Clinical trial results:
An Open-label, Multi-center, Expanded Access Protocol of Blinatumomab for the Treatment of Pediatric and Adolescent Subjects with Relapsed and/or Refractory B precursor Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2014-001700-21
Trial protocol	GB DE IT AT FR
Global end of trial date	10 January 2020

Results information

Result version number	v1 (current)
This version publication date	16 July 2020
First version publication date	16 July 2020

Trial information

Trial identification

Sponsor protocol code	20130320

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02187354
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to estimate the incidence rate of treatment emergent and treatment related adverse events during treatment with blinatumomab in pediatric and adolescent subjects with B cell precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The regulations or guidelines were applicable to all regions where the study was conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. All study centers complied with the local regulations.
The investigator or his/her designee informed the subject (or their legal representative) of all aspects regarding the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 2015
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	Austria: 3
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	110
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)	13
Children (2-11 years)	63
Adolescents (12-17 years)	34
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 16 centers: 13 in Europe and 3 in the United States. The first subject was enrolled on 29 January 2015 and the last subject was enrolled on 25 July 2018.

Pre-assignment

Screening details:

During the 2-week screening and prephase period, administration of dexamethasone or hydroxyurea was permitted to reduce tumor burden and the incidence of tumor lysis syndrome.

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:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m^2/day for the first 7 days, escalated to 15µg/m^2/day on Days 8-29. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.
Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of 15µg/m^2/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.

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

Dosage and administration details:

Blinatumomab is administered as a continuous intravenous infusion (CIVI).

Number of subjects in period 1	Blinatumomab
Started	110
Completed	47
Not completed	63
Consent withdrawn by subject	6
Death	57

Baseline characteristics

Reporting groups	
Reporting group title	Blinatumomab

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m^2/day for the first 7 days, escalated to 15µg/m^2/day on Days 8-29. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.
Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of 15µg/m^2/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.

Reporting group values	Blinatumomab	Total	
Number of subjects	110	110	
Age Categorical Units: Subjects			
0 to < 2 years	13	13	
2 to 6 years	31	31	
7 to 17 years	66	66	
Age Continuous Units: years			
arithmetic mean	8.5		
standard deviation	± 5.0	-	
Gender Categorical Units: Subjects			
Female	48	48	
Male	62	62	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	3	3	
Multiple (Asian/White)	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
White	93	93	
Other, Not Specified	3	3	
Missing	8	8	
Ethnicity Units: Subjects			
Hispanic/Latino	18	18	
Not Hispanic/Latino	92	92	

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval).

In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m^2/day for the first 7 days, escalated to 15µg/m^2/day on Days 8-29. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.
Subjects with M2 bone marrow or M1 bone marrow with a minimal residual disease (MRD) relapse at screening, started at an initial dose of 15µg/m^2/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related Adverse Events (TRAEs)[1]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence. A serious AE is defined as 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. TEAEs were those occurring after the first dose of study drug through 30 days after the last dose of study drug. Severity was graded as 1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death. Events of interest included neurologic events, infections, cytokine release syndrome, elevated liver enzyme, infusion reactions, tumor lysis syndrome, capillary leak syndrome, medication errors, decreased immunoglobulins, embolic and thrombotic events, leukoencephalopathy, neutropenia and febrile neutropenia, and acute pancreatitis.

End point type	Primary

End point timeframe:

From the first dose of study drug through 30 days post-dose. Median overall duration of each treatment cycle was 31.4 days (range: 3 to 140 days); median number of cycles started and completed was 1.0 (range: 1.0 to 5.0).

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: Descriptive statistics are presented per protocol.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: subjects				
TEAE	109			
TEAE Grade >/= 3	71			
TEAE Grade >/= 4	31			
TEAE, Serious	50			
TEAE, Fatal	9			
TEAE Leading to Discontinuation (DC) of Study Drug	7			
TEAE Leading to DC of Study Drug, Serious	6			
TEAE Leading to DC of Study Drug, Fatal	2			

TEAE Leading to Interruption (INT) of Study Drug	25			
TEAE Leading to INT of Study Drug, Serious	17			
TEAE Leading to INT of Study Drug, Fatal	3			
TEAE, Events of Interest	101			
TRAE	81			
TRAE Grade >/= 3	29			
TRAE Grade >/= 4	3			
TRAE, Serious	21			
TRAE, Fatal	0			
TRAE Leading to DC of Study Drug	4			
TRAE Leading to DC of Study Drug, Serious	4			
TRAE Leading to DC of Study Drug, Fatal	0			
TRAE Leading to INT of Study Drug	18			
TRAE Leading to INT of Study Drug, Serious	11			
TRAE Leading to INT of Study Drug, Fatal	0			
TRAE, Events of Interest	68			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Complete Response (CR) Within the First 2 Cycles of Blinatumomab

End point title	Percentage of Subjects With Complete Response (CR) Within the First 2 Cycles of Blinatumomab

End point description:

CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

Within the first 2 cycles (data cutoff 27 September 2018). The median (range) duration of the first treatment cycle was 27.9 (3 to 31) days, and 27.9 (0 to 37) days for the second treatment cycle.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: percentage of subjects				
number (confidence interval 95%)	62.7 (53.0 to 71.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First 2 Cycles of Blinatumomab

End point title	Percentage of Participants With a Minimal Residual Disease (MRD) Response Within the First 2 Cycles of Blinatumomab

End point description:

MRD response is defined as a quantifiable MRD load of < 10^-4 by the end of the first 2 cycles of blinatumomab. MRD response only included subjects who reached CR. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

Within the first 2 cycles (data cutoff 27 September 2018). The median (range) duration of the first treatment cycle was 27.9 (3 to 31) days, and 27.9 (0 to 37) days for the second treatment cycle.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	69[2]			
Units: percentage of subjects				
number (confidence interval 95%)				
MRD Response	82.6 (71.6 to 90.7)			
MRD Non-Response	14.5 (7.2 to 25.0)			
No MRD Response Data	2.9 (0.4 to 10.1)			

Notes:

[2] - subjects with a CR

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Relapse-Free Survival (RFS), Subjects With a CR

End point title	Kaplan-Meier Estimate of Relapse-Free Survival (RFS), Subjects With a CR

End point description:

RFS was calculated as the time to an event of relapse. defined as high-risk extramedullary disease, or death (all cause). Progressive disease, defined as an increase from baseline of at least 25% or an absolute increase of at least 5000 cells/ìL (whichever is greater) in the number of circulating leukemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive

disease, was also counted as an event.

RFS only included subjects who reached CR. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 11.5 months (range: 0.0 to 16.3 months).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	68[3]			
Units: months				
median (confidence interval 95%)	8.5 (4.7 to 14.0)			

Notes:

[3] - subjects with a CR

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival

End point title	Kaplan-Meier Estimate of Overall Survival

End point description:

Overall survival was calculated relative to the start of protocol-directed therapy until death (due to any cause), and was summarized by the Kaplan Meier methodology. Subjects still alive at the time of the analysis were censored at the date last known to be alive.

End point type	Secondary

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: months				
median (confidence interval 95%)	14.6 (11.0 to 24.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Allogeneic Hematopoietic Stem Cell Transplant (HSCT) After Blinatumomab, Subjects With a CR

End point title	Percentage of Subjects With Allogeneic Hematopoietic Stem Cell Transplant (HSCT) After Blinatumomab, Subjects With a CR

End point description:

Percentage of subjects receiving allogeneic HSCT after blinatumomab, in subjects with a CR within the first 2 cycles of treatment. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	68[4]			
Units: percentage of subjects				
number (confidence interval 95%)				
HSCT after CR	73.5 (61.4 to 83.5)			
No HSCT after CR	26.5 (16.5 to 38.6)			

Notes:

[4] - Subjects with a CR

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Allogeneic HSCT After Blinatumomab, Subjects Without CR

End point title	Percentage of Subjects With Allogeneic HSCT After Blinatumomab, Subjects Without CR

End point description:

Percentage of subjects receiving allogeneic HSCT after blinatumomab, in subjects without a CR within the first 2 cycles of treatment. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	25[5]			
Units: percentage of subjects				
number (confidence interval 95%)				
HSCT	24.0 (9.4 to 45.1)			
No HSCT	76.0 (54.9 to 90.6)			

Notes:

[5] - subjects without a CR

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of 100-day Mortality After Allogeneic HSCT, Subjects With a CR

End point title	Kaplan-Meier Estimate of 100-day Mortality After Allogeneic HSCT, Subjects With a CR

End point description:

Percentage of subjects experiencing death (any cause) 100 days after allogeneic HSCT, estimated by Kaplan Meier method, for subjects with a CR within the first 2 cycles who received an HSCT. CR was defined as having < 5% blasts in the bone marrow (M1 bone marrow) and no evidence of disease (M1 bone marrow with full recovery of peripheral blood counts or M1 bone marrow with incomplete recovery of peripheral blood counts or M1 bone marrow with neither full nor incomplete recovery of peripheral blood counts).

End point type	Secondary

End point timeframe:

From the first dose of study drug through final data cutoff (10 January 2020). Median follow up time was 18.2 months (range: 1.1 to 25.6 months).

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	50[6]			
Units: percentage of subjects				
number (confidence interval 95%)	4.0 (1.0 to 15.1)			

Notes:

[6] - subjects with a CR who received an allogeneic HSCT

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through 30 days post-dose. Median overall duration of each treatment cycle was 31.4 days (range: 3 to 140 days); median number of cycles started and completed was 1.0 (range: 1.0 to 5.0).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Up to 5 6-week cycles of blinatumomab treatment (4 weeks of treatment followed by a 2-week treatment-free interval). In the first cycle, subjects with an M3 bone marrow received an initial dose of 5µg/m^2/day for the first 7 days, escalated to 15µg/m^2/day on Days 8-29. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment. Subjects with M2 bone marrow or M1 bone marrow with an MRD relapse at screening, started at an initial dose of 15µg/m^2/day for the first 7 days of treatment with no dose step at Day 8. All subsequent cycles were dosed at 15µg/m^2/day for 4 weeks of continuous treatment.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 110 (45.45%)		
number of deaths (all causes)	58		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	5 / 110 (4.55%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Leukaemia recurrent			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphocytic leukaemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences causally related to treatment / all	8 / 14		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	5 / 110 (4.55%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device defective			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			

subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count increased				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Inappropriate schedule of product administration				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Amnesia				

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Meningism			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
VIth nerve paralysis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Febrile neutropenia			
subjects affected / exposed	5 / 110 (4.55%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			

subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	3 / 110 (2.73%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	4 / 110 (3.64%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymph gland infection			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonas infection			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	4 / 110 (3.64%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 110 (0.91%)		
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	105 / 110 (95.45%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 110 (8.18%)		
occurrences (all)	12		
Hypotension			

subjects affected / exposed	14 / 110 (12.73%)		
occurrences (all)	17		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	7 / 110 (6.36%)		
occurrences (all)	10		
Fatigue			
subjects affected / exposed	7 / 110 (6.36%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	18 / 110 (16.36%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	90 / 110 (81.82%)		
occurrences (all)	183		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	17 / 110 (15.45%)		
occurrences (all)	17		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 110 (17.27%)		
occurrences (all)	20		
Epistaxis			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	20		
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 110 (6.36%)		
occurrences (all)	7		
Fluid balance positive			

subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	17		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	7		
Platelet count decreased			
subjects affected / exposed	11 / 110 (10.00%)		
occurrences (all)	36		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 110 (24.55%)		
occurrences (all)	47		
Tremor			
subjects affected / exposed	8 / 110 (7.27%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 110 (18.18%)		
occurrences (all)	45		
Febrile neutropenia			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	9		
Neutropenia			
subjects affected / exposed	9 / 110 (8.18%)		
occurrences (all)	13		
Thrombocytopenia			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	15		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 110 (10.91%)		
occurrences (all)	13		

Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 8		
Constipation subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 11		
Diarrhoea subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 13		
Nausea subjects affected / exposed occurrences (all)	20 / 110 (18.18%) 31		
Stomatitis subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 8		
Vomiting subjects affected / exposed occurrences (all)	30 / 110 (27.27%) 41		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 6		
Pruritus subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7		
Rash subjects affected / exposed occurrences (all)	12 / 110 (10.91%) 13		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 12		
Bone pain subjects affected / exposed occurrences (all)	6 / 110 (5.45%) 7		
Pain in extremity			

subjects affected / exposed occurrences (all)	13 / 110 (11.82%) 16		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	 8 / 110 (7.27%) 9		
Metabolism and nutrition disorders Fluid overload subjects affected / exposed occurrences (all) Fluid retention subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 6 / 110 (5.45%) 6 7 / 110 (6.36%) 9 6 / 110 (5.45%) 7 12 / 110 (10.91%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2014	• Addition of hematology (CBC with differential), blood chemistry, and coagulation laboratory assessments during screening/prephase, as well as on cycle 1 days 1 and 2 for the monitoring of TLS, and prior to the start of treatment in subsequent cycles • Revision of eligibility criteria to be inclusive of a broader population of pediatric subjects with relapsed/refractory ALL • Refinement of guidelines for adverse event and serious adverse event reporting to minimize safety reporting burden on investigators: o Only CTCAE grade 3-5 adverse events, irrespective of etiology, were required to be reported o Only related serious adverse events were required to be reported after the protocol-required reporting period o Events from a prespecified list of expected disease-related serious adverse events were not required to be reported to Amgen within 24 hours following the investigator's knowledge of the event
27 October 2014	• Addition of hematology (CBC with differential), blood chemistry, and coagulation laboratory assessments during screening/prephase, as well as on cycle 1 days 1 and 2 for the monitoring of TLS, and prior to the start of treatment in subsequent cycles • Revision of eligibility criteria to be inclusive of a broader population of pediatric subjects with relapsed/refractory ALL • Refinement of guidelines for adverse event and serious adverse event reporting to minimize safety reporting burden on investigators: o Only CTCAE grade 3-5 adverse events, irrespective of etiology, are required to be reported o Only related serious adverse events were required to be reported after the protocol-required reporting period o Events from a prespecified list of expected disease-related serious adverse events were not required to be reported to Amgen within 24 hours following the investigator's knowledge of the event • Inclusion of references to country-specific protocol procedures and requirements • Clarification made to definition of end of enrollment in a given country

21 December 2015	• To align regional requests into 1 global protocol, including changes that were requested by the EU agencies and that were assembled in a protocol supplement for the EU region. • Additional changes included: o An increase of the sample size from ~ 40 to ~ 80 subjects o Implementation of the following dosing changes and changes in treatment schedule to be aligned with other pediatric and adult blinatumomab studies at Amgen: Subjects with M2 bone marrow at screening will start treatment at 15 µg/m2/day and not have a dose step The maximum dose administered was 28 µg/day Hydroxyurea may be used instead of dexamethasone for prephase treatment o Rules for infusion interruptions after CNS events and rules for treatment discontinuation were adapted, as well as some clarifications on premedication requirements for restart of infusion after interruptions added. o Changes to the contraception requirements post blinatumomab in line with a request from the EMA. o Overdoses > 10% were defined as medically important events that were to be reported as serious adverse events o Lactation and Pregnancy Notification Worksheets were replaced with the current version o Correction and clarification of some inconsistencies in the protocol o The definition of complete response was updated in Appendix E of the SAP o Appendix H of the SAP Pregnancy and Contraceptive Guidelines were added.
20 April 2016	• Added sections to the protocol to align with recent updates to the protocol template (v13). • Section 6.2.1 dosage language changed to set limits on daily dosing of blinatumomab. Rationale: Previously, dosage was based on BSA without an upper limit; change reflects an upper limit regardless of BSA, cytomorphology, or immunophenotype. • Updated contraceptive language to align with the recent ICF amendment (v5) and changes to the Core Risk and Discomforts document (contraception requirement changed from 24 hours after last dose to 48 hours). • Updated safety and safety reporting language to align with Amgen's adverse and serious adverse events policy, as well as align with recent updates to the protocol template (v13). • Updated the safety event form and Lactation and Pregnancy Notification Worksheets to current versions.
23 August 2016	• Replaced all event reporting time frames from "1 business day" to "24 hours" per an EU request
13 March 2017	• Updated Section 2.3 (Pediatric Risk Assessment) to include the most current number of adults and pediatric/adolescent subjects that have received study drug in research studies • Updated inclusion criterion to broaden the level of blasts in bone marrow at study enrollment. • Updated Section 5 (Subject Enrollment) and Section 7 (Study Procedures) to include the Product History Form for subjects who were enrolled in a previous Amgen blinatumomab study • To align Section 9 (Safety Data Collection, Recording, and Reporting), Section 12.6 (Publication Policy), and End of Study language with current protocol template language
07 July 2017	• Increased sample size from 80 to 100 subjects • Moved the endpoint of MRD remission rate within 2 cycles of treatment with blinatumomab from the final analysis to the primary analysis
07 June 2018	• Extended the long-term follow-up in the study past 18 months for pediatric subjects who did not receive a transplantation after blinatumomab treatment (maintenance therapy). • Clarified the frequency and types of data that will be collected for subjects in the extended long-term follow-up group until they are 18 years old.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported