CMR)

End point title	Phase 2: Percentage of Participants who Achieved Complete Metabolic Response (CMR)[1]

End point description:

Complete metabolic response (CMR) was determined by central radiographic assessment of positron emission tomography and computed tomography (PET/CT) scans using the Lugano Classification.

End point type	Primary

End point timeframe:

Up to 12 weeks after first dose of blinatumomab

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: No formal statistics were planned

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[2]			
Units: Percentage of participants				
number (confidence interval 95%)	22.0 (10.6 to 37.6)			

Notes:

[2] - Full analysis set (FAS): All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Primary: Phase 3: Number of Participants who Achieved Complete Metabolic Response (CMR)

End point title	Phase 3: Number of Participants who Achieved Complete Metabolic Response (CMR)[3]

End point description:

Complete metabolic response (CMR) was determined by central radiographic assessment of positron emission tomography and computed tomography (PET/CT) scans using the Lugano Classification.

End point type	Primary

End point timeframe:

Up to 12 weeks after first dose of study treatment

Notes:

[3] - 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: No formal statistics were planned.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Participants				
number (not applicable)				

Notes:

[4] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization until death due to any cause.

OS was calculated using Kaplan-Meier estimates.

99999 = no data to present. The upper limit was not reached.

End point type	Secondary

End point timeframe:

From randomization until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[5]			
Units: Months				
median (confidence interval 95%)	11.2 (5.9 to 99999)			

Notes:

[5] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Objective Response Rate (ORR)

End point title	Phase 2: Objective Response Rate (ORR)

End point description:

ORR is inclusive of all participants who achieved CMR or those who achieved partial metabolic response (PMR), as determined by central radiographic assessment of PET/CT scans using the Lugano Classification.

End point type	Secondary

End point timeframe:

Up to 12 weeks after first dose of blinatumomab

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[6]			
Units: Percentage of participants				
number (confidence interval 95%)	36.6 (22.1 to 53.1)			

Notes:

[6] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression Free Survival (PFS)

End point title	Phase 2: Progression Free Survival (PFS)

End point description:

PFS was defined as the time from start of treatment with blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. PFS was estimated using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From first dose of blinatumomab until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[7]			
Units: Months				
median (confidence interval 95%)	2.9 (2.3 to 5.3)			

Notes:

[7] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR)

End point description:

DOR was calculated only for participants who achieve a response (CMR or PMR). The duration was calculated from the date a response, CMR or PMR, was first achieved until the earliest date of a disease assessment indicating disease progression or death, whichever occurred first. DOR was estimated using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From first dose of blinatumomab up to 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[8]			
Units: Months				
median (confidence interval 95%)	6.1 (2.5 to 10.7)			

Notes:

[8] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants who Experienced Successful Mobilization

End point title	Phase 2: Percentage of Participants who Experienced Successful Mobilization

End point description:

Successful mobilization rate was defined as the percentage of participants who initiated mobilization while in remission and without any other anti-tumor therapy where the mobilization procedure had an outcome of 'Successful'. Successful mobilization was dictated by institutional standards and defined when the target cell dose was no less than 2 x 10^6 CD34+ cells/kg.

Responder Analysis Set: All participants who had a CMR or PMR per central review during the first 12 weeks after initiation of blinatumomab.

End point type	Secondary

End point timeframe:

From first dose of blinatumomab until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	15[9]			
Units: Percentage of participants				
number (confidence interval 95%)	40.0 (16.3 to 67.7)			

Notes:

[9] - Responder Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

End point title	Phase 2: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

End point description:

The percentage of responders per investigator’s review (participants who achieved either CMR or PMR during the treatment) who have undergone allogeneic (allo) HSCT or autologous (auto) HSCT while in remission and without any other anti-cancer treatment.

End point type	Secondary

End point timeframe:

From baseline HSCT until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[10]			
Units: Percentage of participants				
number (confidence interval 95%)				
AlloHSCT	6.7 (0.2 to 31.9)			
AutoHSCT	53.3 (26.6 to 78.7)			

Notes:

[10] - FAS: All participants who received blinatumomab.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Cumulative Incidence Function Estimate of 100-day Mortality After HSCT Presented as Percentage of Participants that Died Not Due to Relapse,

with Relapse and Death Due to Relapse as Competing Events

End point title	Phase 2: Cumulative Incidence Function Estimate of 100-day Mortality After HSCT Presented as Percentage of Participants that Died Not Due to Relapse, with Relapse and Death Due to Relapse as Competing Events

End point description:

Non-relapse mortality rate at 100 days after HSCT was calculated as the percentage of participants who died not due to relapse. Only participants who achieved a response per investigator's review and underwent autoHSCT are included.

AutoHSCT Analysis Set: All participants who achieved a response and underwent autoHSCT while in remission and without any other anti-cancer treatment.

End point type	Secondary

End point timeframe:

100 days after HSCT

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	9[11]			
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 0.0)			

Notes:

[11] - AutoHSCT Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Blinatumomab Steady State Concentrations (Css)

End point title	Phase 2: Blinatumomab Steady State Concentrations (Css)

End point description:

Pharmacokinetic (PK) parameters were estimated by non compartmental analysis. The Css of blinatumomab was summarized as the observed concentrations collected after at least 24 hours after the start of continuous IV infusion or start of dose step, where appropriate.

PK analysis Set: All participants who received blinatumomab at each individual dose and had at least one PK sample collected.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and post-dose on Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

End point values	Phase 2: Blinatumomab 9 µg/day	Phase 2: Blinatumomab 28 µg/day	Phase 2: Blinatumomab 112 µg/day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41[12]	38[13]	32[14]	
Units: Picograms/millilter (pg/mL)				
arithmetic mean (standard deviation)	249 (± 200)	804 (± 513)	3470 (± 3700)	

Notes:

[12] - PK Analysis Set

[13] - PK Analysis Set

[14] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Blinatumomab Clearance (CL)

End point title	Phase 2: Blinatumomab Clearance (CL)

End point description:

Serum blinatumomab CL was calculated as CL=R0/Css,DN; where R0 is the infusion rate (µg/hr) and Css,DN is the dose normalized average Css. For the CL calculation, the Css,DN was normalized to the 112 µg/day dose in which the value of dose in units of µg/hr was used for the infusion rate.

PK analysis Set: All subjects who received blinatumomab at each individual dose and had at least one PK sample collected.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and post-dose on Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[15]			
Units: Liter/hour (L/hr)				
arithmetic mean (standard deviation)	1.78 (± 0.747)			

Notes:

[15] - PK Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Half-life of Blinatumomab

End point title	Phase 2: Half-life of Blinatumomab

End point description:

Blinatumomab half-life was not reported as the serum blinatumomab concentration data collected for PK assessments did not support its estimation. This is in adherence with the considerations for reporting of PK assessments as detailed in Protocol Section 10.6.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: Hours				
arithmetic mean (standard deviation)	()			

Notes:

[16] - Insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Phase 2: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

Treatment-emergent adverse events were events with an onset after the administration of the first dose of blinatumomab.

TEAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limited age appropriate instrumental activities of daily life (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limited self care ADL.

Grade 4 Life-threatening consequences; urgent interventions indicated.

End point type	Secondary

End point timeframe:

From first dose of blinatumomab until 30 days after last dose. The maximum treatment duration for blinatumomab was 114 days

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	41[17]			
Units: Participants				
TEAEs	41			
Grade ≥ 2 TEAEs	37			
Grade ≥ 3 TEAEs	29			
Grade ≥ 4 TEAEs	12			
Serious TEAEs	20			
TEAEs leading to discontinuation of blinatumomab	7			
TEAEs leading to interruption of blinatumomab	13			
Fatal TEAEs	7			

Notes:

[17] - FAS: All participants who received blinatumomab

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Objective Response Rate (ORR)

End point title	Phase 3: Objective Response Rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks after first dose of study treatment

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[18]			
Units: percentage of participants				
number (not applicable)				

Notes:

[18] - No participants were enrolled for Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Progression Free Survival (PFS)

End point title	Phase 3: Progression Free Survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

From first dose of study treatment until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[19]			
Units: Months				
median (full range (min-max))	(to)			

Notes:

[19] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Duration of Response (DOR)

End point title	Phase 3: Duration of Response (DOR)

End point description:

End point type	Secondary

End point timeframe:

From first dose of study treatment up to 12 weeks

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[20]			
Units: Months				
median (confidence interval 95%)	(to)			

Notes:

[20] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who Experienced Successful Mobilization

End point title	Phase 3: Percentage of Participants who Experienced Successful Mobilization

End point description:

End point type	Secondary

End point timeframe:

From baseline until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: Percentage of participants				
number (not applicable)				

Notes:

[21] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who had Allogeneic or Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

End point title	Phase 3: Percentage of Participants who had Allogeneic or

	Autologous Post-baseline Hematopoietic Stem Cell Transplant (HSCT)

End point description:

End point type	Secondary

End point timeframe:

From baseline HSCT until the end of study, up to 30 months

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[22]			
Units: Percentage of participants				
number (not applicable)				

Notes:

[22] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Percentage of Participants who Died within 100 Days after Hematopoietic Stem Cell Transplantation (HSCT) that was Not Due to Relapse

End point title	Phase 3: Percentage of Participants who Died within 100 Days after Hematopoietic Stem Cell Transplantation (HSCT) that was Not Due to Relapse

End point description:

End point type	Secondary

End point timeframe:

100 days after HSCT

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[23]			
Units: Percentage of participants				
number (not applicable)				

Notes:

[23] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Change from Baseline in Patient Reported Clinical Outcome Assessments Quality of Life (QOLCOA) Scores

End point title	Phase 3: Change from Baseline in Patient Reported Clinical

	Outcome Assessments Quality of Life (QOLCOA) Scores

End point description:

End point type	Secondary

End point timeframe:

Up to 30 days after last dose after study treatment

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[24]			
Units: Percentage of participants				
number (not applicable)				

Notes:

[24] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Phase 3: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

End point type	Secondary

End point timeframe:

From first dose of study treatment until 30 days after last dose

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[25]			
Units: Participants				
number (not applicable)				

Notes:

[25] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Serum Blinatumomab Steady State Concentration (Css)

End point title	Phase 3: Serum Blinatumomab Steady State Concentration (Css)

End point description:

End point type	Secondary

End point timeframe:

24 hours after first dose of blinatumomab

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[26]			
Units: pg/mL				
arithmetic mean (standard deviation)	()			

Notes:

[26] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Blinatumomab Clearance (CL)

End point title	Phase 3: Blinatumomab Clearance (CL)

End point description:

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[27]			
Units: L/hr				
arithmetic mean (standard deviation)	()			

Notes:

[27] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Half-life of Blinatumomab

End point title	Phase 3: Half-life of Blinatumomab

End point description:

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and Days 2, 9 and 16 of Cycle 1 (Cycle 1 was 70 days)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	0[28]			
Units: Hours				
arithmetic mean (standard deviation)	()			

Notes:

[28] - No participants were enrolled in Phase 3.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of blinatumomab until 30 days after last dose. The maximum treatment duration for blinatumomab was 114 days

Adverse event reporting additional description:

All-cause mortality, serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

No data is available for Phase 3, In March 2019, the decision was made to not proceed with Phase 3 and no participants were enrolled. The data below is only inclusive of participants in Phase 2.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Phase 2: Participants entered a single 70-day dose step cycle, and received a total of 56 days of blinatumomab continuous infusion which was administered as 7 days at 9 microgram (µg)/day, 7 days at 28 µg/day, and 42 days at 112 µg/day, followed by a treatment-free period of 14 days. Eligible participants could then enter an optional Cycle 2, 2 to 4 weeks after the end of the previous cycle. The optional Cycle 2 consisted of a 28-day cycle of blinatumomab continuous infusion administered as 7 days at 9 µg/day, 7 days at 28 µg/day, and 14 days at 112 µg/day.
Phase 3: The decision made to not proceed with Phase 3 and no participants were enrolled.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 41 (48.78%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diffuse large B-cell lymphoma refractory			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Lymphoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neurotoxicity			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Bacteraemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 41 (2.44%)		
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	29 / 41 (70.73%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	5		
Nervous system disorders			
Aphasia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	10 / 41 (24.39%)		
occurrences (all)	16		
Paraesthesia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	13		
Neutropenia			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	6		
Oedema peripheral			
subjects affected / exposed	8 / 41 (19.51%)		
occurrences (all)	14		
Pyrexia			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	15		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	7		
Diarrhoea			

subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	8		
Stomatitis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	9		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	11		
Pain in extremity			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2017	The following changes were made: • Clarified duration of cycle and dose steps for blinatumomab for consistency within the protocol • Added specification of the duration between end of cycle 1 and beginning of optional cycle 2 of blinatumomab • Clarified that creatinine was to be calculated using the Cockcroft Gault equation • Added the dose and duration of each step in the dosing schema of blinatumomab optional cycle 2 to clarify procedures • Added mantle cell lymphoma as a histology that excluded eligibility for enrollment • Added procedure by which scans were to be submitted to determine eligibility for participants who have had only 1 cycle of previous chemotherapy • Revised requirements for blinatumomab infusion interruptions and dose modifications per request of the Food and Drug Administration (FDA) • Updated blinatumomab stopping and/or withholding rules to include cytokine storm • Added time point at week 68 for collection of cell pellet sample for optional pharmacogenetic testing • Specified that lipase samples should be collected at the investigator's discretion if pancreatitis was suspected • Clarified that vital signs to be monitored every 4 to 8 hours postdose • Clarified that participants are prohibited from receiving additional chemotherapy after the last response assessment before enrollment • Clarified that PET imagining of the neck to be done as clinically indicated • Clarified procedures for bone marrow biopsy • Added the EuroQol- 5 Dimension (EQ-5D) and Functional Assessment of Cancer Therapy - Lymphoma (FACT Lym) instruments as appendices
16 March 2017	Amendment dated 16 March 2017 continued: • Specified that disease progression is considered a disease related event and procedures for recording as an adverse event • Revised list of disease-related adverse events • Added reporting of events for participants who are partial response/minor response at baseline per Lugano who do not go to transplantation within 30 days of first response assessment • Revised procedures for reporting laboratory abnormalities as adverse events
07 May 2019	This following changes were made: • Provided post facto option of not proceeding to Phase 3 • Provided 2 years of long term follow up for Phase 2 cohort • Clarified end of study and end of follow up for Phase 2 • Redefined primary and final analyses endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Phase 3 part of the study was not initiated after Phase 2 data was reviewed. No participants were screened or enrolled for Phase 3.

Notes: