Clinical trial results:
An Open-label, Multicenter Phase 2 Study to Investigate the Efficacy, Safety, and Tolerability of the Bi-specific T-cell Engager (BiTE®) MT103 in Patients with Minimal Residual Disease (MRD) of Positive B-precursor Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2006-006520-19
Trial protocol	DE
Global end of trial date	03 November 2014

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016

Trial information

Trial identification

Sponsor protocol code	MT103-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00560794
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2009
Global end of trial reached?	Yes
Global end of trial date	03 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether the bispecific T-cell engager (BiTE®) blinatumomab (MT103) is effective in the treatment of patients with ALL and minimal residual disease.

Protection of trial subjects:

This study was conducted in accordance with applicable laws and regulations, Good Clinical Practice (GCP), and the ethical principles that have their origin in the Declaration of Helsinki. All informed consent documents were compliant with the International Conference on Harmonisation (ICH) guidelines on GCP.
The study protocol including any amendments (if applicable), informed consent form,
and any accompanying material provided to the subject (such as information or descriptions of the study used to obtain informed consent) were reviewed and approved by the IEC. A copy of the written approval of the protocol and informed consent form received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.
The subject's free and expressed informed consent was to be obtained in writing prior to any enrollment into the study according to all applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 32 subjects were enrolled and screened in this study; 11 subjects screen failed and 21 subjects received ≥ 1 infusion of investigational product and were included in the safety analysis set.

Period 1

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

Arms

Arm title	Blinatumomab

Arm description:

Participants received blinatumomab as continuous intravenous infusion at constant flow rate over 4 weeks followed by a 2-week treatment-free period (defined as one treatment cycle), for up to a maximum of 10 cycles. The initial dose was 15 µg/m²/day. A dose increase to 30 µg/m²/day was permitted with evidence for insufficient response to blinatumomab treatment.

Arm type	Experimental
Investigational medicinal product name	Blinatumomab
Investigational medicinal product code	MT103
Other name	BLINCYTO™
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by continuous intravenous infusion (CIV) over 4 weeks per cycle

Number of subjects in period 1	Blinatumomab
Started	21
Completed 1 Treatment Cycle	20
Completed	10
Not completed	11
Received Bone Marrow Transplant	6
Adverse event, non-fatal	2
Hematological Relapse	1
Patient was not Compliant	1
Minimal Residual Disease Relapse	1

Baseline characteristics

Reporting groups	
Reporting group title	Blinatumomab
Reporting group description:	
Participants received blinatumomab as continuous intravenous infusion at constant flow rate over 4 weeks followed by a 2-week treatment-free period (defined as one treatment cycle), for up to a maximum of 10 cycles. The initial dose was 15 µg/m²/day. A dose increase to 30 µg/m²/day was permitted with evidence for insufficient response to blinatumomab treatment.	

Reporting group values	Blinatumomab	Total	
Number of subjects	21	21	
Age, Customized Units: participants			
18-64 years	15	15	
65-84 years	6	6	
Age Continuous Units: years			
arithmetic mean	48.3		
standard deviation	± 19	-	
Gender, Male/Female Units: participants			
Female	12	12	
Male	9	9	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	21	21	

End points

End points reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Participants received blinatumomab as continuous intravenous infusion at constant flow rate over 4 weeks followed by a 2-week treatment-free period (defined as one treatment cycle), for up to a maximum of 10 cycles. The initial dose was 15 µg/m²/day. A dose increase to 30 µg/m²/day was permitted with evidence for insufficient response to blinatumomab treatment.

Primary: Percentage of Participants with a Minimal Residual Disease (MRD) Response Within 4 Cycles of Treatment

End point title	Percentage of Participants with a Minimal Residual Disease (MRD) Response Within 4 Cycles of Treatment[1]

End point description:

MRD Response is defined as:
- If Philadelphia Chromosome (Ph) positive (+) or translocation (t) (4;11), response was achieved when Ph or t(4;11) was below detection limit and individual rearrangements of immunoglobulin or T-cell receptor genes are below 10^-4.
- If Ph and t(4;11) negative, response was achieved when individual rearrangements of immunoglobulin or T-cell receptor genes are below 10^-4.

The full analysis set included all participants who received ≥ 1 infusion of blinatumomab who completed at least the first treatment cycle and for whom at least one minimal residual disease (MRD) response assessment was available.

End point type	Primary

End point timeframe:

Within 4 treatment cycles, 24 weeks

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: The EudraCT system does not allow statistical analyses to be entered for studies with just one treatment arm.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (confidence interval 95%)	80 (56.3 to 94.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an MRD Response After Each Treatment Cycle

End point title	Percentage of Participants with an MRD Response After Each Treatment Cycle

End point description:

MRD Response is defined as:

- If Philadelphia Chromosome (Ph)+ or t(4;11), response was achieved when Ph or t(4;11) was below detection limit and individual rearrangements of immunoglobulin or T-cell receptor genes are below 10^-4.
- If Ph and t(4;11) negative, response was achieved when individual rearrangements of immunoglobulin or T-cell receptor genes are below 10^-4.

End point type	Secondary

End point timeframe:

At the end of each treatment cycle - Weeks 4, 10, 16, and 22.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (confidence interval 95%)				
MRD negativity achieved after cycle 1	80 (56.3 to 94.3)			
MRD negativity achieved after cycle 2	80 (56.3 to 94.3)			
MRD negativity achieved after cycle 3	80 (56.3 to 94.3)			
MRD negativity achieved after cycle 4	80 (56.3 to 94.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hematological Relapse

End point title	Time to Hematological Relapse

End point description:

The time to hematological relapse is defined as the time between start of first infusion of blinatumomab and the first result of hematological relapse. Participants without an event of hematological relapse were censored on their last available date of bone marrow aspiration/biopsy.
Hematological relapse is defined as > 5% leukemia cells in bone marrow.
Time to hematological relapse was analyzed using Kaplan-Meier methods. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 14 January 2010; maximum duration of follow-up was 564 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to MRD Progression

End point title	Time to MRD Progression

End point description:

Time to MRD progression is defined for participants who do not show MRD response at any time during the study as the time from start of first infusion until the first result of MRD progression or hematological relapse, if no MRD progression was diagnosed before hematological relapse. For participants who showed MRD response during the study the time to MRD progression is defined as the time from the date of the first MRD response to the date of MRD relapse. Participants without an event of MRD progression were censored on the day of their last bone marrow aspiration/biopsy. Participants who received a bone marrow transplant were censored on the last day of bone marrow aspiration/biopsy before transplantation.

MRD progression is defined as the increase in the MRD level by 1 log as compared to the baseline level (equal to a 10-fold increase in the number of MRD cells), and had to be confirmed within 6 weeks. "99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 14 January 2010; Median follow-up time was 155 days

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: days				
median (confidence interval 95%)	221 (170 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to MRD Relapse

End point title	Time to MRD Relapse

End point description:

Time to MRD relapse is defined only for participants with an MRD response during the study, defined as the time between the date of the first MRD response and the date of MRD relapse. If a participant experienced hematological relapse without having shown MRD positivity before then the time point of MRD relapse is defined as the time point of hematological relapse. Participants without an event of MRD relapse or hematological relapse were censored on the day of their last available bone marrow aspiration/biopsy. If a participant received a bone marrow transplant the last day of bone marrow aspiration/biopsy before transplantation was used as time point for censoring.
MRD relapse is defined as reappearance of bcr/abl, and/or t(4;11) translocation at any detection level,

and/or by individual rearrangements of immunoglobulin or T-cell receptor genes ≥10^-4 for at least 1 individual marker measured by an assay with a sensitivity of minimum 10^-4 and should be confirmed within 6 weeks.

End point type	Secondary

End point timeframe:

Up to the data cut-off date of 14 January 2010; Median follow-up time was 116.5 days

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The severity (or intensity) of AEs was evaluated according to the grading scale provided in the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, or according to the following: Grade 1 – Mild AE; Grade 2 – Moderate AE; Grade 3 - Severe AE; Grade 4 - Life-threatening or disabling AE; Grade 5 - Death.
The investigator used medical judgment to determine if there was a causal relationship (ie, related, unrelated) between an adverse event and blinatumomab.
A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. In addition, all laboratory abnormalities of grade four severity that occur during or after administration of the investigational drug, any overdose and a pregnancy or fathering were reported as SAEs.

End point type	Secondary

End point timeframe:

From the start of study treatment until up to 4 weeks after the end of study treatment. The median treatment duration was 87.3 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
number (not applicable)				
Any adverse event	21			
Adverse events of at least CTC grade 3	17			
Treatment-related adverse events	21			
Related adverse events of at least CTC grade 3	13			

Serious adverse evets	10			
Related serious adverse events	9			
AEs leading to discontinuation of blinatumomab	1			
AEs leading to death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Screening Value in B-cell Count During Cycle 1

End point title	Change From Screening Value in B-cell Count During Cycle 1

End point description:

B-cells were measured by flow cytometry.

End point type	Secondary

End point timeframe:

At Screening and in Cycle 1 at the start of infusion, 45 minutes, 2, 6, 12, 24 hours and at Days 2, 7, 14, 21, 28 and 35 after the start of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: cells/µL				
arithmetic mean (standard deviation)				
Start of infusion (N=19)	0.0181 (± 0.0803)			
45 minutes (N=19)	-0.0098 (± 0.0402)			
2 hours (N=18)	-0.0361 (± 0.0621)			
6 hours (N=19)	-0.0435 (± 0.0685)			
12 hours (N=16)	-0.0417 (± 0.0689)			
24 hours (N=18)	-0.0403 (± 0.07)			
Day 2 (N=17)	-0.031 (± 0.0589)			
Day 7 (N=18)	-0.0462 (± 0.0717)			
Day 14 (N=18)	-0.049 (± 0.0745)			
Day 21 (N=18)	-0.0494 (± 0.0747)			
Day 28 (N=17)	-0.0392 (± 0.0634)			
Day 35 (N=18)	-0.0493 (± 0.0748)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Screening Value in T-cell Count During Cycle 1

End point title	Change From Screening Value in T-cell Count During Cycle 1

End point description:

T-cells were measured by flow cytometry.

End point type	Secondary

End point timeframe:

At Screening and in Cycle 1 at the start of infusion, 45 minutes, 2, 6, 12, 24 hours and at Days 2, 7, 14, 21, 28 and 35 after the start of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: cells/µL				
arithmetic mean (standard deviation)				
Start of infusion (N=19)	-0.0418 (± 0.2925)			
45 minutes (N=19)	-0.3208 (± 0.3137)			
2 hours (N=18)	-0.4976 (± 0.3454)			
6 hours (N=19)	-0.5227 (± 0.3432)			
12 hours (N=16)	-0.539 (± 0.3649)			
24 hours (N=18)	-0.478 (± 0.3774)			
Day 2 (N=17)	-0.3328 (± 0.3704)			
Day 7 (N=18)	0.1231 (± 0.3051)			
Day 14 (N=18)	0.1172 (± 0.4671)			
Day 21 (N=18)	0.1975 (± 0.5596)			
Day 28 (N=17)	0.1687 (± 0.3119)			
Day 35 (N=18)	0.2271 (± 0.3739)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Cytokine Peak Levels in Cycle 1

End point title	Serum Cytokine Peak Levels in Cycle 1

End point description:

The activation of immune effector cells was monitored by the measurement of peripheral blood cytokine levels including interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α and interferon gamma (IFN)-γ using fluorescence-activated cell sorter (FACS)-based cytometric bead array (CBA) system. The limit of detection (LOD) for the cytokine determination was 20 pg/mL, the limit of quantification (LOQ) was 125 pg/mL.
"99999" indicates levels less than the limit of quantification or detection.

End point type	Secondary

End point timeframe:

Cycle 1 at pre-dose and at post infusion start at 45 minutes; 2, 6, 12, 24, and 48 hours; 7, 14, 21, and 28 days.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: pg/mL				
arithmetic mean (standard deviation)				
IL-2	99999 (± 99999)			
IL-4	99999 (± 99999)			
IL-6	693.2 (± 1122.9)			
IL-8	99999 (± 99999)			
IL-10	1135.3 (± 1155.6)			
IFN-γ	408.5 (± 614.3)			
TNF-α	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Blinatumomab Concentration at Steady State

End point title	Serum Blinatumomab Concentration at Steady State

End point description:

The mean serum concentration of blinatumomab during cycle 1.
The LOQ of the assay was 100 pg/mL, and the limit of detection (LOD) was 3 pg/mL.

End point type	Secondary

End point timeframe:

Cycle 1 at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of the cycle, and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: pg/mL				
arithmetic mean (standard deviation)	696 (± 147)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Drug Concentration-time Curve From Time Zero to Infinity

End point title	Area Under the Drug Concentration-time Curve From Time Zero to Infinity

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of the cycle, and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	481 (± 106)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution

End point title	Apparent Volume of Distribution

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of the cycle, and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: L/m²				
arithmetic mean (standard deviation)	2 (± 0.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life of Blinatumomab

End point title	Terminal Half-life of Blinatumomab

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of the cycle, and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: hours				
arithmetic mean (standard deviation)	1.47 (± 0.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance of Blinatumomab

End point title	Clearance of Blinatumomab

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 at predose and at 2, 6, and 12 hours after start of infusion then weekly until end of the cycle, and at 1, 2, 4, 6, 8, and 24 hours after stop of infusion.

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: L/hr/m²				
arithmetic mean (standard deviation)	0.939 (± 0.199)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hematological Relapse Free Survival (RFS)

End point title	Hematological Relapse Free Survival (RFS)

End point description:

RFS was calculated from time of start of first infusion until hematological relapse or death.
Hematological relapse was defined as ≥ 5% leukemia cells in the bone marrow.
Subjects without an event were censored on their last available date of bone marrow aspiration/biopsy.
"99999" indicates data not estimable.

End point type	Secondary

End point timeframe:

Up to 5 years (median follow-up time was 1550 days)

End point values	Blinatumomab			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: months				
median (confidence interval 95%)	99999 (5.1 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment until up to 4 weeks after the end of study treatment. The median treatment duration was 87.3 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Blinatumomab

Reporting group description:

Participants received blinatumomab as continuous intravenous infusion at constant flow rate over 4 weeks followed by a 2 week treatment-free period (defined as one treatment cycle), for up to a maximum of 10 cycles. The initial dose was 15 µg/m²/day. A dose increase to 30 µg/m²/day was permitted with evidence for insufficient response to blinatumomab treatment.

Serious adverse events	Blinatumomab		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Medical device complication			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Leukopenia				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				
subjects affected / exposed	6 / 21 (28.57%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacterial sepsis				
subjects affected / exposed	1 / 21 (4.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				

subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter related infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 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	21 / 21 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Catheter site pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	9 / 21 (42.86%)		
occurrences (all)	11		
Fatigue			

subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	12		
Oedema peripheral			
subjects affected / exposed	8 / 21 (38.10%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	21 / 21 (100.00%)		
occurrences (all)	45		
Immune system disorders			
Immunodeficiency			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	8		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	6		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Blood immunoglobulin A decreased			
subjects affected / exposed	14 / 21 (66.67%)		
occurrences (all)	14		
Blood immunoglobulin G decreased			
subjects affected / exposed	13 / 21 (61.90%)		
occurrences (all)	13		

Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Blood immunoglobulin M decreased			
subjects affected / exposed	10 / 21 (47.62%)		
occurrences (all)	10		
Blood potassium decreased			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
Coagulation factor XIII level increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	9		
Fibrin D dimer increased			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	8		
Monocyte count increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Immunoglobulins decreased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
Weight increased			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	10		
Cardiac disorders			

Bradycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2 4 / 21 (19.05%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 5 / 21 (23.81%) 7 10 / 21 (47.62%) 17 5 / 21 (23.81%) 9		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 7 / 21 (33.33%) 13 5 / 21 (23.81%) 6 6 / 21 (28.57%) 6		
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 4 / 21 (19.05%) 4 5 / 21 (23.81%) 7		

Dry mouth subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2 5 / 21 (23.81%) 12 3 / 21 (14.29%) 9		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 3 / 21 (14.29%) 4 2 / 21 (9.52%) 3 4 / 21 (19.05%) 7 5 / 21 (23.81%) 5		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 5 / 21 (23.81%) 7		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Growing pains subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2 6 / 21 (28.57%) 8 5 / 21 (23.81%) 6		

Myalgia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	10		
Oral herpes			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
Hypokalaemia			

subjects affected / exposed occurrences (all)	10 / 21 (47.62%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2008	- removal of subject upper age limit for inclusion in study - bone marrow assessment procedure changed to include bone marrow aspiration for measurement of MRD - change in necessary number of treatment cycles for evaluation of response for dose escalation (at least 1 cycle required instead of 2 cycles) - deletion of exclusion criterion #10; such that subjects with fulfilled criteria and available donor for allogeneic stem cell transplantation eligible for enrollment - modification of exclusion criterion #2; changed to current "relevant" CNS pathology - modification of exclusion criterion #7; added "low dose maintenance therapy such as vinca alkaloids, mercaptopurine, methotrexate, steroids" as acceptable prior therapy) - adjustment of infusion restart timepoint rules (corrected to day 0 and day 1) - modification of the formulation of the blinatumomab IV bag diluent (to minimize the formation of yellow color due to the oxidation of polysorbate 80, the IV Bag Diluent was formulated with 25 mM citric acid as an additional excipient) - shelf life extension for blinatumomab (up to 48 months)
27 October 2008	- extension of inclusion criterion #2 to bcr/abl and/or t(4;11) translocation at any detection level measured by RT-PCR - modification of exclusion criterion #15 to threshold of the antithrombin activity for exclusion of subjects from < lower limit of normal (LLN) to < 70% - modification of exclusion criterion #16 to allow subjects with history of malignancy other than ALL - change in the time of mandatory anticoagulation during study treatment to first 7 days of each treatment cycle - change in criteria for dose escalation - addition of secondary endpoint of MRD response after any treatment cycle
24 March 2009	- recommendation of intrathecal prophylaxis during treatment - reduction of number of PD and PK assessments - prolongation of hospitalization for monitoring following dose escalation - adaption of informed consent form - change of principal investigator at Dresden site
25 January 2010	- change in post-study follow-up period assessments and times - change from electronic CRFs to paper version in post study follow-up period - specification of duration of subject participation/duration of study to up to 62 weeks for core study - change in planned statistical analysis to remove comparison of time to event analyses to historical control data
02 March 2011	- prolong the administration period of blinatumomab final solution from 7 to 10 days - administrative changes regarding study site personnel contact information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported