Clinical trial results:
A Phase 2 Open-Label Study to Determine the Effect of Blinatumomab on Minimal Residual Disease in Subjects With High-risk Diffuse Large B-cell Lymphoma Post-autologous Hematopoietic Stem-cell Transplantation

Summary

EudraCT number	2016-003255-30
Trial protocol	GR BE IT
Global end of trial date	30 September 2019

Results information

Result version number	v1
This version publication date	19 September 2020
First version publication date	19 September 2020

Trial information

Trial identification

Sponsor protocol code	20150291

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03298412
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, 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	30 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine minimal residual disease (MRD) negative rate following blinatumomab treatment in high-risk Diffuse Large B-cell Lymphoma (DLBCL) subjects who are MRD-positive post-autologous hematopoietic stem cell transplantation (aHSCT).

Protection of trial subjects:

This study was conducted in accordance with International Council for 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	23 May 2018
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	Australia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	10
EEA total number of subjects	5

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)	7
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled participants from Australia, France, Greece, Italy, Switzerland, and the United States. The first participant enrolled on 23 May 2018, and the last participant enrolled on 05 August 2019.

Pre-assignment

Screening details:

The study included a Screening period (up to 28 days), and a run-in period of up to 24 months to evaluate minimal residual disease (MRD) status and assess eligibility for treatment assignment.

Period 1

Period 1 title	Run-in Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Blinatumomab

Arm description:

After a run-in period of up to 24 months to evaluate MRD status and assess eligibility for treatment assignment, participants received blinatumomab intravenous (IV) infusion at an initial dose of 9 µg/day for the first 7 days of treatment, escalated (dose-step) to 28 µg/day starting on Day 8 (Week 2), followed by a dose-step to 112 µg/day starting on Day 15 (Week 3) and continuing until completion of therapy (Day 57 of Cycle 1). Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval.

Arm type	Experimental
Investigational medicinal product name	blinatumomab (given after the run-in period)
Investigational medicinal product code	AMG 103, MT103
Other name	Blincyto
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per protocol, blinatumomab was given after the run-in period (at the start of the treatment period).

Number of subjects in period 1	Blinatumomab
Started	10
Completed	1
Not completed	9
Ineligibility Determined	1
Decision by Sponsor	6
Disease Progression	1
Other, Not Specified	1

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Blinatumomab

Arm description:

Blinatumomab intravenous (IV) infusion at an initial dose of 9 µg/day for the first 7 days of treatment, escalated (dose-step) to 28 µg/day starting on Day 8 (Week 2), followed by a dose-step to 112 µg/day starting on Day 15 (Week 3) and continuing until completion of therapy (Day 57 of Cycle 1). Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval.

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

Dosage and administration details:

Blinatumomab wa administered as a continuous intravenous (IV) infusion.

Number of subjects in period 2	Blinatumomab
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Blinatumomab

Reporting group description:

After a run-in period of up to 24 months to evaluate MRD status and assess eligibility for treatment assignment, participants received blinatumomab intravenous (IV) infusion at an initial dose of 9 µg/day for the first 7 days of treatment, escalated (dose-step) to 28 µg/day starting on Day 8 (Week 2), followed by a dose-step to 112 µg/day starting on Day 15 (Week 3) and continuing until completion of therapy (Day 57 of Cycle 1). Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval.

Reporting group values	Blinatumomab	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 48.7 ± 18.4	 -	
Sex: Female, Male Units:			
Female	5	5	
Male	5	5	
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	0	0	
White	6	6	
More than one race	0	0	
Unknown or Not Reported	3	3	

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

After a run-in period of up to 24 months to evaluate MRD status and assess eligibility for treatment assignment, participants received blinatumomab intravenous (IV) infusion at an initial dose of 9 µg/day for the first 7 days of treatment, escalated (dose-step) to 28 µg/day starting on Day 8 (Week 2), followed by a dose-step to 112 µg/day starting on Day 15 (Week 3) and continuing until completion of therapy (Day 57 of Cycle 1). Cycle 1 of blinatumomab treatment is 12 weeks (84 days) in duration and includes 8 weeks (56 days) of blinatumomab IV infusion followed by a 4-week (28-day) treatment-free interval.

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Primary: MRD-Negative Rate at the End of Cycle 1

End point title	MRD-Negative Rate at the End of Cycle 1[1]

End point description:

The estimated MRD-negative rate, calculated as the percentage of participants with MRD-negative status after treatment with blinatumomab. MRD-negative status was assessed by positron emission tomography-computed tomography (PET-CT) or computed tomography (CT).

Full analysis set (all participants who received any infusion of blinatumomab).

End point type	Primary

End point timeframe:

12 weeks (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: One participant received/completed treatment; available data is presented in the data table.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: percentage of participants				
number (confidence interval 95%)	100 (2.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate: Progression-Free Survival (PFS)

End point title	Kaplan-Meier Estimate: Progression-Free Survival (PFS)

End point description:

PFS, calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of relapse of lymphoma (by PET-CT, CT, clinical assessment or relapse biopsy, whichever was the preferred method), or date of death, whichever was earliest. Participants who were alive and who did not have progression or new anti-tumor treatment (excluding any stem cell transplantation) were to be censored at last date of tumor assessment.

Full analysis set (all participants who received any infusion of blinatumomab).

End point type	Secondary

End point timeframe:

up to 1 year from first dose of blinatumomab

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	1[2]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[2] - 99999=Not estimable (1 participant in analysis set).

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate: Duration of MRD-Negative Status

End point title	Kaplan-Meier Estimate: Duration of MRD-Negative Status

End point description:

The duration of MRD-negative status, assessed only in participants who achieve MRD-negative status after blinatumomab treatment, was defined as the time when a negative MRD result was first established until documented MRD-positive re-occurrence, disease progression or, death due to any cause. Participants without any of these events at the time of the analysis were to be censored at their last disease assessment date. MRD-negative status was assessed by PET-CT or CT.

Full analysis set (all participants who received any infusion of blinatumomab).

End point type	Secondary

End point timeframe:

up to 1 year from first dose of blinatumomab

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	1[3]			
Units: months				
median (confidence interval 95%)	10.26 (-99999 to 99999)			

Notes:

[3] - -/+99999=Not estimable (1 participant analyzed).

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate: Overall Survival (OS)

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

End point description:

OS, defined as time from the first dose of blinatumomab treatment until death due to any cause. Participants still alive at the time of the analysis were censored at date last known to be alive.

Full analysis set (all participants who received any infusion of blinatumomab).

End point type	Secondary

End point timeframe:

up to 1 year from first dose of blinatumomab

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	1[4]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[4] - 99999=Not estimable (1 participant in analysis set).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is defined as any untoward medical occurrence. A serious AE is defined as an AE that is: fatal; life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; a congenital anomaly/birth defect; other medically important serious event. TEAEs are events with an onset after the administration of the first dose of blinatumomab treatment through 30 days after the end of blinatumomab treatment. Events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death).

End point type	Secondary

End point timeframe:

From first dose of study drug through 30 days after the last dose of study drug. The treatment duration for the participant who received blinatumomab was 57 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: participants				
Any TEAE	1			
Grade 3 TEAE	1			
Serious TEAE	0			
TEAE Leading to Study Drug Discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through 30 days after the last dose of study drug. The treatment duration for the participant who received blinatumomab was 57 days.

Adverse event reporting additional description:

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Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Blinatumomab

Reporting group description: -

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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	1 / 1 (100.00%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2017	This protocol is being amended to: • Include stopping rules for excessive toxicity, define dose limiting toxicity (DLT) evaluable subjects, and add interim analyses to review DLT rate • Clarify timing and purpose of MRD tests that occur before treatment and on cycle 1 day 1 • Remove language related to sensitivity analysis performed on the MRD-negative rate at the end of cycle 1 of blinatumomab • Make administrative and editorial updates (this includes an update to the Schedule of Assessments table to re-add 2 PET assessments that were mistakenly deleted during publication of original protocol)
24 August 2017	This protocol is being amended to: • include stopping rules for disease progression. • add hepatitis serology and human immunodeficiency virus testing. • add benefit/risk assessment language. • make administrative and editorial updates.
18 July 2018	This protocol is being amended to: • Increase the screening window to 28 days. • Clarify when pathology tumor block/slides should be collected and MRD tests should be performed during screening. • Clarify that the MRD plasma sample needs to be drawn after the post aHSCT PET-CT scan. • Clarify that subjects will be excluded from receiving blinatumomab if there is evidence of central nervous system (CNS) involvement with DLBCL at disease evaluation prior to starting blinatumomab. • Clarify that grade 4 hematologic toxicity and grade 4 laboratory abnormalities lasting ≥ 7 days exclude lymphopenia. This lymphopenia is reported to last for 6 months or as long as a year after therapy completion (Chiappella et al, 2017; Coffier, 2007; Plosker and Figgitt, 2003). Lymphopenia is also a known adverse event with blinatumomab that does resolve after the therapy is completed. Lymphopenia is not an immediately life-threatening threatening event, is treated well with supportive care, and reverses after completion of R-chemotherapy and blinatumomab infusion. • Clarify when vital signs will be obtained for hospitalized subjects versus subjects in the outpatient clinic. • Make administrative and editorial updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported