Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Blinatumomab (rch)

Proprietary Product Name: Blincyto

Sponsor: Amgen Australia Pty Ltd

First round report: April 2015
Second round report: September 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website < https://www.tga.gov.au/product-information-pi >

Contents

List of abbreviations

Abbreviation	
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AMG103	Blinatumomab (drug development code)
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AT	Anti-thrombin
ATC	Anatomical Therapeutic Chemical
AV	Atrioventricular
b/l	Baseline
B-ALL	B cell acute lymphoblastic leukaemia
bcr/abl	Breakpoint cluster region of ABL1 genes
BiTE	Bispecific T cell engager
BLOQ	Below the lower limit of quantification
BSA	Body surface area
BTCR	B cell: T cell ratio
CD	Cluster of differentiation
CD19	Marker on B cells
CD197	Also called CCR7; marker for T cell differentiation
CD28	Cluster of Differentiation 28; one of the molecules expressed on T cells that provide co-stimulatory signals, which are required for T cell activation
CD3	Marker on T cells
CD4	Marker on a subset of T cells (CD4+ T cells)

Abbreviation	Meaning
CD45RA	Isoform of CD45 expressed on distinct subsets of T cells; marker for T cell differentiation
CD8	Marker on a subset of T cells (CD8+ T cells)
CI	Confidence interval
CL	Clearance
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum observed concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CPR	Cardiopulmonary resuscitation
CR	Complete remission
CR	Complete response/remission
CrCL	Creatinine clearance estimated by Cockcroft-Gault formula
CRF	Case report form
CRh*	Complete remission with partial haematological recovery
CRO	Contract Research Organisation
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C_{ss}	Concentration at steady state
CST	Clinical study team
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTM4	Clinical Trial Material 4
CTM5	Clinical Trial Material 5 (clinical trial material from the market manufacturing process)

Abbreviation	Meaning
CV	coefficient of variation
DBP	Diastolic blood pressure
dF	Degree of freedom
DFS	Disease free survival
DIC	Disseminated intravascular coagulation
DMC	Data monitoring committee
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EDC/CDM	Electronic data capture/clinical data management
EFS	Efficacy Set
ELISA	Enzyme-linked immunosorbent assay
EoCS	End of core study
EOI	Events of interest
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGTγ	Glutamyltransferase
GvHD	Graft versus-host disease
H0	Null hypothesis
HAMA	Human anti-mouse antibodies
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

Abbreviation	Meaning
HLA/HLA-DR	Human leukocyte antigen/human leukocyte antigen
HSCT	Haematopoietic stem cell transplantation
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IIV	Interindividual variability
IL	Interleukin
INR	International normalised ratio (of prothrombin time)
IOV	Interoccasion variability
IPRED	Individual predictions
IRB	Institutional Review Board
IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
LFA	1 lymphocyte function-associated antigen 1
LLOQ	Lower limit of quantification
LOD	Limit of detection
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MT103	Blinatumomab (drug development code)

Abbreviation	Meaning
MVOF	Minimum value of objective function
n.e.	Not estimable
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NONMEM	Nonlinear mixed effects modelling
NPC	Numerical predictive checks
NPDE	Normalised prediction distribution errors
NSAID	Nonsteroidal anti-inflammatory drug
OS	Overall survival
PAS	Primary Analysis Set
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDS	Pharmacodynamics Data Set
pg	Picogram
Ph+	Philadelphia chromosome (Philadelphia-positive subtype)
PK	Pharmacokinetics
PKS	Pharmacokinetic Data Set
PPS	Per Protocol Set
Pre-B-ALL	Immunophenotypic subtype of adult B-Precursor ALL defined by the detection of HLA-DR, TdT, CD19, CD10 and cytoplasmic μ-chains
Pro-B ALL	Immunophenotypic subtype of adult B-Precursor ALL defined by the detection of HLA-DR, TdT, CD19
PT	Prothrombin time

Abbreviation	Meaning
PTT	Partial thromboplastin time
QRS interval	Time from the beginning to the end of the QRS complex on ECG
QT interval	Time from the beginning of the QRS complex to the end of the T wave on ECG
QTcB	Bazette's correction to QT interval
QTcF	Fridericia's correction to QT interval
R/R	Refractory or relapsed
R0	Infusion rate
RFS	Relapse free survival
RR	Interval of time from the peak of one R wave to that of the following R wave on ECG
RSE	Relative standard error
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST: aspartate aminotransferase)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
sWFI	Sterile water for injection
TCM	Central memory T cell
TCR	T cell receptor
TEM	Type of effector memory T cell
TKI	Tyrosine kinase inhibitor
TLS	Tumour lysis syndrome
TNF	Tumour necrosis factor

Abbreviation	Meaning
TVCL	Typical value of systemic clearance
ULN	Upper limit of normal
V	Volume of distribution for the central compartment
Vz	Volume of distribution
WBC	White blood cell
WHO	World Health Organization
θ	Theta typical value of a structural model parameter
σ2 sigma2	Variance of the residual error
ω2 omega2	Inter-individual variance

1. Introduction

1.1. Drug class and therapeutic indication

This is a full submission to register the new chemical entity, blinatumomab (rch)

Blinatumomab is a novel single chain antibody construct of the bispecific T cell engager (BiTE) class that selectively binds with high affinity to CD19 (expressed on lymphocytes of B-lineage origin) and CD3 (expressed on T lymphocytes).

The proposed indication is:

> *"Blincyto is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)'.*

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

A composite pack which contains:

- One single use vial containing 38.5 mcg of blinatumomab, citric acid monohydrate, trehalose dehydrate, lysine hydrochloride, polysorbate 80 and sodium hydroxide lyophilised powder for reconstitution with 3 mL of preservative free sterile water for injections.
- One single use vial of intravenous solution stabiliser containing citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide (for pH adjustment) and water for injections.

2. Clinical rationale

2.1. Clinical rationale

Adult Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) are aggressive leukaemias that carry very poor prognoses, with median overall survivals reported to be 3 to 5 months with current chemotherapy treatments. Thus, refractory or relapsed and MRD positive ALL remains an unsolved therapeutic problem, for which therapies with an alternative mechanism of action are needed.

When patients relapse, the response rate is low, and if a CR is obtained, it is generally of very short duration. Current treatment options are limited, the most common including different combinations of multi-drug chemotherapy regimens, with the goal of inducing remission to allow allogeneic haematopoietic stem cell transplantation (HSCT; currently the only potentially curative option), or to obtain long-term remission if allogeneic HSCT is not possible. The outcome of adult ALL, regardless of age or treatment, is extremely poor. All treatment approaches are based on small studies with complete remission rates of 25% to 50% that are very short. The poor outcome of relapsed ALL is highlighted in children by the fact that in the last 20 years, no study was able to show an improvement in all relapsed risk groups.

Consequently, most new agents will be first used in the relapsed setting. Blinatumomab is a single-chain antibody with dual specificity against CD3 and CD19 (bispecific T cell engaging or BiTE antibody), which brings normal cytotoxic T cells into close proximity with normal and malignant CD19-positive B cells. Conventional monoclonal antibodies, which lack the dual

specificity of BiTE antibodies, do not draw T cells and B-ALL cells together for the same degree of potent tumour-cell killing. The proposed use of blinatumomab is as a targeted therapy option for relapsed or refractory Philadelphia chromosome negative ALL, with the aim to achieve a second CR and enable a prompt allogeneic HSCT with any available suitable donor.

2.2. Formulation development

A total of 2 drug product formulations have been used in the context of the blinatumomab clinical program and the 6 drug substance manufacturing processes.

- Process 1 and Process 2: The drug product formulation used in early clinical trials was provided as a liquid formulation containing 1 µg/mL blinatumomab in phosphate buffered saline (PBS), supplemented with 0.1% human serum albumin (HSA).
- Process 3 to Commercial Process**:** A single major formulation change was implemented beginning with Process 3. This formulation was selected for both drug substance and drug product and was used for most of the Phase II clinical trials and the ongoing Phase III clinical trial.

Formulation development initiated with Process 3 was designed to:

- Increase the blinatumomab concentration to 55 µg/mL
- Remove HSA
- Improve the blinatumomab stability and prevent adsorption to surfaces
- Support a lyophilised formulation with acceptable stability when stored at 2°C to 8°C and after reconstitution

2.3. Guidance

TGA has adopted the following EU guidelines relevant to this submission:

- EMA/CHMP/205/95/Rev.4 Guideline on the evaluation of anticancer medicinal products in man Replaces: CPMP/EWP/205/95/Rev.3/Corr (Adopted by TGA June 2006)
  Effective: 1 April 2014
- CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations
  Effective: December 2006

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety.

The submission contained the following clinical information:

- 4 clinical studies in adults (Studies MT103-104, MT103-202, MT103-206 and MT103-211) in which pharmacokinetic and pharmacodynamic properties of blinatumomab were assessed in addition to safety/efficacy.
- 1 pivotal efficacy/safety study (Study MT103-211), which also provided pharmacodynamic and pharmacokinetic data.

- 1 efficacy/safety study (Study MT103-206), which also provided pharmacodynamic and pharmacokinetic data.
- 2 efficacy/safety studies (Study MT103-202; Study MT103-203) for indications which differed from the current application and which also provided pharmacodynamic and pharmacokinetic data.
- 1 study analysing historical comparator data (Study 20120310).
- 2 model based meta-analyses (Studies 118427 and 119834).

In addition, the submission contained the following: A Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, Quality Overall Summaries of Blinatumomab and Intravenous Stabiliser Solution tabulations and statistical analysis plan and literature references.

3.2. Paediatric data

Results from Phase I of the ongoing Phase I/II Study MT103-205, were included in the submission. This was a first paediatric study, not a first in human study. This was an open label, combined 2 part multicentre clinical study. Phase I was a dose finding study to investigate the PK, safety, and clinical activity of escalating levels (3.7 to 60 μg/m^2/day) of blinatumomab in paediatric and adolescent patients with relapsed or refractory B-precursor ALL. Once a recommended dose was selected in the Phase I part of the study, the Phase II part (2 stage single arm design) was begun to assess the safety and efficacy of the recommended dose level of blinatumomab. The study consisted of a screening period, a treatment period, and an end of core study visit 30 days after the last dose of study medication. After the last treatment cycle all subjects were followed for efficacy and survival up to 24 months after treatment start.

3.3. Good clinical practice

All of the studies at US sites were conducted under a United States Investigational New Drug Application (IND). All non-US sites complied with local regulations. All of the sites (US and non-US) were conducted in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All patients provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

An overview of the clinical pharmacology of blinatumomab, including support for the fixed dose regimen and schedule for adults with relapsed/refractory ALL (9 μg/day for the first 7 days of treatment, followed by 28 μg/day starting from Week 2, as a continuous intravenous (IV) infusion at a constant flow rate over 4 weeks followed by a treatment free interval of 2 weeks)

was presented in the Summary of Clinical Pharmacology Studies. Table 1, shown below, gives the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in target population (adults)	Phase I, non-randomised, non-controlled, open label, interpatient dose escalation study	MT103-104	Determine the maximal tolerable dose, PK, PD, and antitumor activity
	Phase II, non-randomised, non-controlled, open label study	MT103-202	Investigate the efficacy (MRD response rate), safety, tolerability, PK, and PD
	Phase II, open label, multicentre, exploratory study	MT103-206	Evaluate the efficacy, safety, tolerability, PK, and PD
	Phase II, open label, multicentre, single arm study	MT103-211	Evaluate the efficacy, safety, tolerability, PK, and PD
PK in special populations (paediatric subjects < 18 years)	Phase II, multicentre, single arm study preceded by dose evaluation	MT103-205	Investigate the efficacy, safety, and tolerability of blinatumomab in paediatric and adolescent subjects with R/R ALL

None of the studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

There was no specific pharmacokinetics and pharmacodynamics clinical study in the blinatumomab clinical program. Pharmacokinetics and pharmacodynamics were assessed along with safety and efficacy in 4 clinical studies (Studies MT103-104, MT103-202, MT103-206 and MT103-211). In addition, the interim pharmacokinetic results for the paediatric Study MT103-205 were provided. The effects of intrinsic factors on the blinatumomab pharmacokinetics were evaluated using integrated data obtained from the adult studies. An absorption study was not conducted because the intended route of administration for blinatumomab is via continuous IV infusion.

A formal drug-drug interaction study (for example with CYP450 enzyme inhibitors) was not conducted as blinatumomab is not expected to be eliminated via hepatic metabolism (for example, by CYP450 enzymes) and blinatumomab is primarily intended to be administered as a single agent. The indirect effect of cytokine elevation on CYP450 activities following blinatumomab administration was evaluated with physiologically based pharmacokinetic (PBPK) modelling and simulations were conducted to evaluate the effect of blinatumomab-induced cytokine elevation on CYP450 activities (Study 117730).

Formal pharmacokinetic studies in subjects with renal impairment or hepatic impairment were not conducted. The effects of renal and hepatic impairment on blinatumomab pharmacokinetics were assessed by retrospective analysis of data from the 4 adult clinical trials.

No thorough QTc study was conducted. The relationship between blinatumomab concentrations and QT prolongation was assessed using the integrated data from Studies MT103-203 and MT103-206.

4.2.1. Physicochemical characteristics of the active substance

Blinatumomab is a bispecific T cell engager (BiTE) antibody construct that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). Using recombinant DNA technology, Blincyto is produced in a well characterised mammalian cell (Chinese hamster ovary) culture. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

4.2.2. Pharmacokinetics in the target population

4.2.2.1. Pharmacokinetic assessments

The pharmacokinetic sampling strategy for each study (either intense or limited serial sampling) is indicated below in Table 2. A validated bioassay was used to quantify serum blinatumomab concentrations. The assay is based on the principle that the CD69 activation marker is expressed on T cells in a blinatumomab concentration dependent manner; therefore the assay measures 'active form' of blinatumomab. The pharmacokinetic parameters of blinatumomab were analysed by non-compartmental analysis and population pharmacokinetic analysis.

4.2.2.2. Immunogenicity assessments

Subjects were monitored throughout each study to characterise the development of anti-blinatumomab antibodies and to explore the impact of any positive anti-drug antibody (ADA) on the pharmacokinetics of blinatumomab. Immunogenicity was assessed by a validated ELISA method to determine if anti-idiotype antibodies directed against blinatumomab and/or human anti-mouse antibodies were detectable.

4.3. Summary of results of individual studies

Table 2, shown below, provides brief descriptions of the 4 adult and 1 paediatric clinical studies included in this summary of clinical pharmacology. Information includes main study design components, key study results, and pharmacokinetic/pharmacodynamic assessments. Further details are provided in the subsequent sections.

Table 2: Blinatumomab pharmacokinetic parameter estimates following continuous IV infusion in adult subjects with NHL, MRD+ ALL, and R/R ALL

Study ID	Study design; objectives	Test products, dosage regimens, and route of administration	Key entry criteria	Number of subjects randomised	PK/PD sampling scheme (subjects)	Key study and clinical pharmacology results
MT 103-104	Phase I, nonrandomised, non-controlled, open label, interpatient dose escalation study to determine the maximal tolerable dose, PK, PD, and antitumor activity.	CTM4, 0.5, 1.5, 5, 15, 30, 60, and 90 µg/m^2/day cIV for 4 to 8 weeks	Adults with relapsed NHL	76	Intensive (76)	60 µg/m^2/day was identified as the maximal tolerable blinatumomab dose based on efficacy (69% objective response rate (ORR)) and safety/ tolerability profiles. PK was linear with cIV infusion up to 90 µg/m^2/day. Drug exposure was stable over the duration of infusion and systemic clearance was fast with limited renal excretion at the clinical viable doses. T cell, B-cell and cytokine profiles were characterised.

Study ID	Study design; objectives	Test products, dosage regimens, and route of administration	Key entry criteria	Number of subjects randomised	PK/PD sampling scheme (subjects)	Key study and clinical pharmacology results
MT 103-202	Phase II, non randomised, non controlled, open label study to investigate the efficacy (MRD response rate), safety, tolerability, PK, and PD	CTM4, 15 / 30 µg/m^2/day[a], cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with B-precursor ALL in complete haematological remission with MRD	21	Intensive (21)	Blinatumomab showed a high MRD response rate (88%) and a favourable safety profile at 15 µg/m^2/day. C_{ss} increased dose-dependently and remained stable over time. Risk:benefit profiles were similar at doses of 15 and 30 µg/m^2/day.
MT 103-206	Phase II, open label, multicentre, exploratory study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4, 5/15/30 µg/m^2/day[b] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	36	Less Intensive (36)	Blinatumomab showed single-agent activity with a CR/CRh* rate of 69.4% and a clinically manageable toxicity profile. With cIV over 4 weeks, mean C_{ss} values increased approximately dose proportionally. Efficacy and tolerability profiles support a dosing regimen of 5-15 µg/m^2/day.

Study ID	Study design; objectives	Test products, dosage regimens, and route of administration	Key entry criteria	Number of subjects randomised	PK/PD sampling scheme (subjects)	Key study and clinical pharmacology results
MT 103-211	Phase II, open label, multicentre, single arm study to evaluate the efficacy, safety, tolerability, PK, and PD	CTM4 & CTM5, 9/28 µg/day[c] cIV for 4 weeks followed by 2 weeks off drug per cycle	Adults with R/R ALL	189	Less intensive (189)	Blinatumomab demonstrated clinical meaningful therapeutic benefits to ALL patients with a CR/CRh* rate of 42.9% within 2 cycles. Efficacy and tolerability profiles support a dosing regimen of 9/28 µg/day cIV. The results showed similar C_{ss} values for CTM4 and CTM5 after cIV and therefore support the conclusion of PK comparability between CTM5 and CTM4.

Study ID	Study design; objectives	Test products, dosage regimens, and route of administration	Key entry criteria	Number of subjects randomised	PK/PD sampling scheme (subjects)	Key study and clinical pharmacology results
MT 103-205	Phase II, multicentre, single arm study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in paediatric and adolescent subjects with R/R ALL	Phase I: 3.75 to 60 µg/m^2/day cIV, 4 weeks on followed by 2 weeks off Phase II: Up to 5 cycles with dose of blinatumomab established in Phase I	Paediatric subjects < 18 years with ALL	Phase I: up to 48 planned Phase II: up to 40 evaluable subjects	Intensive (41)	C_{ss} was achieved within a day and remained stable over time. Mean C_{ss} values increased approximately dose proportionally over the dose range from 5 µg/m^2/day to 30 µg/m^2/day. The selected dose regimen for Phase II was 5 µg/m^2/day for Week 1 and 15 µg/m^2/day for weeks 2 through 4 of Cycle 1; and 15 µg/m^2/day in subsequent cycles.

ALL = acute lymphoblastic leukaemia; cIV = continuous intravenous infusion; CTM4 = process 4 clinical material; CTM5 = process 5 clinical material; CR = complete remission; CRh* = complete remission with partial haematological recovery; C_{ss} = steady state concentration; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; PD = pharmacodynamic; PK = pharmacokinetic; R/R = relapsed/refractory. a) In Study MT 103-202, the dose regimen was 15 µg/m^2/day; intrapatient dose escalation to 30 µg/m^2/day was permitted for patients with stable disease who had not responded after 1 cycle at the 15 µg/m^2/day dose; b) Study MT 103-206 had 3 dosing schedules: (1) a 15 µg/m^2/day flat dose, (2) a 5 µg/m^2/day starting dose with intrapatient dose escalation to 15 µg/m^2/day, (3) a 5 µg/m^2/day starting dose with intrapatient dose escalation to 15 µg/m^2/day and then to 30 µg/m^2/day; c) In Study MT 103-211, the starting dose was 9 µg/day with intrapatient dose escalation to 28 µg/day. Fixed dosing was used in this study versus BSA dosing used in the other 3 cIV infusion studies.

4.3.1. Study MT103-104 Phase I Study in Subjects with NHLs

4.3.1.1. Study objectives and design

This trial was a Phase I non-randomised, non-controlled, open label, interpatient dose escalation study in 76 adult subjects with relapsed B-lineage NHL. The primary objective was to determine the safety and tolerability of cIV infusions of blinatumomab at different dose levels in order to determine the maximal tolerable dose. The secondary objectives were to determine the

pharmacokinetic, pharmacodynamic (cytokine levels, T- and B-cell count), and anti-tumour activity of blinatumomab.

Blinatumomab was administered as 4 or 8-week cIV infusion at 7 dose levels ranging from 0.5 to 90 µg/m^2/day. Subjects were treated with either a consistent dose throughout the treatment period or intra-individual dose escalations, for example, 5/60 or 5/15/60 µg/m^2/day. All subjects were to be treated for at least 4 weeks unless dose limiting toxicities or disease progression occurred. Intense pharmacokinetic and pharmacodynamic samples were collected over the treatment period.

Blinatumomab serum concentrations at doses of 0.5 and 1.5 µg/m^2/day were below the lower limit of quantification (LLOQ = 100 pg/mL) of the bioanalytical assay and therefore the pharmacokinetic parameters were not able to be estimated. The summary statistics of C_{ss} during cIV infusion from 5 to 90 µg/m^2/day and blinatumomab pharmacokinetic parameter estimates are presented below in Table 3.

In the statistical analysis of dose proportionality, individual C_{ss} values were used and repeated measures from the same subject were taken into account via a random subject effect. Based on the available data in this study, the blinatumomab exposure levels increased approximately linearly with dose (slope = 1.07, 95% CI: 1.028, 1.114) (see Figure 1, below.)

Figure 1: Mean serum blinatumomab concentration at steady state (C_{ss}) versus dose

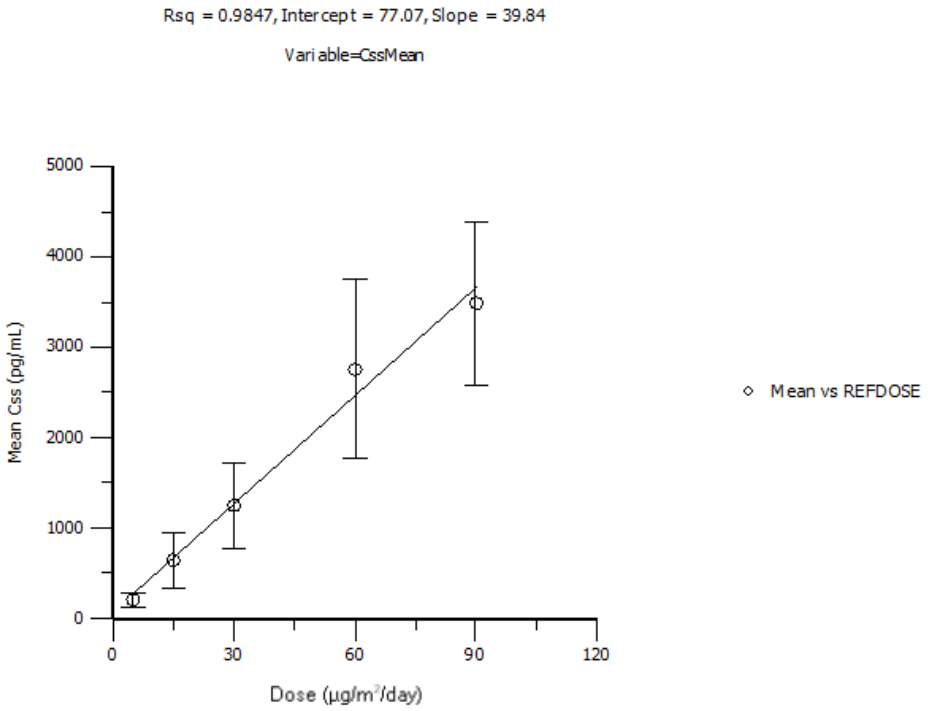


Table 3: Descriptive statistics of blinatumomab pharmacokinetic parameter estimates following continuous IV infusion over 4 or 8 weeks in subjects with relapsed non-Hodgkin's lymphoma

Dose (µg/m²/day)	5 pg/mL	15 pg/mL	30 pg/mL	60 pg/mL	90 pg/mL	$t_{1/2,z}$ (hr)	CL (L/hr/m²)	Vz (L/m²)
N	32	36	6	34	4	33	66	33
Mean	210	651	1210	2730	3490	2.44	1.16	2.30
SD	84.9	307	476	985	904	1.62	0.585	1.27
CV%	40.5	47.2	39.4	36.0	25.9	66.3	50.5	55.2
Min	100	154	493	1070	2490	0.906	0.402	0.960
Median	195	618	1180	2820	3460	1.93	0.990	2.07
Max	431	1550	1920	5640	4540	8.31	3.27	6.37
Geometric Mean	194	574	1120	2550	3400	2.07	1.05	2.04
CV% Geometric Mean	41.4	58.5	48.6	4.04	26.9	59.4	45.4	51.8

C_{ss} = concentration at steady state; CL = clearance; CV% = coefficient of variance; min = minimum; max = maximum; SD = standard deviation; N = number of subjects; $t_{1/2,z}$ = terminal half-life; Vz = terminal Phase volume of distribution.

Data obtained with cIV infusion of 60 µg/m²/day over 8 weeks indicate that blinatumomab concentrations were stable over the treatment period. Urine samples collected at steady state (Day 16) from subjects that received the 60 µg/m²/day dose were analysed; negligible amounts of blinatumomab were detected in urine.

This study established the maximum tolerated dose for blinatumomab at 60 µg/m²/day in subjects with relapsed/refractory NHL. A dose-dependent clinical efficacy of single-agent blinatumomab was evident in subjects with relapsed NHL and the highest response rate was 69% achieved at the 60 µg/m²/day dose. Blinatumomab showed linear pharmacokinetic behaviours up to a dose of 90 µg/m²/day and the serum concentrations were stable over treatment period under cIV infusion. Blinatumomab showed a rapid clearance and a short half-life (around 2 hours), indicating the necessity of maintaining a sustainable effective concentration range via cIV.

4.3.2. Study MT103-202 Phase II study in Subjects with MRD+ ALL

4.3.2.1. Study Objectives and Design

Study MT 103-202 was a Phase II, open label, multicentre, single arm study designed to investigate the efficacy, safety, and tolerability of blinatumomab in adult subjects with MRD following established standard induction/consolidation therapy of B-precursor ALL. The study included a Simon's 2 stage design and a run in dose finding part. The primary endpoint was MRD response rate defined by the incidence of MRD negativity within 4 cycles of treatment with

blinatumomab. Key secondary endpoints included MRD response rate after any treatment cycle, pharmacokinetics, pharmacodynamics, and overall incidence and severity of adverse events.

During the run-in dose finding part of the study, subjects (n = 21) received blinatumomab at a dose of 15 µg/m^2/day cIV for 4 weeks followed by 2 weeks treatment free (1 cycle was 6 weeks). The blinatumomab dose was increased to 30 µg/m^2/day cIV for subjects who did not achieve a reduction in MRD level by ≥ 1 log unit. Subjects achieving MRD response were permitted to receive 3 additional consolidation cycles of treatment with blinatumomab. Subjects who showed neither MRD progression nor response were allowed to receive up to 7 cycles of blinatumomab (up to a maximum of 10 cycles). Following the last treatment cycle, subjects were assessed at every 6 weeks until disease progression but not longer than 5 years after the end of the last cycle.

With cIV infusion of 15 µg/m^2/day of blinatumomab over 4 weeks, C_{ss} remained stable during the infusion period. During Cycle 1 with a 15 µg/m^2/day blinatumomab dose, the mean (SD) C_{ss} was 696 (147) pg/mL (see Table 4, below). The mean C_{ss} in Cycle 1 and in subsequent cycles were comparable. 3 subjects received blinatumomab at the 30 µg/m^2/day dose. A dose-dependent increase in drug exposure was observed.

Table 4: Descriptive statistics of blinatumomab C_{ss} (pg/mL) and pharmacokinetic parameter estimates following continuous IV infusion of blinatumomab at 15 µg/m^2/day over 4 weeks in Cycle 1 to patients with positive MRD B-precursor ALL

	12 h	D7	D14	D21	D28	Cycle 1 mean	AUC_{inf} (h x ng/mL)	Vz (L/m^2)	CL (L/h/m2)	$t_{1/2,z}$ (h)
N	19	19	19	19	19	19	18	18	19	18
Mean	584	777	703	725	690	696	481	2.00	0.939	1.47
SD	192	281	219	226	189	147	106	0.95	0.199	0.53
Min	261	543	346	411	250	446	344	0.943	0.627	0.660
Median	558	625	662	670	668	656	466	1.81	0.953	1.42
Max	1210	1730	1210	1290	1000	984	678	4.31	1.40	2.54
CV%	32.8	36.2	31.2	31.1	27.5	21.1	22.1	47.6	21.2	36.1

AUC_{inf} = area under the drug concentration-time curve from time zero to infinity; CL = drug clearance after IV administration calculated by CL = R0/C_{ss}; C_{ss} = drug concentration at steady state; %CV = coefficient of variation D = day; h = hour; IV = intravenous; LLOQ = lower limit of quantification; max = maximum; min = minimum; SD = standard deviation; $t_{1/2,z}$ = terminal half-life; Vz = volume of distribution based on the terminal phase. Note: LLOQ = 100 pg/mL.

4.3.3. Study MT103-206 Phase II study in Subjects with R/R ALL

4.3.3.1. Study objectives and design

Study MT 103-206 was a Phase II, open label, multicentre, exploratory study to evaluate the efficacy, safety, and tolerability of blinatumomab in 36 adult subjects with relapsed and/or refractory B-precursor ALL (R/R ALL). The primary study endpoint was the rate of CR/CRh within 2 cycles of blinatumomab treatment. Other measures of efficacy such as individual response rates, measures of survival, time to haematological relapse, proportion of patients

eligible for allogeneic haematopoietic stem cell transplantation (HSCT), and the rate of MRD response were also evaluated. Other secondary objectives were to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of blinatumomab in subjects with R/R ALL.

This single arm study used a dose finding run-in and a modified Simon's 2 stage design. In this study, subjects were initially enrolled at a dose of 15 µg/m^2/day; however, to reduce first dose effects on safety, the next cohort was enrolled at 5 µg/m^2/day for the first 7 days and 15 µg/m^2/day for the remaining 3 weeks of Cycle 1 (a cycle was 4 weeks on treatment, 2 weeks off) and received 15 µg/m^2/day for the whole duration of subsequent cycles. As this dosing was tolerated, a third cohort was enrolled at 5 µg/m^2/day for the first 7 days, 15 µg/m^2/day for the subsequent 7 days and 30 µg/m^2/day for the remaining 2 weeks of Cycle 1 and the whole duration of subsequent cycles (5 to 15 to 30 µg/m^2/day).

With cIV infusion of blinatumomab over 4 weeks, C_{ss} remained stable over time. Mean (standard deviation (SD)) C_{ss} values for blinatumomab at 5, 15, and 30 µg/m^2/day were 167 (66), 553 (238), 1180 (820) pg/mL, respectively. Mean C_{ss} increased approximately dose proportionally. The calculated mean (SD) CL estimate was 1.34 (0.61) L/hr/m^2.

4.3.4. Study MT103-211: Pivotal Phase II study in subjects with R/R ALL

4.3.4.1. Study Design and Objectives

Study MT 103-211 is an ongoing Phase II, open label, multicentre, global, single arm study designed to evaluate the efficacy and safety of blinatumomab in adult subjects with Ph negative, relapsed/refractory B-precursor ALL. The primary study endpoint was the rate of CR/CRh within 2 cycles of blinatumomab treatment. Other measures of efficacy were also evaluated. The overall incidence and severity of adverse events were also assessed. In addition, the pharmacokinetic profiles of blinatumomab manufactured with 2 different processes were assessed (Process 4 and Process 5, resulting in clinical trial material 4 (CTM4) and CTM5, respectively).

A fixed dose regimen of cIV was tested in this study. An initial dose of 9 µg/day was administered for the first 7 days, followed by a 28 µg/day dose starting at Week 2 and continuing for the remaining 3 weeks of the first cycle. There was a 2 week drug free period between cycles. In subsequent cycles, the 28 µg/day dose was administered over the 4 weeks of each cycle. Subjects who achieved CR or CRh within 2 cycles could receive up to 3 additional cycles of treatment. The 9 µg/day and 28 µg/day doses corresponds to the 5 µg/m^2/day and 15 µg/m^2/day doses, respectively, that were used in prior studies.

Blinatumomab serum concentrations of CTM4 and CTM5 were assessed following continuous IV infusion over 4 weeks. Mean (SD) C_{ss} were similar between the 2 materials in both the first and second treatment cycles (see Table 5, shown below). Moreover, in a statistical comparison of C_{ss} values for CTM4 (reference) and CTM5 (test material), the ratio (test/reference) of least squares geometric mean of C_{ss} between CTM5 and CTM4 was 0.91 (90% CI: 0.72, 1.15) for Cycle 1 and 1.13 (0.89, 1.42) for Cycle 2. Body size (baseline body weight, body surface area (BSA)) did not affect blinatumomab clearance (CL), providing further support for a fixed dose regimen.

Table 5: Descriptive statistics of blinatumomab steady-state concentrations (C_{ss}) and clearance (CL) values following continuous IV infusion of blinatumomab over 4 weeks

	Cycle 1 C_{ss} (pg/mL)		Cycle 2 C_{ss} (pg/mL)
Dose	9 µg/day	28 µg/day	28 µg/day
CTM4			

	Cycle 1 C_{ss} (pg/mL)		Cycle 2 C_{ss} (pg/mL)
N	89	113	56
Mean	198	640	709
SD	202	535	458
Min	51.0	66.0	79.0
Median	124	503	634
Max	991	2850	2760
Geometric Mean	143	476	585
Geometric Mean CV%	84.4	95.8	73.4
CTM5			
N	43	47	32
Mean	238	575	771
SD	346	414	423
Min	54.0	57.0	159
Median	137	475	648
Max	1780	2130	1670
Geometric Mean	154	431	659
Geometric Mean CV%	92.5	101.7	65.4

C_{ss} = steady state concentration; CTM4 = Clinical Trial Material 4; CTM5 = Clinical Trial Material 5; CV% = coefficient of variance; SD = standard deviation.

Pharmacokinetic assessment demonstrated that the blinatumomab PK is predictable and PK, efficacy and safety profiles across treatment cycles for CTM4 and CTM5 blinatumomab generated from 2 manufacturing processes were similar, thereby supporting the clinical pharmacological comparability of the materials used in many of the earlier clinical studies (CTM4) and the recent studies (CTM5).

4.3.5. Study MT103-205: Phase II study in paediatric Subjects with R/R ALL

4.3.5.1. Study design and objectives

Study MT103-205 is an ongoing, open label, single arm, multicentre Phase II study, preceded by a Phase I dose evaluation part, designed to investigate the efficacy, safety, and tolerability of blinatumomab in paediatric and adolescent subjects (< 18 years) with relapsed/refractory B-

precursor ALL. The primary endpoint of the Phase I part of the study was to determine the recommended Phase II dose of blinatumomab by assessing the maximal tolerated dose of blinatumomab. Other objectives were to assess the safety, pharmacokinetics, pharmacodynamics, and efficacy of blinatumomab. The primary endpoint of the Phase II part of the study (ongoing) is the rate of CR within the first 2 cycles of blinatumomab treatment.

The Phase I part of the study (up to 48 subjects) was designed to evaluate different dose levels and different dosing regimens of blinatumomab in different age groups (< 2 years, 2 to 6 years, and 7 to 17 years). Doses from 3.75 to 60 µg/m^2/day cIV were proposed for testing. Based on data from the first phase, the Data Review Committee and Data Safety Monitoring Board defined a recommended dose for the Phase II part of the study. After a Phase II dose was selected, a pharmacokinetic expansion of Phase I enrolled an additional 6 subjects in each of the 2 older age groups (2 to 6 and 7 to 17 years) for comprehensive PK/PD assessments. Enrolment of an additional 6 subjects into the younger age group (< 2 years) is ongoing and enrolment of subjects in this age group into the Phase II part of the study will begin after the 6 subjects in the pharmacokinetic expansion have been treated at the recommended dose.

In the Phase II part of the study (efficacy Phase), subjects < 18 years of age will be enrolled according to a 2-stage design. In the first stage, 21 subjects will be enrolled. If more than 2 of 21 subjects are observed with a response, an additional 19 subjects will be enrolled in the second stage. Eligible subjects will receive blinatumomab at the recommended Phase II regimen (that is, 5 µg/m^2/day in Week 1 and 15 µg/m^2/day in weeks 2-4 in Cycle 1, and then 15 µg/m^2/day in remaining cycles). In total, up to 40 subjects will be recruited into this 2 stage efficacy part of the trial.

Following continuous IV infusion, the steady state serum concentration (C_{ss}) was achieved within a day and remained stable over time. Mean C_{ss} increased approximately dose proportionally over the dose range from 5 µg/m^2/day to 30 µg/m^2/day. Under the selected Phase II regimen (that is, 5 µg/m^2/day for Week 1 and 15 µg/m^2/day for Weeks 2 through 4 of Cycle 1; and 15 µg/m^2/day in subsequent cycles), mean (SD) C_{ss} at 5 and 15 µg/m^2/day doses were 178 (175) and 390 (286) pg/mL in the 2 to 6 years age group and 154 (103) and 620 (305) pg/mL in the 7 to 17 years age group, respectively. The mean (SD) terminal elimination half-life ($t_{1/2}$) was 2.19 (1.53) hours, clearance (CL) was 2.01 (2.08) L/hr/m^2 and volume of distribution based on terminal phase (Vz) was 3.99 (3.31) L/m^2 across both age groups. Data from the younger age group (< 2 years) was not available for the interim analysis and was therefore not presented.

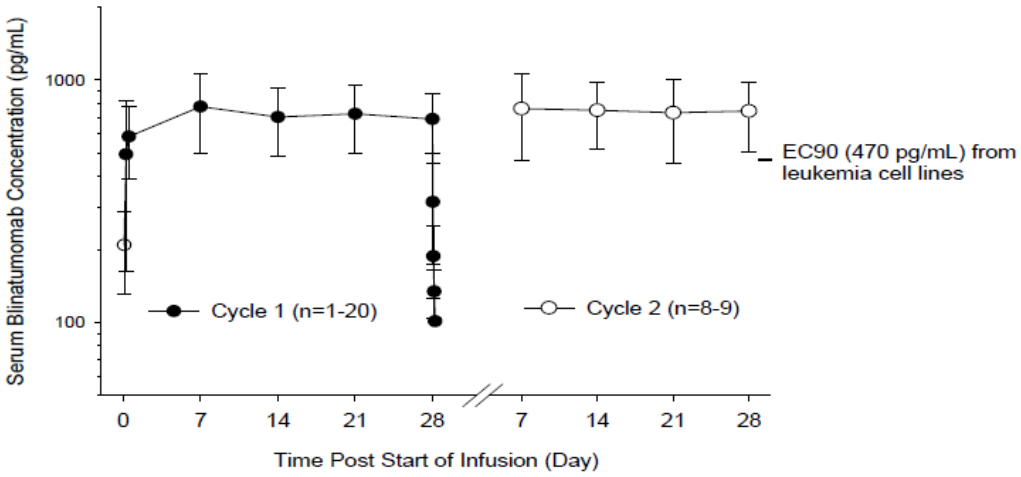
4.3.6. Conclusions

Based on BSA based doses, blinatumomab exhibited linear pharmacokinetics, and pharmacokinetic parameters were similar in the 2 to 6 years and 7 to 17 years age groups. The 15 µg/m^2/day (BSA based) dose was identified as the maximal tolerated dose. The regimen selected for the pharmacokinetic expansion cohort and for the Phase II portion of the study was 5 µg/m^2/day in Week 1 and 15 µg/m^2/day in weeks 2 to 4 in Cycle 1, and then 15 µg/m^2/day in remaining cycles.

4.4. General description of blinatumomab pharmacokinetics

The pharmacokinetics of blinatumomab were assessed over a range of doses (5 to 90 µg/m^2/day that were approximately equivalent to fixed doses of 9 to 162 µg/day) in adult subjects with ALL and NHL. With continuous intravenous infusion (cIV), steady state serum concentrations (C_{ss}) remained stable across the infusion period (see Figure 2, below). Mean C_{ss} values increased approximately dose proportionally over the dose range tested (see Table 6, below).

Figure 2: Mean (SD) serum concentration-time profiles of blinatumomab under continuous IV infusion at 15 µg/m²/day over 4 Weeks in Cycles 1 and 2



IV = intravenous; SD = standard deviation. Note: Dashed line indicated the effective concentration needed for 90% suppression of B-cells (EC_{90}) in in vitro studies conducted with leukaemia cell lines.

The estimated overall mean (CV%) volume of distribution based on terminal phase (Vz) was 4.52 L (64%), indicating that blinatumomab is mainly distributed in the vascular space. As a therapeutic protein, blinatumomab is likely cleared mainly via the normal catabolic degradation to small peptides and individual amino acids. Results from in vitro testing with human hepatocytes suggested that blinatumomab did not affect CYP450 enzyme activities (details given in Report NSX0011 [not reproduced here]) thus a pharmacokinetic interaction between blinatumomab and drugs metabolised by CYP450 enzymes is not expected.

Body size (body weight and body surface area (BSA)) did not affect drug clearance in adult patients. Mean C_{ss} values under the BSA based (initiate at 5 µg/m²/day and step to 15 µg/m²/day) and fixed dosing (initiate at 9 µg/day and step to 28 µg/day) were similar, supporting the use of a fixed dosing regimen. C_{ss} values were similar in adult and paediatric patients at the equivalent dose levels based on BSA based dosing regimens. Pharmacokinetic parameters in subjects with different disease states (ALL and NHL) were similar. The frequency of neutralising anti-blinatumomab antibodies was less than 1% (3 out of 325 subjects) in the 4 clinical studies.

The mean blinatumomab C_{ss} by dose across diseases and studies is given in Table 6, shown below.

Table 6: Mean (SD) blinatumomab steady state concentration (C_{ss}) by dose in subjects with NHL, MRD+ ALL and R/R ALL

Mean ± SD C_{ss} (pg/mL) (N)					
Disease Study (dosing)	**5 µg/m² or 9 µg**	**15 µg/m² or 28 µg**	**30 µg/m²**	**60 µg/m²**	**90 µg/m²**
Adult Subjects					
NHL					
MT103-104 (µg/m²/d)	210 ± 85 (n = 32)	651 ± 307 (n = 36)	1210 ± 476 (n = 6)	2730 ± 985 (n = 34)	3490 ± 904 (n = 4)
MRD + ALL					
MT103-202 (µg/m²/d)	NA	696 ± 147 (n = 19)	NA	NA	NA
R/R ALL					
MT103-206 (µg/m²/d)	167 ± 66 (n = 31)	552 ± 237 (n = 34)	1180 ± 820 (n = 5)	NA	NA
MT103-211 (µg/d)	211 ± 258[a] (n = 132)	621 ± 502[a] (n = 160)	NA	NA	NA
Paediatric Subjects (2 to 17 years of age)					
R/R ALL MT103-205					
(2 to 6 years) (µg/m²/d)	178 ± 175 (n = 9)	390 ± 286 (n = 14)	1090 (n = 1)	NA	NA
(7 to 17 years) (µg/m²/d)	154 ± 103 (n = 10)	620 ± 305 (n = 12)	1210 ± 635 (n = 5)	NA	NA
(2 to 17 years) (µg/m²/d)	165 ± 138 (n = 19)	496 ± 312 (n = 26)	1190 ± 570 (n = 6)	NA	NA

C_{ss} = steady state concentration, C_{ss} in Cycle 1 of each studies are included as it contained the most subjects; d = day; MRD+ = minimal residual disease positive; N = number of patients; NA = not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation; a) Fixed dosing (9 µg/day and 28 µg/day) was administered in the MT 103-211 study.

The estimated mean (CV%) clearance was 2.92 (97%) L/hr, and the mean terminal elimination half-life was 2.1 (68%) hours, as shown below in Table 7, showing that blinatumomab is rapidly eliminated from the body upon administration. Continuous IV infusion is thus required to maintain therapeutic concentrations of blinatumomab in the circulation. The estimated mean

fraction of excreted unchanged blinatumomab in urine was approximately 0.2% at the 60 µg/m²/day dose under continuous IV infusion, indicating limited renal excretion of blinatumomab.

Table 7: Blinatumomab pharmacokinetic parameter estimates following continuous IV infusion in adult subjects with NHL, MRD+ ALL, and R/R ALL

Study	Disease	Clearance (CL) (L/hr) N	Mean (SD)	Geo mean (CV%)	Median (Range)	Volume of distribution (Vz) (L) N	Mean (SD)	Geo mean (CV%)	Median (Range)	Terminal half life (t ½,z) (hr) N	Mean (SD)	Geo mean (CV%)	Median (Range)
Adult subjects													
MT103-104	NHL	66	2.29 (1.18)	2.06 (47.4)	2.00 (0.714 to 6.35)	32	4.84 (3.15)	4.19 (55.3)	4.00 (1.86 to 17.4)	32	2.47 (1.64)	2.10 (60.1)	2.02 (0.906 to 8.31)
MT103-202	MRD+ ALL	19	1.81 (0.576)	1.73 (29.7)	1.67 (1.10 to 3.43)	18	3.93 (2.32)	3.42 (57.8)	3.23 (1.48 to 10.6)	18	1.47 (0.53)	1.38 (39.0)	1.42 (0.660 to 2.54)
MT103-206	R/R ALL	36	2.50 (1.20)	2.31 (39.0)	2.13 (1.29 to 7.31)		NA	NA	NA		NA	NA	NA
MT103-211	R/R ALL	177	3.36 (3.48)	2.43 (87.9)	2.20 (0.422 to 20.5)		NA	NA	NA		NA	NA	NA
All adult studies	Combined	298	2.92 (2.83)	2.28 (71.7)	2.11 (0.422 to 20.5)	50	4.52 (2.89)	3.89 (56.7)	3.65 (1.48 to 17.4)	50	2.11 (1.42)	1.80 (57.5)	1.58 (0.660 to 8.31)
Paediatric Subjects (2 -17 years of age)[a]													
		Clearance (CL) (L/hr)				Volume of distribution (Vz) (L)				Terminal half-life (t ½,z) (hr)			
MT103-205		N	Mean (SD)	Geo mean (CV%)	Median (Range)	N	Mean (SD)	Geo mean (CV%)	Median (Range)	N	Mean (SD)	Geo mean (CV%)	Median (Range)
2 to 6 yrs	R/R ALL	19	2.45 (2.54)	1.69 (104.2)	1.44 (0.43 to 10.7	9	5.12 (4.21)	3.58 (120.7)	3.56 (0.878 to 12.1)	9	2.41 (1.86)	1.96 (72.0)	1.69 (0.862 to 6.04)
7 to 17 yrs	R/R ALL	17	1.51 (1.31)	1.23 (64.5)	1.05 (0.641 to 5.84)	11	3.06 (2.13)	2.43 (84.6)	2.30 (0.745 to 6.99)	11	2.01 (1.28)	1.71 (63.2)	1.69 (0.653 to 4.62)
2 to 17 yrs	R/R ALL	36	2.01 (2.08)	1.45 (86.9)	1.27 (0.43 to 10.7)	20	3.99 (3.31)	2.89 (100.9)	2.98 (0.745 to 12.1)	20	2.19 (1.53)	1.82 (65.5)	1.69 (0.653 to 6.04)

ALL = acute lymphoblastic leukaemia; CL = clearance; CV% = coefficient of variance; Geo mean = geometric mean; hr = hour; L = litre; MRD+ = minimal residual disease positive; NA = not available; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation; t1/2,Z = terminal half-life; Vz = volume of distribution based on terminal phase; a) the mean body surface area in patients between 2 and 17 years of age was 0.96 m². PK data for subjects < 2 years in Study MT 103-205 is not yet available

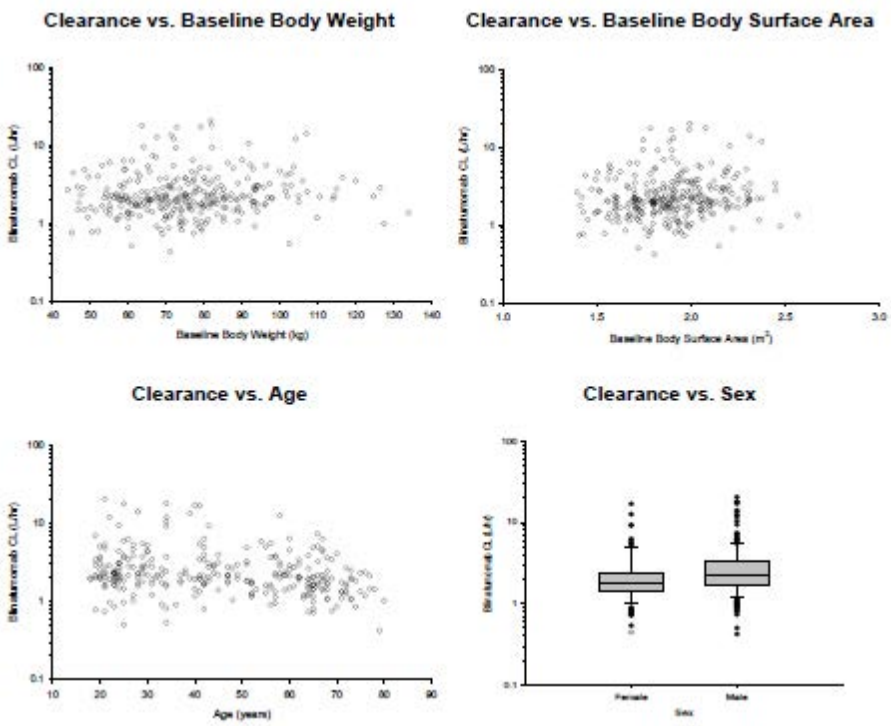
4.4.1. Intrinsic factors, extrinsic factors, and special populations

4.4.1.1. Effect of demographics and baseline factors on pharmacokinetics

The demographic factors evaluated included body weight, body surface area (BSA), age and sex. Demographic data from the 4 adult studies were used for the analysis. The body weight ranged from 44 to 134 kg, BSA ranged from 1.4 to 2.6 m², age ranged from 18 to 80 years, and there were 192 males versus 108 females. An assessment of the effect of race could not be conducted as the majority (> 90%) of subjects were Caucasian. Relationships between blinatumomab clearance and these factors are shown graphically in Figure 3. No impact on blinatumomab clearance was evident for any of the factors examined.

Blinatumomab was studied using a BSA-based dosing in Studies MT103-104, MT103-202, and MT103-206 and a fixed dosing in Study MT 103-211. Mean blinatumomab exposures were comparable at a given dose regardless of the dosing regimen. Lack of demographic effect on drug clearance (see Figure 3, below) further supports the more convenient fixed dosing regimen in adult patients without regard to age (young versus elderly), sex (male or female), and body size (body weight or body surface area).

Figure 3: Effect of demographics on blinatumomab clearance in subjects with ALL and NHL

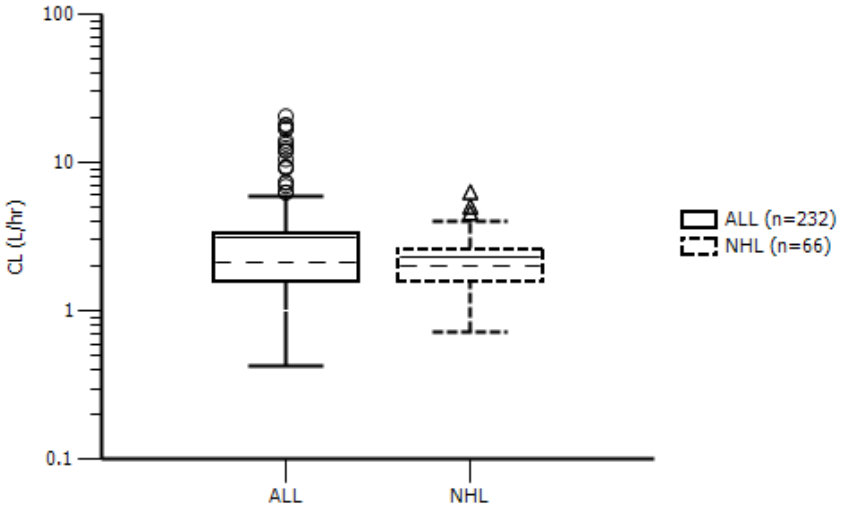


ALL = acute lymphoblastic leukaemia; CL = clearance; NHL = non-Hodgkin's lymphoma.

4.4.1.2. Effect of disease type on pharmacokinetics

Blinatumomab pharmacokinetics across patient populations of NHL and ALL were compared. Similar CL values were observed across disease types, ranging from 1.82 to 3.36 L/hr with an average (SD) of 2.92 (2.83) L/hr across the 4 clinical trials of adult patients with NHL and ALL (see Table 7 above and Figure 4, below). With non-compartmental analysis, the volume of distribution based on terminal Phase and the elimination half-lives were also similar among these patients.

Figure 4: Blinatumomab clearance in subjects with NHL and ALL



ALL = acute lymphoblastic leukaemia; CL = clearance; NHL = non-Hodgkin's lymphoma.

4.4.1.3. Effect of renal function on pharmacokinetics

The results of a retrospective analysis of the effects of renal function (represented by creatinine clearance (CrCL)) on blinatumomab clearance, as estimated by non-compartmental analysis, are shown in Figure 5, below. A summary of clearance values by renal function groups (normal, mild, or moderate renal impairment) is provided in Table 8.

The CrCL values were calculated by Cockcroft-Gault formula and were provided in the clinical datasets of Studies MT103-104, MT103-202, MT103-206, and MT103-211. With the available clearance data from the 4 clinical trials, 215 subjects exhibited normal renal function (CrCL ≥ 90 mL/min), 62 subjects exhibited mild renal dysfunction (CrCL ranging from 60 to 89 mL/min) and 21 subjects exhibited moderate renal dysfunction (CrCL ranging from 30 to 59 mL/min). No patients with severe renal impairment (CrCL < 30 mL/min) were enrolled in these trials.

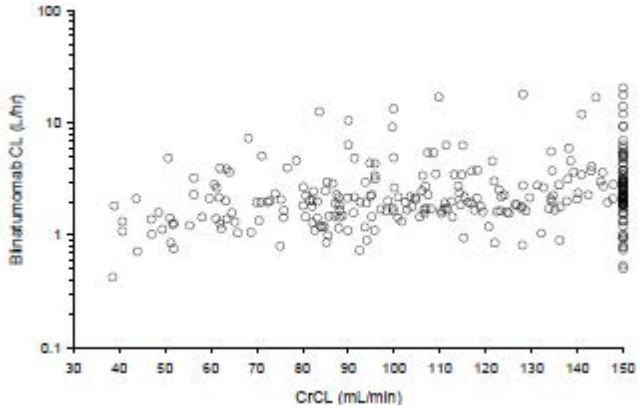
Non-compartmental analyses indicated that there was an approximately 2 fold difference in mean blinatumomab clearance in subjects with moderate renal dysfunction compared to those with normal renal function (Table 8). However, high intersubject variability was discerned in all groups (CV% ranged from 61.6 to 95.6%), and the clearance ranges estimated in subjects with mild and moderate renal impairment were essentially within the range estimated in subjects with normal renal function. In addition, urine samples were collected at steady state (Day 16) from 10 subjects receiving 60 µg/m^2/day continuous IV infusions over 4 to 8 weeks in Study MT103-104 to estimate pharmacokinetic parameters. The estimated mean fraction of blinatumomab excreted unchanged in urine was approximately 0.2% of the administered dose, indicating renal is a limited pathway for blinatumomab excretion. Since no clinically meaningful impact on efficacy and safety in these patient populations is expected, dose adjustment for patients with mild and moderate renal impairment does not appear to be necessary.

Table 8: Summary of blinatumomab clearance by renal function groups

CrCL	Blinatumomab Clearance(L/hr)				
	N	Median (Range)	Mean	SD	%CV
Normal (CrCL ≥ 90 mL/min)	215	2.21 (0.501 to 20.5)	3.26	3.11	95.6
Mild (CrCL = 60 to 89 mL/min)	62	1.87 (0.445 to 12.5)	2.22	1.76	78.9
Moderate (CrCL = 30 to 59 mL/min)	21	1.32 (0.422 to 4.84)	1.58	0.98	61.6

CrCL = creatinine clearance; CV = coefficient of variance; SD = standard deviation. Note: Clearance values estimated from non-compartmental analysis are summarised in this table.

Figure 5: Effect of creatinine clearance (CrCL) on blinatumomab clearance in subjects with NHL and ALL

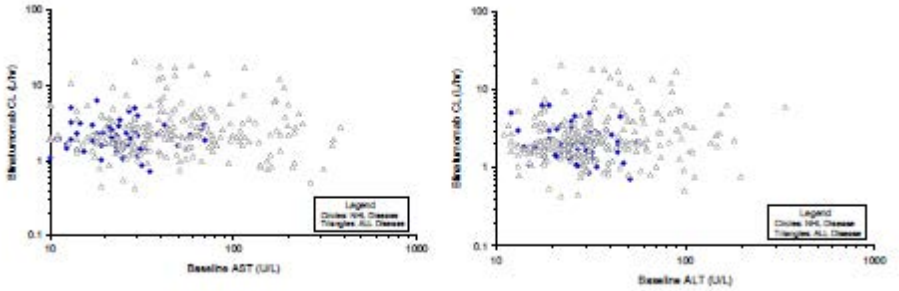


ALL = acute lymphoblastic leukaemia; CL = clearance; NHL = non-Hodgkin's lymphoma. Note: Clearance values estimated from non-compartmental analyses were used in the plot; creatinine clearance values > 150 mL/min were set to 150 mL/min.

4.4.1.4. Effect of hepatic function on pharmacokinetics

Blinatumomab is a therapeutic protein and an effect of hepatic function on clearance of the drug is not expected. Baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were used to assess the effect of hepatic function on the clearance of blinatumomab. As shown below in Figure 6, there is no apparent association between ALT or AST levels and the clearance of blinatumomab.

Figure 6: Effect of hepatic function on pharmacokinetics



ALL = acute lymphoblastic leukaemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CL = clearance; NHL = non-Hodgkin's lymphoma.

4.4.1.5. Effect of immunogenicity on pharmacokinetics

As the formation of anti-drug antibodies (ADA) requires B cells, and the primary mechanism of blinatumomab is to deplete the B-cell population, a low rate of ADA is anticipated. Consistent with this assumption, a low incidence of immunogenicity (< 1%, 3 out of 325 subjects, neutralising ADA showed in all 3 cases) was found in the 4 reported adult studies. 2 out of the 3 subjects who showed positive neutralising ADA had reduced blinatumomab exposure based on the drug concentrations-time profiles. Descriptions of the 3 cases of neutralising ADA formation are provided below and the associated pharmacokinetic profiles are depicted in Figure 7, below.

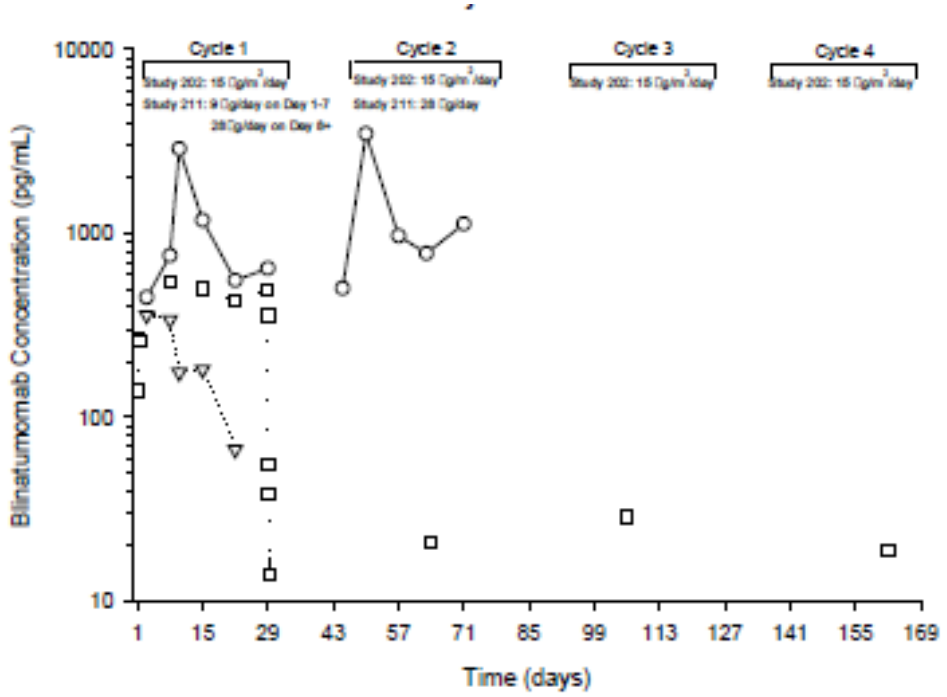
Case 1, Study MT103-202: The subject received 15 µg/m^2/day blinatumomab for 4 cycles. Pharmacokinetic samples were collected through the 4 cycles, and drug concentrations were normal in Cycle 1 but fell below LLOQ in the rest of cycles, possibly due to onset of ADA. However, no samples were collected for immunogenicity testing at the end of Cycle 1 but only at the end of study (that is, Cycle 4). Positive ADA were detected in a sample collected at the end of

the study after 4 treatment cycles and neutralising effects on the bioactivity of blinatumomab were detected with the neutralisation assay. The subject was a responder based on criteria defined in the protocol (that is, achieving MRD negativity within 4 cycles of treatment), thus there was no evidence that the ADA affected clinical efficacy.

Case 2, Study MT103-211: The subject received scheduled treatment (that is, 9 µg/day for 7 days and 28 µg/day for 21 days in Cycle 1, and 28 µg/day for 28 days in the remaining cycles). Pharmacokinetic samples were collected in the first 2 cycles and drug concentrations for this subject were normal in both cycles. Positive ADA were detected in samples collected in Cycle 3 and at the end of the study. Since drug concentrations were only measured up to Cycle 2, the effect of ADA on blinatumomab exposure could not be assessed. The subject responded well to treatment and was a responder as defined by the study protocol (that is, achieving CR/CRh* within 2 cycles of treatment).

Case 3, Study MT103-211: The subject received scheduled treatments (that is, 9 µg/day for 7 days and 28 µg/day for 21 days in Cycle 1) but ended treatment after Cycle 1 due to disease progression. Pharmacokinetic samples were collected in the first cycle and drug concentrations were in the expected range in the first week, but declined rapidly thereafter to an undetectable level while the cIV infusion was ongoing. Positive ADA were detected in a sample collected at the end of study (Cycle 1). The subject was a non-responder to treatment (that is, did not achieve CR/CRh* within 2 cycles of treatment). Due to multiple factors that could contribute to disease progression, it is unknown if the onset of ADA was the only factor leading to non-response to the treatment.

Figure 7: Blinatumomab pharmacokinetic profiles in subjects with positive ADA



ADA = anti-drug antibody; EOS = end of study. Note: The square plots denote the subject from Study MT103-202 (15 µg/m²/day (tested for ADA at Day 169 (EOS)); the triangular plots denote one subject from Study MT103-211 (tested for ADA at Day 43 (Cycle 2)) and circular plots denote another subject from Study MT103-211 (tested for ADA at Day 31 (EOS). Both subjects were dosed at 9 to 28 µg/m²/day.

4.4.1.6. Effect of Blinatumomab Exposure on CYP450

Direct Effect of Blinatumomab Exposure on CYP450

Blinatumomab is a protein therapeutic, cleared mainly via non-specific fluid-Phase endocytosis and proteolysis. Results of an in vitro test with human hepatocytes to assess the direct effects of blinatumomab on CYP450 suggested that blinatumomab did not affect CYP450 enzyme activities (taken from Report NSX0011), thus it is not anticipated to have a direct effect on the pharmacokinetics of drugs metabolised by CYP450 enzymes.

Indirect Effect of Blinatumomab Exposure on CYP450

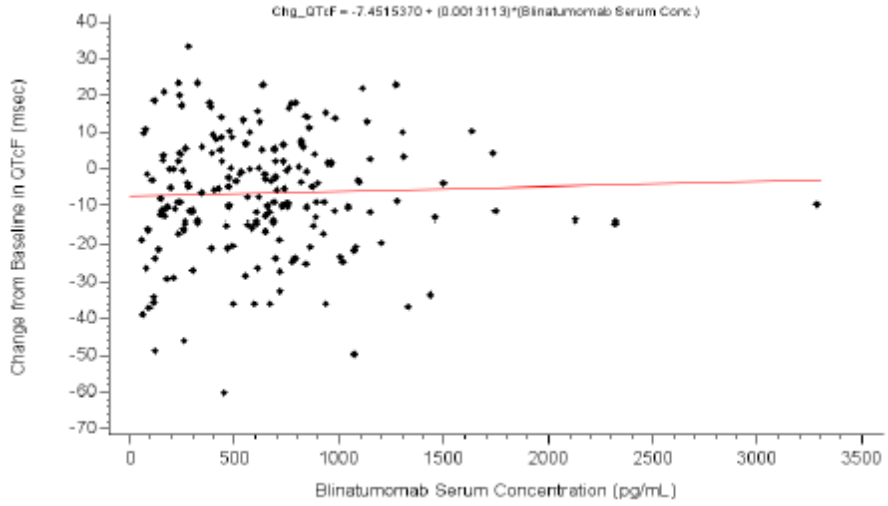
An indirect effect of blinatumomab administration on CYP450 may occur via the transient cytokine elevation observed in some patients 1 to 2 days after the start of blinatumomab infusion in the first cycle. The potential effect of cytokines on CYP450 activities was evaluated via a physiological-based pharmacokinetic (PBPK) model. Results indicated that the potential of pharmacokinetic drug interaction secondary to the transient blinatumomab-mediated cytokine elevation is low.

4.4.1.7. Effect of Blinatumomab Exposure on QT Prolongation

A through QTc study was not conducted. Clinical evaluations included electrocardiogram (ECG) monitoring and evaluation results were provided in the submission

A linear mixed effects modelling approach was used to examine the relationship between the baseline adjusted/corrected change in QTc intervals and serum concentrations of blinatumomab. Results indicated that there was no evidence of linear association between blinatumomab concentrations and QTcF (p = 0.75) or QTcB (p = 0.73). A plot was generated using blinatumomab concentration data from individual subjects and time-matched QTc data (see Figure 8, below). No significant effect of blinatumomab exposure on cardiac repolarisation was observed as measured by the flat to slightly positive slope.

Figure 8: QTcF Changes from Baseline versus serum blinatumomab concentrations collected at the corresponding time point



4.5. Study 119137 Population pharmacokinetic analysis

A summary of the objectives, methods and key findings of the population pharmacokinetic analysis (PopPK report) are provided below.

4.5.1. Objectives

The primary objectives of the blinatumomab population pharmacokinetic analysis in adult subjects with haematological malignancies, including subjects with R/R ALL were: 1) to quantitatively characterize blinatumomab pharmacokinetics after continuous intravenous (cIV) administration and to quantify its inter-individual variability and 2) to evaluate effects of patients' demographic characteristics and other covariates on the pharmacokinetic parameters of blinatumomab.

4.5.2. Data Included in the Population Analysis

Data from 4 clinical studies, including one Phase I study in adult patients with relapsed NHL (Study MT103-104), and 3 Phase II studies in adult patients with ALL in complete haematological remission and MRD (Study MT103-202) or with R/R ALL (Studies MT103-206 and MT103-211) were used in the blinatumomab population pharmacokinetic analysis.

Intensive pharmacokinetic sampling following administration of blinatumomab was available in the Phase I (Study MT103-104) and one of the Phase II (Study MT103-202) studies, while the same sparse sampling scheme was implemented in the remaining 2 clinical studies (Studies MT103-206 and MT103-211). The dataset consisted of a total of 2587 serum samples from 322 subjects receiving blinatumomab intravenously as a continuous infusion over 4 weeks, at doses ranging from 0.5 to 90 µg/m^2/day or a 9 to 28 µg/day fixed dosing regimen.

The median age of patients was 45 years (range: 18 to 80 years). The median body weight was 74 kg (range: 44 to 134 kg). In total, 207 men and 115 women were included in the analysis; 91.7% were White, 2.65% Black, 1.99% Asian, and 3.66% Other. The median CrCL was 111 mL/min and ranged from 38 to 150 mL/min. The liver function of a typical patient was characterised by mean values of 34.4 IU/L for AST, 29.3 IU/L for ALT, 38 g/L for albumin, and 0.0086 mmol/L for total bilirubin. Within the dataset, 34.6% and 54.8% of patients presented with an Eastern Cooperative Oncology Group performance status (ECOG) performance status evaluated as 0 or 1, respectively; only 10.6% of patients had an ECOG performance status of 2. The mean value of lactate dehydrogenase (LDH) and haemoglobin was 807 IU/L and 10 g/dL, respectively. The median CD19+ B cell count was 0.297 x 10^9/L while the median CD3+ T cell count was 0.343 x 10^9/L, and the median CD19+ B to CD3+ T cell ratio (BTCR) was 0.962.

4.5.3. Population pharmacokinetic model development

A one compartment linear pharmacokinetic model was selected to characterise blinatumomab pharmacokinetics. The model was parameterised in terms of systemic clearance (CL) and volume of distribution for the central compartment (V). Pharmacokinetic parameters were assumed to be log-normally distributed and an exponential inter-individual variability term was estimated for CL. Residual variability was modelled using an additive error model in the log domain.

The base model described above was used to evaluate the effect of the covariates on the pharmacokinetic parameters of blinatumomab. The selected covariates included demographic factors (age, body weight, body surface area, sex), estimates of renal function (CrCL, calculated by the Cockcroft and Gault equation) and liver function (AST, ALT, total bilirubin, albumin), and disease status (ECOG, LDH, haemoglobin, CD19+ B and CD3+ T cell counts, and BTCR). A forward inclusion ($p < 0.005$) and backward elimination ($p < 0.001$) process was used for covariate selection. Inferences about the clinical relevance of parameters were based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors).

4.5.4. Key results

An open one-compartment linear pharmacokinetic model, comprising a mixture model to identify 2 subpopulations with different CL and separate estimates of residual variability for single versus multicentre studies was suitable to describe the time course of blinatumomab

concentrations after cIV administrations of different doses in patients with haematological malignancies, including patients with NHL, MRD+ ALL, and R/R ALL. Population pharmacokinetic parameters estimates of blinatumomab are presented below in Table 9.

Table 9: Population pharmacokinetic parameters of blinatumomab

Parameter (Units)	Typical Value	95% CI
Volume (V, L)	3.40	2.82 to 3.94
Clearance (CL)[a]		
Subpopulation 1 (L/h/90mL/min)	1.36	1.24 to 1.50
Subpopulation 2 (L/h/90mL/min)	5.49	2.94 to 7.81
Proportion in Subpopulation 1	0.90	0.74 to 0.95
Effect of CrCL on CL (θ)	0.58	0.41 to 0.75
Inter-individual variability (CV%)		
$^{\omega}$CL	41.9	35.6 to 46.5
$^{\omega}$EPS	36.3	31.3 to 41.2
Residual variability (CV%)		
For Study MT103-211	56.6	51.9 to 61.2
For other studies	40.1	37.3 to 43.4

CI = confidence interval; CL = clearance; CrCL = creatinine clearance; CV = coefficient of variation; a) CLi = CL·(CrCL/90)θ

The typical value (geometric mean) of blinatumomab volume in adult patients was estimated to be 3.40 L, very close to plasma volume and similar to the values reported for other large molecules. A majority of the population (90%) had a typical blinatumomab clearance value of 1.36 L/h, while for unknown reasons a small subset of the population (10%) had a typical clearance value of 5.49 L/h which was about 4 fold higher than the majority. Consistent with previous findings with the non-compartmental analysis approach, renal function was identified as a significant factor on clearance. A 50% reduction in CrCL was associated with a 30% reduction in blinatumomab systemic CL. However, the magnitude of this effect is relatively lower than the unexplained between-subject variability in blinatumomab pharmacokinetics, and considering that no clinically meaningful impact on efficacy and safety in subjects with moderate renal dysfunction is expected, dose adjustment for patients with mild and moderate renal impairment does not appear to be necessary.

On average, for a typical adult subject with a CrCL of 30, 60 and 90 mL/min, the blinatumomab half-life in subpopulation 1 was estimated to be 3.28, 2.19 and 1.73 hours, respectively, and in subpopulation 2 was estimated to be 0.81, 0.54 and 0.43 hours, respectively. Therefore, the vast majority of the subjects achieved C_{ss} within the first day of a 28 day cycle, regardless of renal function.

Other than CrCL, none of the covariates evaluated (age, body weight, body surface area, sex, AST, ALT, total bilirubin, albumin, performance status, LDH, haemoglobin, CD19+ B and CD3+ T cell counts, and BTCR) were found to significantly contribute to the between-patient variability of blinatumomab pharmacokinetic parameters.

4.5.5. Conclusions

An open one-compartment pharmacokinetic model with linear elimination was suitable to describe the time course of serum blinatumomab concentration following cIV administration of doses ranging from 0.5 to 90 µg/m^2/day or 2 fixed dose levels of 9 and 28 µg/day in patients with haematological malignancies, including R/R ALL patients.

The blinatumomab volume of distribution in adults was estimated to be 3.40 L, very close to the plasma volume. For 90% of the population, the blinatumomab clearance was 1.36 L/h, while for the remaining 10% of the population; the blinatumomab clearance was 4 fold higher (5.49 L/h).

A 50% reduction in CrCL was associated with a 30% reduction in blinatumomab systemic CL. However, the magnitude of this effect was relatively lower than the unexplained between-subject variability in blinatumomab pharmacokinetics, and considering that no clinically meaningful impact on efficacy and safety in subjects with moderate renal dysfunction is expected, dose adjustment for patients with mild and moderate renal impairment does not appear to be necessary.

Within the range of covariate values analysed in the current population pharmacokinetic exercise, age, bodyweight, BSA, sex, AST, ALT, albumin, total bilirubin, ECOG performance status, LDH, haemoglobin, CD19+ B and CD3+ T cell counts, and BTCR were not found to significantly explain part of the between patient variability of blinatumomab pharmacokinetic parameters. Accordingly, pharmacokinetically-driven dose adjustments to control blinatumomab exposure on the basis of these covariates are not warranted, and a fixed blinatumomab dose of 28 µg/day for 28 days in patients with R/R ALL is recommended.

4.6. Evaluator's overall conclusions on pharmacokinetics

There was no specific pharmacokinetics clinical study in the blinatumomab clinical program. However, the pharmacokinetics of blinatumomab were extensively studied in 4 clinical studies (see Table 1, above). These included a study in subjects with NHL (MT103-104), a study in subjects with MRD+ ALL (Study MT103-202) and 2 studies in subjects with R/R ALL (Studies MT103-206 and MT103-211). In addition, the interim pharmacokinetic results for the paediatric Study MT103-205 were also presented. The effects of intrinsic factors on the blinatumomab pharmacokinetics were evaluated using integrated data obtained from the adult studies.

The pharmacokinetics of blinatumomab was linear over the dose range examined. Serum concentration profiles increased approximately proportionally with increased dose ranging from 5 to 90 µg/m^2/day. Steady state serum concentrations were achieved within a day and remained constant over 4 weeks under continuous IV infusion. Pharmacokinetics of blinatumomab was not affected by body weight, body surface area, age, sex, or disease type in adults. Mild or moderate renal impairment or hepatic dysfunction did not have a clinically meaningful impact on blinatumomab exposure, although an association was observed between creatinine clearance and blinatumomab clearance. The incidence of neutralising ADA was < 1% and ADA may affect blinatumomab exposure.

Blinatumomab has a low potential for clinically meaningful drug-drug interactions, with no effect on CYP450 enzyme activities observed in vitro. PBPK analysis indicated the transient cytokine elevation following blinatumomab initial administration may suppress CYP3A4, CYP1A2, and CYP2C9 activities by 30% in the first week of treatment, with less than a 2 fold increase in the exposure of CYP450 sensitive substrates.

Based on the assessments of clinical PK, the recommended blinatumomab regimen for the treatment of R/R ALL is a cIV infusion for 4 weeks followed by a 2 week treatment free period between cycles. In Cycle 1, the starting dose is 9 µg/day in Week 1; the dose is then increased to 28 µg/day over weeks 2 to 4. For subsequent cycles, the dose is 28 µg/day for the entire cycle.

The proposed PI is an adequate summary of the PK presented in the submission.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There was no specific pharmacodynamics clinical study in the blinatumomab clinical program. Pharmacodynamics were assessed along with safety and efficacy in 4 clinical studies, which included a study in subjects with NHL (Study MT103-104), a study in subjects with MRD+ ALL (Study MT103-202) and 2 studies in subjects with R/R ALL (Studies MT103-206 and MT103-211). Based on the blinatumomab mode of action, pharmacodynamic assessments focused primarily on the evaluation of dynamic changes of T cells, B cells, and cytokines during the treatment of blinatumomab in selected clinical studies. The dynamics of other cell types (natural killer (NK) cells, natural killer T cells (NKT), monocytes) were mainly assessed in a subset of subjects.

Peripheral blood mononuclear cell surface markers were measured by Fluorescence-Activated Cell Sorter (FACS) analysis, including, but not limited to, B-cell counts and B-cell lysis (for example, CD19, CD20), T cell and subset counts (including CD3, CD4, CD8, γ/δ TCR, CD45 RA), T cell activation marker (such as CD25, CD69), apoptosis marker (for example, annexin V), and lymphocyte adhesion and migration marker (LFA-1).

Cytokines (primarily interleukin (IL)-2, IL-6, IL-8, IL-10, IL-12, tumour necrosis factor alpha (TNFα) and interferon gamma (IFNγ)) were measured using enzyme linked immunosorbent assay (ELISA) and cytometric bead array (CBA) techniques.

5.1.1. Summary of results of individual studies

5.1.1.1. Study MT103-104: Phase I study in subjects with NHL

Pharmacodynamics

Consistent with its mode of action, blinatumomab caused a complete and sustainable depletion of circulating B-cells at dose level of ≥ 5 µg/m^2/day.

T cell kinetics showed characteristic redistribution after start of infusion and any increase in dose. Circulating T cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days. Although not directly engaged by blinatumomab, redistribution of NK cells and monocytes exhibited kinetics similar to those observed for T cells.

In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days. The magnitude of cytokine elevation appeared to be dose dependent. A similar observation was noted for TNFα and IFNγ in some subjects.

Cytokine elevation (primarily IL-2, IL-6, and IL-10, as well as TNFα and IFNγ in some subjects) was the highest at doses ≥ 60 µg/m^2/day. With 3 out of 4 subjects experiencing dose limiting toxicities (1 Grade 3 event of convulsion and 2 Grade 3 events of encephalopathy) at the 90 µg/m^2/day dose level, 60 µg/m^2/day was established as the maximum tolerated dose in this study.

5.1.1.2. Study MT103-202 Phase II study in subjects with MRD+ ALL

Pharmacodynamics

Peripheral B-cell depletion occurred within 48 hours after infusion start and was sustained throughout treatment. T cells disappeared from peripheral blood within the first 6 to 12 hours after infusion start and returned to baseline levels within the first week of each cycle. Elevation of serum cytokines (IL-6, IL-10 and INF-γ) occurred in the first day of treatment, and cytokine levels returned to below assay quantification levels within 2 days in Cycle 1. The magnitude of cytokine elevation was lower in subsequent cycles.

5.1.1.3. Study MT103-206 Phase II study in subjects with R/R ALL

Pharmacodynamics

In most of the subjects, peripheral CD19+ B cells dropped to ≤ 1 cell/μL during the first week of treatment and remained undetectable throughout treatment.

Peripheral T cells showed a redistribution characterised by disappearance within the first 2 to 6 hours of drug infusion and a subsequent recovery to baseline levels within several days in each treatment cycle. After this initial redistribution, CD4+ and CD8+ T cell levels remained stable in most subjects and T cell expansion was observed in some patients. Measured in a subset of subjects, the T cell activation marker CD69 was transiently upregulated on CD4+ and CD8+ T cells during the first 48 hours of infusion, indicating a blinatumomab-induced T cell activation.

Although not directly engaged by blinatumomab, redistribution of NK cells and monocytes after infusion start and dose step was observed. Distinct treatment related changes in granulocytes were not apparent.

A transient elevation of the T cell effector molecule granzyme B was detectable in serum in the majority of subjects analysed during the first 48 hours of infusion, indicating cytotoxic activity of blinatumomab-engaged T cells.

Serum levels of cytokines IL-2, TNFα, IL-10, IL-6, and IFNγ showed transient elevation in most subjects shortly after infusion start which quickly diminished within 1 to 2 days while the infusion was ongoing. In subsequent cycles, cytokine elevation was either absent or at a lower magnitude.

5.1.1.4. Study MT103-211 Pivotal Phase II study in subjects with R/R ALL

Pharmacodynamics

In most subjects, peripheral B cell counts dropped to ≤ 10 cells/μL during the first treatment cycle and remained low to undetectable throughout treatment. Peripheral B-cell depletion was observed in all subjects who responded to treatment; B-cell depletion was also observed in some subjects who did not respond to treatment (that is, non-responders).

Peripheral T cell dynamics were similar to those observed in previous studies; however, a detailed profile could not be constructed due to a sparse sampling scheme. The kinetics of T cell subtypes appeared to be similar in both responders (those who achieved complete remission (CR) or complete remission with partial haematological recovery (CRh*)) and non-responders.

Lower proportions of CD19+ B lymphocytes and higher proportions of CD3+ lymphocytes, as well as lower proportions of lymphocytes and higher proportions of granulocytes in the leukocyte compartment of peripheral blood at screening were significantly associated with the achievement of CR/CRh*.

Cytokine levels increased immediately after start of blinatumomab infusion at 9 μg/day, with peak concentrations observed within 24 hours, and then declined quickly to below the limit of detection within 48 hours. Lower magnitude elevations of cytokines were observed when the

dose was increased from 9 μg/day to 28 μg/day in Cycle 1 and at beginning of subsequent cycles.

5.2. Summary of pharmacodynamics

The sponsor included 4 studies in the PD section of the submission, a study in subjects with NHL (Study MT103-104), a study in subjects with MRD+ ALL (Study MT103-202) and 2 studies in subjects with R/R ALL (Studies MT103-206 and MT103-211).

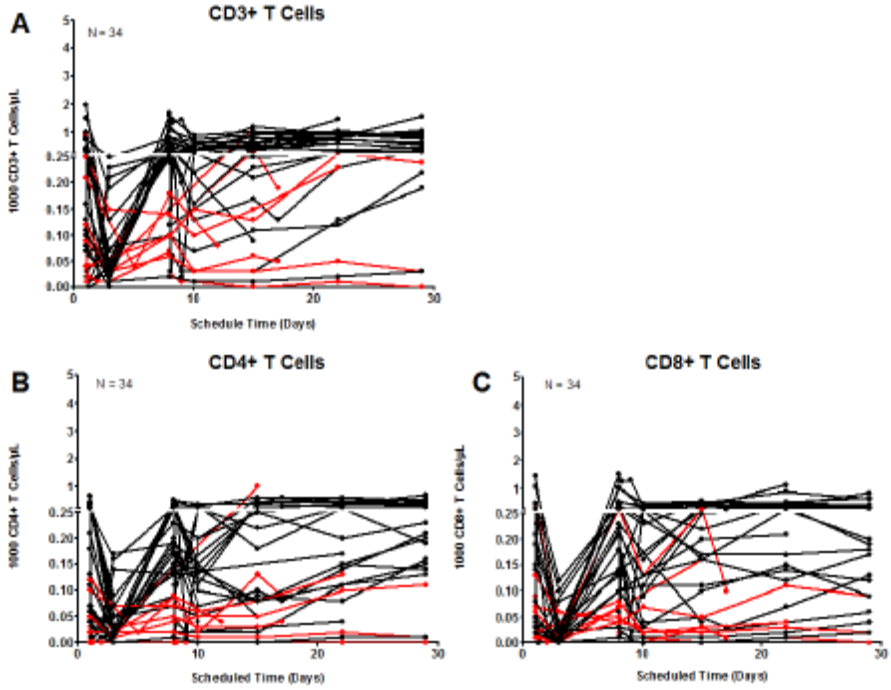
5.2.1. Mechanism of action

Blinatumomab activates endogenous T cells by connecting CD3ε in the T cell receptor (TCR) complex with CD19 on benign and malignant B cells; including B-precursor ALL cells. The proximity induced by blinatumomab leads to the formation of a cytolytic synapse and triggers target cell-specific cytotoxicity which closely resembles a natural cytotoxic T cell reaction.

Blinatumomab is associated with transient up regulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines and proliferation of T cells, and results in elimination of CD19+ cells. In clinical studies, pharmacodynamic measures included lymphocytes, lymphocyte subsets, and cytokines. Consistent pharmacodynamic profiles were observed across clinical trials in subjects with ALL or NHL following the continuous IV infusion regimen. The pharmacodynamic response to blinatumomab was characterised primarily by T cell redistribution, activation, and expansion, B-cell depletion, and transient cytokine elevation.

Following initiation of blinatumomab continuous IV infusion, peripheral T cells initially declined quickly to very low levels, a phenomenon described as redistribution. After the initial decline, T cells started to increase and reached baseline levels. The time to return to baseline was variable across patients (7 to 30 days). An expansion of T cells above baseline was observed in some patients. Similar dynamic profiles were observed for CD4+ and CD8+ T cells. A high inter-individual variability was observed in baseline levels of T cells (see Figure 9, below). Individual T cell dynamic profiles from R/R ALL patients (Study MT103-206) are also presented in Figure 9. T cell dynamic profiles were similar in evaluated subjects with NHL and ALL.

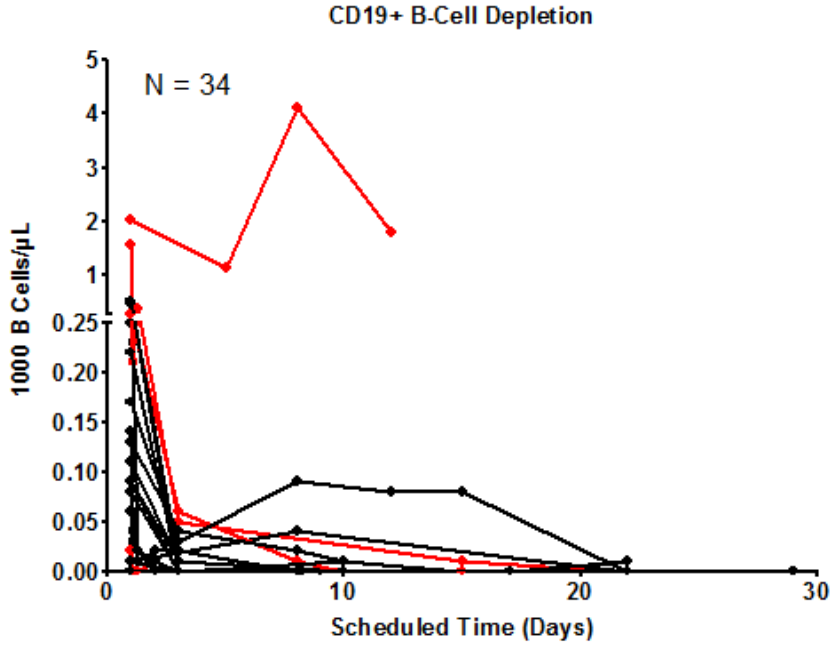
Figure 9: CD3+ T cell dynamics in peripheral blood in Cycle 1 of treatment



Note: (A) Individual CD3+, (B) CD4+, and (C) CD8+ T cell counts detected in peripheral blood of 34 evaluable patients during the first 28-day continuous blinatumomab IV infusion. Black lines represent patients who achieved a haematological complete remission (CR/CRh*) during the first 2 cycles of blinatumomab treatment; red lines represent patients without CR/CRh* during the first 2 treatment cycles. Source: Study MT103-206

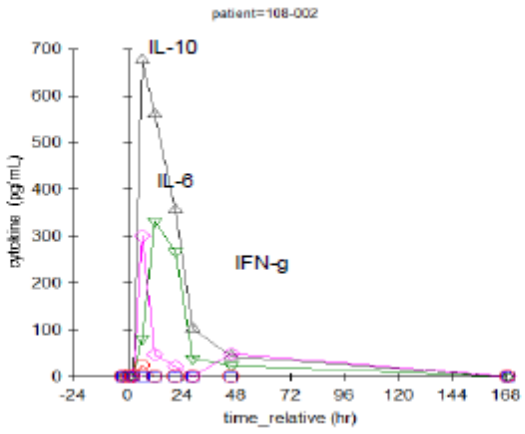
B-cells in peripheral blood declined rapidly and became undetectable during treatment with doses ≥ 5 µg/m^2/day in the majority of subjects (see Figure 10, below). No recovery of peripheral B-cells was observed during the drug free period between treatment cycles. Incomplete depletion of B cells was observed at doses of 0.5 and 1.5 µg/m^2/day and in few non-responders at higher doses. Individual B-cell dynamic profiles from R/R ALL patients (Study MT103-206) are presented in Figure 10, below. The B-cell dynamic profiles were similar in evaluated subjects with NHL and ALL.

Figure 10: CD19+ B-cell dynamics in peripheral blood in Cycle 1 of treatment



The measured cytokines were TNFα, IL2, IL6, IL8, IL10, IL12, IL4, and IFNγ. Transient elevation of cytokines (primarily IL10, IL6, and IFNγ) was observed in some patients in the first 2 days following the initiation of blinatumomab IV infusion, as shown in the representative cytokine dynamic profile for 1 subject with NHL in Figure 11, shown below. The elevated cytokine levels returned to baseline within 24 to 48 hours while the infusion was ongoing. In subsequent treatment cycles, cytokine elevation was observed in fewer patients with less intensity, as shown in Table 10, below. Cytokine dynamics were similar in evaluated subjects with NHL and ALL.

Figure 11: Representative individual cytokine concentration-time profiles following blinatumomab continuous IV infusion



IFN-g = interferon gamma; IL = interleukin; IV = intravenous.

Table 10: Mean (± SD) serum cytokine peak levels (pg/mL) Following continuous IV infusion of blinatumomab in subjects with R/R ALL

Cycle/week	Dose (µg/d)	No. of subjects	IL10 (pg/mL)	IL6 (pg/mL)	IFNɣ (pg/mL)	IL2 (pg/mL)	TNFα (pg/mL)
C1/W1	9	184	589 ± 822	826 ± 2390	93 ± 409	25 ± 45	30 ± 125
C1/W2	28	175	96 ± 136	234 ± 681	27 ± 83	11 ± 5	10 ± 3
C2/W1	28	95	397 ± 633	315 ± 952	23 ± 46	11 ± 5	12 ± 15
C3/W1	28	41	428 ± 941	69 ± 114	22 ± 28	10 ± 2	12 ± 7.8

C = cycle; W = week, IL = interleukin; IFNɣ = interferon gamma; IV = intravenous; R/R ALL = relapsed/refractory acute lymphoblastic leukaemia; TNFα = tumour necrosis factor alpha; SD = standard deviation.

Cytokine assay lower limit of detection (LOD) was 20 ng/mL and lower limit of quantitation (LOQ) was 125 pg/mL. Data below LOD were set to 10 pg/mL for calculation while data > LOD were used as measured in the summary statistics.

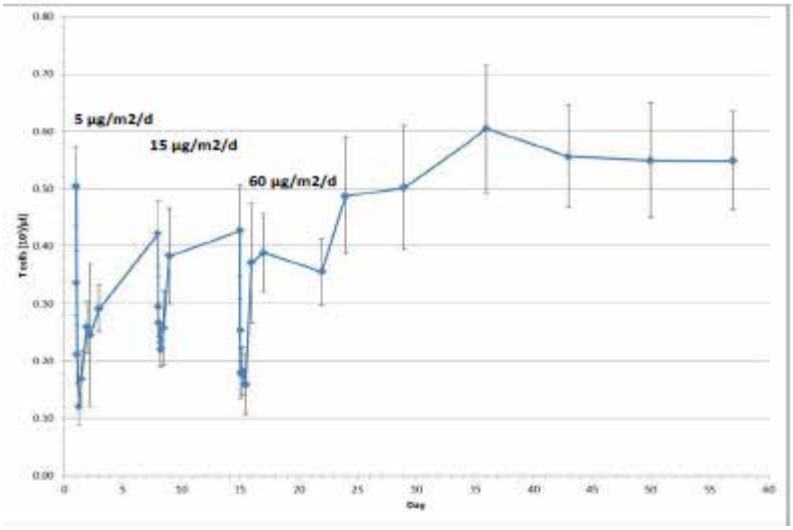
5.2.2. Pharmacokinetic-pharmacodynamic relationships

5.2.2.1. Exposure T cell relationship

It was observed that T cell redistribution occurred when dosing was initiated or when dosing was escalated (see Figure 12, below). T cell expansion has been observed during blinatumomab treatment (see Figure 13, below). T cell redistribution and expansion may be associated with blinatumomab dose (see Table 11, below). As shown in the first 3 rows of Table 11, lower mean nadir T cells were observed in the cohort with higher initial doses. These data suggest that the distribution of T cells may be associated with dose, although inter-subject variability in T cells was high. With a multiple dose stepping regimen from a low initial dose to higher target doses (as shown in Figure 12), the nadir depends on the blinatumomab dose, as well as time of dose stepping as shown in the last row of Table 11.

In nonclinical studies, T cell activation was evaluated by measuring cytokine release and expression of the T cell surface activation markers CD69 and CD25 and was found to be highly dependent on the presence of target cells. In Study MT103-104, it was found that the expression of activation markers CD69 on CD4+ and CD8+ T cells was up-regulated shortly after start of infusion and any dose step, suggesting T cell activation at those times.

Figure 12: T cell dynamics during blinatumomab continuous IV infusion under a step-dosing regimen



IV = intravenous. Blinatumomab was administered via continuous IV infusion at 5 µg/m^2/day on Days 1 to 7, 15 µg/m^2/day on Days 8 to 14 and at 60 µg/m^2/day on ≥ Day 15.

Figure 13: T cell expansion under blinatumomab treatment

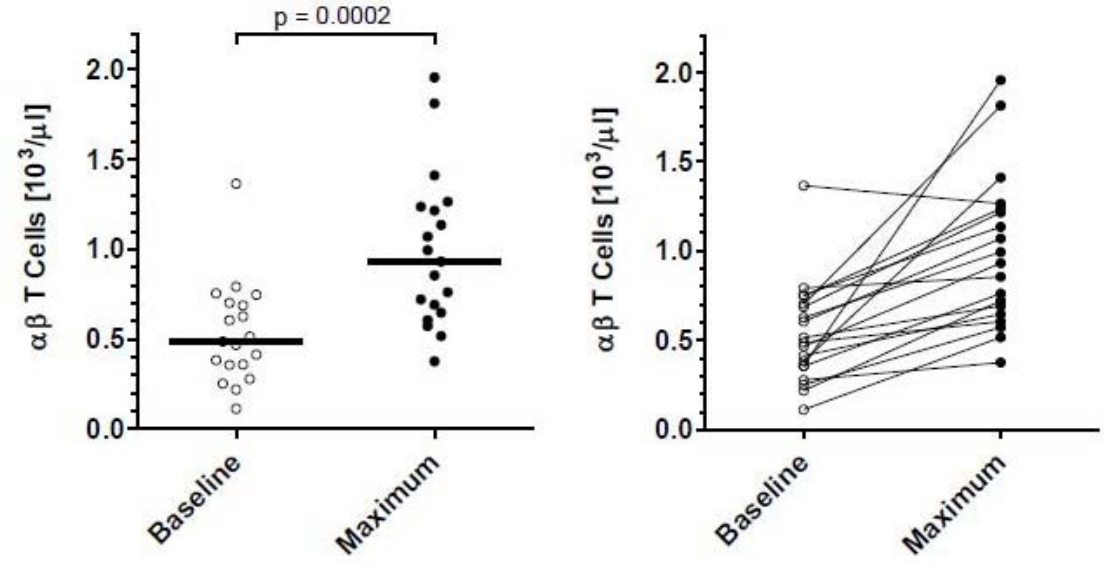


Table 11: T cell dynamic parameters

Dose (N)	Time (day)		Mean (± SEM) T Cells (10^{-3}/µL)		
	Nadir	Maximum	Baseline	Nadir	Maximum
0.5 to 5 µg/m²/day (N = 12)	1.25	29	0.411 ± 0.059	0.098 ± 0.029	0.500 ± 0.113
15 to 30 µg/m²/day (N = 19)	1.5	22	0.342 ± 0.056	0.068 ± 0.028	0.729 ± 0.175
60 to 90 µg/m²/day (N = 13)	1.1	8	0.644 ± 0.173	0.034 ± 0.014	0.770 ± 0.243
60 µg/m²/day target dose achieved with dose stepping [a] (N = 32)	1.25	36	0.503 ± 0.070	0.120 ± 0.003	0.605 ± 0.111
	8.25			0.220 ± 0.031	
	15.5			0.158 ± 0.051	

SEM = standard error of the mean. a) Dose stepping includes 5 to 60, 15 to 60 and 5 to 15 to 60 µg/m²/day with 1 week interval between dose steps.

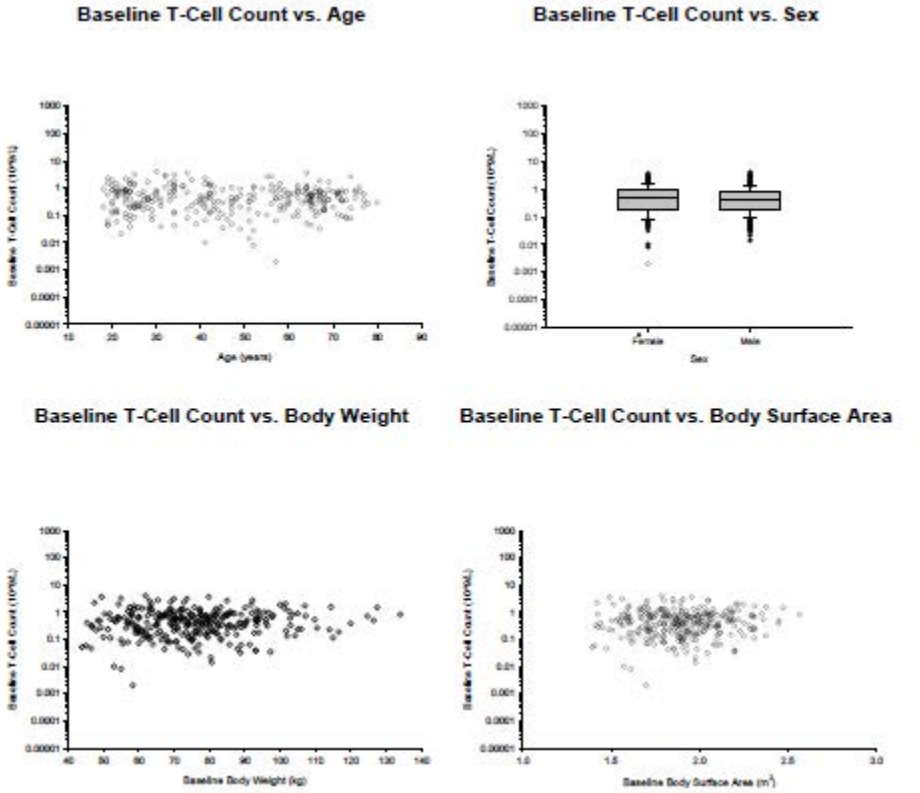
T cell profiles over time appeared to be similar across studies, with no apparent effect of disease type (that is, NHL and ALL) (Study MT103-104 CSR, Study MT103-202 CSR). As T cell dynamics may be associated with baseline T cell levels, the sponsor summarised baseline T cells for the 4 studies and explored associations between baseline T cells with baseline demographic factors. Results showed that baseline T cells appeared to be similar across studies with large inter-subject variability (see Table 12, below) and were not associated with any demographic factors (see Figure 14, also below).

Table 12: Mean (± SD) baseline T cell levels in subjects with NHL, MRD+ ALL and R/R ALL

Study ID	Disease	N	CD3+ T Cells (10^9/L)
MT103-104	NHL	76	0.470 ± 0.395
MT103-202	MRD+ ALL	21	0.499 ± 0.292
MT103-206	R/R ALL	31	0.486 ± 0.619
MT103-211	R/R ALL	174	0.721 ± 0.752

ALL = acute lymphoblastic leukaemia; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation.

Figure 14: Baseline T cells versus age, sex, weight and body surface area



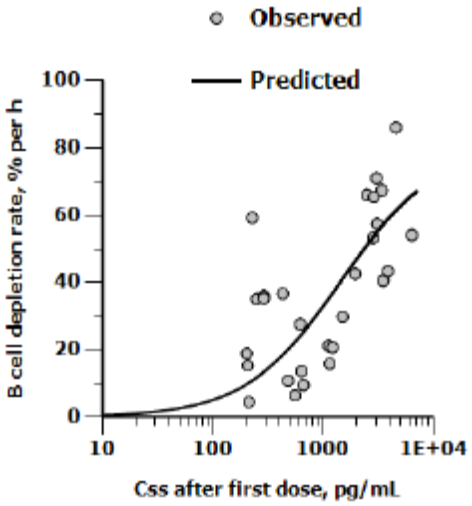
5.2.2.2. Exposure and B cell relationship

B-cell depletion is dependent on blinatumomab dose, and the rate of depletion depended on the initial dose. In clinical studies, complete or near complete depletion of peripheral B cells was observed during the first 2 days of treatment in most patients receiving blinatumomab initial doses ≥ 5 µg/m^2/day (or 9 µg/day). Of note, B-cell depletion was not observed in a few non-responders with R/R ALL (see Figure 15, below).

Data collected in the R/R ALL population (Studies MT103-206 and MT103-211) are limited to 3 initial doses (5 µg/m^2/day (9 µg/day), 15 µg/m^2/day (28 µg/day), and 30 µg/m^2/day), most subjects received stepping doses (for example, increasing from an initial dose of 9 to 28 µg/day or from 5 to 15 µg/m^2/day), and B cell sampling was too sparse to capture the rapid depletion profile. For these reasons, the exposure and B cell relationship was better characterised with data from subjects with NHL in Study MT103-104, in which a wide range of initial doses was evaluated (5 to 90 µg/m^2/day).

In Study MT103-104, the rate of B-cell depletion was determined at early time points (0 to 6 hours) after the start of infusion over the dose range of 5 to 90 µg/m^2/day. The relationship between steady state concentrations (C_{ss}) after initial infusion and the percentage of B-cell depletion per hour (Kdep) is depicted in Figure 15. The B-cell depletion rate increased with increased C_{ss}, suggesting that higher drug levels were associated with faster elimination of peripheral B cells and possibly bone marrow B cells.

Figure15: Relationship between B-cell depletion rate and steady state blinatumomab concentration



C_{ss} = steady-state concentration.

As peripheral B-cell dynamics may be related to baseline B-cell counts, baseline B-cell counts were summarised for the 4 studies, and associations between the baseline B-cell counts and other baseline demographic factors were explored. Large intersubject variability was found in the baseline B-cell counts, with the highest baseline counts observed in Study MT103-211 (see Table 13, below). Within the same disease type (for example, R/R ALL) in Studies MT103-206 and MT103-211, baseline B-cell counts were different ($p < 0.001$). This may reflect differences in patient baseline characteristics for example, a higher percentage of subjects in Study MT103-211 had shorter first remission periods, a higher percentage of blasts in bone marrow, and a higher number of prior relapse. Such differences may affect clinical response rate (that is, CR/CRh*) (see Table 14, below). Baseline B-cell counts did not appear to be associated with any demographic factors (see Figure 16, below).

Table 13: Mean (± SD) Baseline B-cell counts in subjects with NHL, MRD+ ALL and R/R ALL

Study	Disease	N =	CD19+ B Cells (10^9/L)	
			Mean (SD)	Median (range)
MT103-104	NHL	76	0.627 (1.79)	0.0739 (0.00 to 12.3)
MT103-202	MRD+ ALL	21	0.0718 (0.117)	0.0166 (0.00112 to 0.454)
MT103-206	R/R ALL	31	0.232 (0.475)	0.0780 (0.00 to 2.03)
MT103-211	R/R ALL	174	4.66 (11.7)	0.227 (0.00 to 75.5)

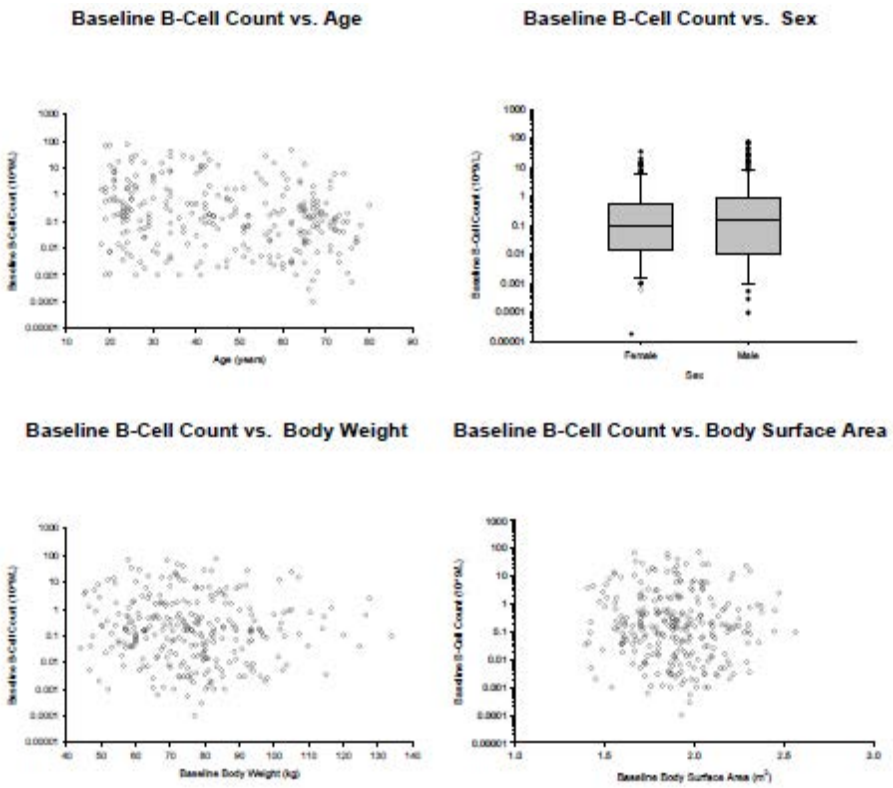
ALL = acute lymphoblastic leukaemia; MRD = minimal residual disease; NHL = non-Hodgkin's lymphoma; R/R = relapsed/refractory; SD = standard deviation.

Table 14: Relationship between mean baseline B-cell counts and clinical response in Subjects with R/R ALL

Study	Dose	N =	CD19+ B Cells (10^9/L)			
			Mean (SD)	Median (range)	N	CR/CRh*
MT103-206	5 to 30 µg/m²/day[a]	27	0.232 (0.475)	0.0780 (0.00 to 2.03)	36	69.4%
MT103-211	9to 28 µg/day	174	4.66 (11.7)	0.227 (0.00 to 75.5)	189	42.9%

ALL = acute lymphoblastic leukaemia; CR/CRh* = complete remission with partial haematological recovery; R/R = relapsed/refractory; SD = standard deviation. [a]Dose regimens in Study MT103-206 were 15 µg/m²/day, or dose steps from 5 to15 µg/m²/day, or 5 to15 to 30 µg/m²/day.

Figure 16: Baseline B-Cells versus age, sex, weight and body surface area

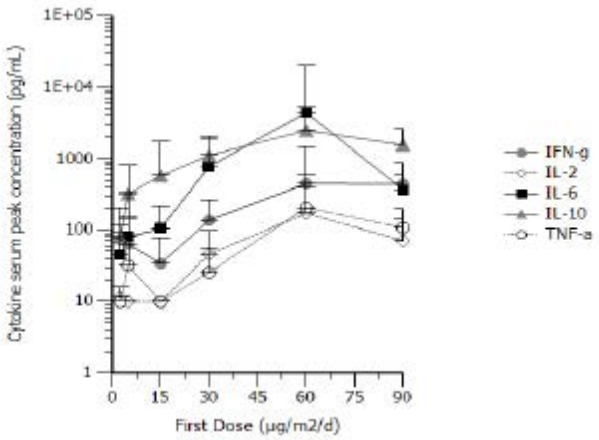


5.2.2.3. Exposure-cytokine relationship

Exposure-cytokine analysis suggests that in the presence of B cells, a higher initial dose may be associated with a higher magnitude of transient cytokine elevation, independent of patient populations (for example, NHL, ALL). For the exposure-B cell analysis, data in the R/R ALL population are limited to 3 doses (mainly 5 µg/m²/day (9 µg/day) and 15 µg/m²/day (28 µg/day), with a small amount of data obtained with the 30 µg/m²/day dose). The dose dependent cytokine elevation was therefore assessed using data obtained from subjects with NHL in Study MT103-104 in which a wide range (5 to 90 µg/m²/day) of blinatumomab doses was tested. Peak cytokine levels following initial dosing in patients with NHL are illustrated in

Figure 17 and summarised in Table 15, both below. Peak cytokine concentrations appeared to plateau at doses ≥ 60 µg/m²/day. Intersubject variability was large. In subsequent treatment cycles, cytokine elevation was observed in fewer patients with less intensity, suggesting that availability of target cells in the periphery is also required for a pronounced cytokine elevation.

Figure 17: Mean (SD) serum peak cytokine concentrations following initiation of blinatumomab treatment



INF = interferon; IL = interleukin; SD = standard deviation; TNF = tumour necrosis factor.

Table 15: Mean (SD) cytokine peak levels in Week 1 following continuous IV Infusion in subjects with NHL

Dose µg/m²/d (n =)	IFNγ (pg/mL)	IL2 (pg/mL)	IL4 (pg/mL)	IL6 (pg/mL)	IL10 (pg/mL)	IL12 (pg/mL)	TNFα (pg/mL)
< 5 (n = 9)	74.2 ± 127	< LOD	< LOD	45.2 ± 47.2	79.4 ± 40.1	< LOD	< LOD
5 (n = 36 to 37)	63.3 ± 94.3	< LOD	< LOD	80.9 ± 255	323 ± 488	< LOD	32.2 ± 116
15 (n = 18)	34.1 ± 42.9	< LOD	< LOD	105 ± 113	573 ± 1135	< LOD	< LOD
30 (n = 7)	137 ± 130	46.1 ± 50.9	< LOD	773 ± 1081	1108 ± 917	< LOD	25.7 ± 31.1
60 (n = 15)	446 ± 1013	171 ± 224	< LOD	4409 ± 15177	2460 ± 2643	< LOD	205 ± 370
90 (n = 4)	440 ± 417	71.3 ± 72.4	< LOD	365 ± 233	1545 ± 1032	< LOD	108 ± 89.9

INF = interferon; IL = interleukin; IV = intravenous; LOD = lower limit of detection; NHL = non-Hodgkin's lymphoma; SD = standard deviation; TNF = tumour necrosis factor. Doses < 5 µg/m² includes 0.5 and 1.5 µg/m²
LOD = 20 pg/mL, half LOD was used in the calculation if LOD was reported.

Similar observations were found in subjects with ALL. Peak cytokine levels observed after the initial blinatumomab dose in patients with MRD+ and R/R ALL are summarised in Table 16. As shown for Study MT103-206, peak cytokine levels were higher with higher initial doses. This finding supports drug initiation with a lower dose in order to reduce transient cytokine peak

levels and associated reactions. At the same initial dose, the magnitude of cytokine elevation tended to be higher in subjects with R/R ALL in Studies MT103-206 and MT103-211 compared to subjects with MRD+ ALL in Study MT103-202.

These data are consistent with the observation that subjects with a low blast count (as observed in Study MT103-202 (MRD+ ALL)) show less pronounced cytokine elevations compared to subjects with a high blast count (as in Study MT103-206 (R/R ALL)) (see Table 16). Similar results were observed in R/R ALL subjects.

Table 16: Mean (± SD) Cytokine peak levels in Week 1 following continuous IV infusion in subjects with MRD+ ALL and R/R ALL

Study Daily Dose	N	IFNγ (pg/mL)	IL2 (pg/mL)	IL4 (pg/mL)	IL6 (pg/mL)	IL10 (pg/mL)	TNFα (pg/mL)
Study MT103-202 (MRD+ ALL)							
15 µg/m²/d	21	410 ± 613	< LOD	< LOD	726 ± 1038	1168 ± 1175	< LOD
Study MT103-206 (R/R ALL)							
5 µg/m²/d	29	143 ± 217	25 ± 26	< LOD	1248 ± 2937	895 ± 1222	48 ± 116
15 µg/m²/d	7	1804 ± 4007	78 ± 90	< LOD	8067 ± 8551	3150 ± 5150	168 ± 193
Study MT103-211 (R/R ALL)							
9 µg/d	184	93.1 ± 409	24.7 ± 44.6	< LOD	826 ± 2390	589 ± 822	30 ± 125

ALL = acute lymphoblastic leukaemia; IFN = interferon; IL = interleukin; MRD = minimal residual disease; R/R = relapsed/refractory; SD = standard deviation; TNF = tumour necrosis factor. Note: Lower limit of detection (LOD) = 20 pg/mL; Lower limit of quantitation (LLOQ) = 125 pg/mL. a 9 µg/day dose is equivalent to 5 µg/m²/day dose.

5.3. Evaluator's overall conclusions on pharmacodynamics

Pharmacodynamics were assessed along with safety and efficacy in 4 clinical studies included in this marketing application, which included a study in subjects with NHL (Study MT103-104; a study in subjects with MRD+ ALL (Study MT103-202) and 2 studies in subjects with R/R ALL (Studies MT103-206 and MT103-211). Peripheral B-cell depletion can be largely achieved at doses ≥ 9 µg/day (or 5 µg/m²/day), which supports a starting dose of 9 µg/day in the stepwise dosing scheme. At the target efficacious dose of 28 µg/day (15 µg/m²/day) for adults, mean C_{ss} were in a range of 553 to 696 pg/mL, which was greater than the in vitro EC90 value of 470 pg/mL for the suppression of B cells in relevant human malignant cell lines.

T cell redistribution occurred when dosing was initiated or when dosing was escalated. B-cell depletion was dependent on blinatumomab dose, and the rate of depletion depended on the initial dose. The B-cell depletion rate increased with increased C_{ss}, which suggests that higher drug levels were associated with faster elimination of peripheral B cells. Exposure-cytokine analysis suggested that in the presence of B cells, a higher initial dose may be associated with a higher magnitude of transient cytokine elevation, independent of patient populations (NHL versus ALL). In subsequent treatment cycles, cytokine elevation was observed in fewer patients

with less intensity, suggesting that availability of target cells in the periphery was also required for a pronounced cytokine elevation.

6. Dosage selection for the pivotal studies

From Study MT103-211: Based on the assessments of clinical PK, PD, efficacy, and safety, the recommended blinatumomab regimen for the treatment of R/R ALL was a cIV infusion for 4 weeks followed by a 2 week treatment free period between cycles. In Cycle 1, the starting dose is 9 µg/day in Week 1; the dose is then stepped up to 28 µg/day over Weeks 2 to 4. For subsequent cycles, the dose is 28 µg/day for the entire cycle.

Blinatumomab is quickly eliminated from the body (mean (CV%) terminal elimination half-life of 2.11 (68%) hours); consequently a continuous IV infusion is needed to maintain effective drug concentrations. The pharmacokinetic profile was not affected by body size (for example, body weight or BSA), and a fixed dose regimen is recommended for adults. Peripheral B-cell depletion is achieved at blinatumomab doses ≥ 9 µg/day (or 5 µg/m^2/day), which supports a starting dose of 9 µg/day. At the target efficacious dose of 28 µg/day (15 µg/m^2/day) for adults, mean C_{ss} were in a range of 553 to 696 pg/mL, which was greater than the in vitro EC90 value of 470 pg/mL for the suppression of B cells in relevant human malignant cell lines.

The majority of cytokine related adverse events were observed in Cycle 1 and the magnitude of cytokine elevation depended on the initial dose. Consequently, a regimen with dose stepping could reduce the first dose effect of cytokine elevation. The safety profile was manageable at the recommended dosing regimen for the treatment of adult relapsed/refractory ALL.

7. Clinical efficacy

Studies for the proposed indication:

> *'Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia'.*

7.1. Pivotal efficacy study

7.1.1. Study MT103-211

This was an open label, multicentre, Phase II study to evaluate efficacy and safety of the BiTE antibody blinatumomab in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL).

7.1.1.1. Study design, objectives, locations and dates

This was an open label, single arm, multicentre, Phase II study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of the BiTE antibody blinatumomab in adult subjects with relapsed/refractory B-precursor ALL. The study was conducted at 37 centres in Germany, Italy, Spain, France, the United Kingdom, and the United States between December 2011 and October 2013.

Primary objective

To evaluate efficacy of blinatumomab in subjects with relapsed/refractory B-precursor ALL.

Secondary objectives

Secondary objectives included:

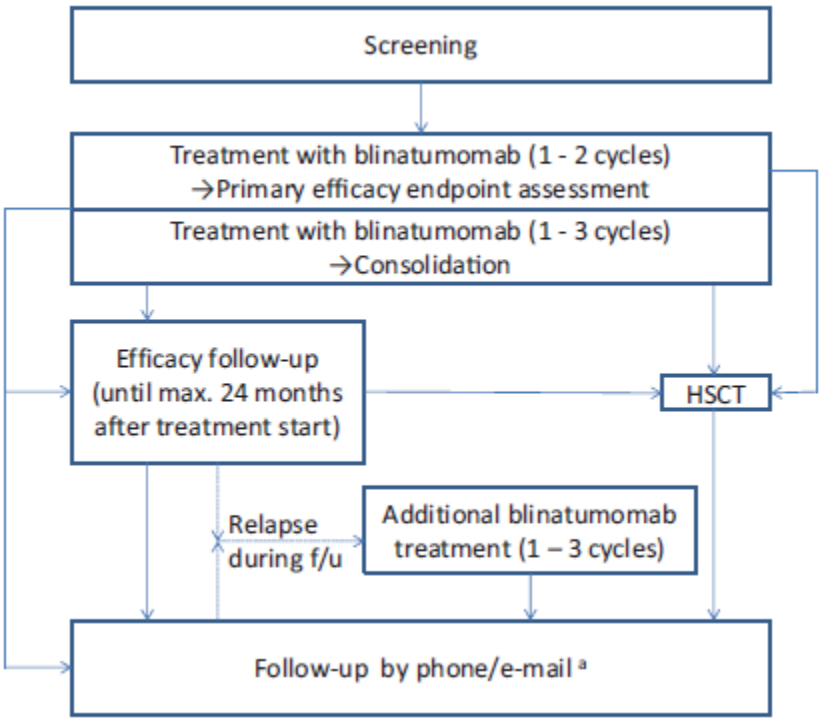
1. To evaluate safety of blinatumomab in subjects with relapsed/refractory B-precursor ALL.

2. To evaluate PK and pharmacodynamics (PD) of blinatumomab

This study consisted of a screening period, a treatment period, and a follow up period. Subjects may have received up to 5 consecutive cycles of blinatumomab treatment. A cycle consisted of a continuous intravenous (cIV) infusion over 4 weeks followed by a treatment free interval of 2 weeks. Following the last treatment cycle, efficacy follow-up visits occurred for up to 24 months after treatment start. Once efficacy follow-up was completed, information on survival was collected at least every 6 months until death or up to 3 years after treatment start, whichever occurred earlier.

If a subject was suitable for allogeneic HSCT after treatment with blinatumomab, then the subject may have undergone an allogeneic HSCT. Subjects who suffered a haematological relapse of B-precursor ALL during the follow-up period (at least 3 months after completion of treatment) were eligible for retreatment with blinatumomab. The study schema is presented in Figure 18, below.

Figure 18: Schema for Study MT103-211



f/u: follow-up; HSCT: haematopoietic stem cell transplant; a) Once efficacy follow-up was completed, information on survival was collected at least every 6 months until death or at least 3 years after treatment start, whichever occurred earlier.

7.1.1.2. Inclusion and exclusion criteria

Inclusion criteria

A patient was eligible for study participation only if all of the following criteria applied:

- Patients with Ph negative B-precursor ALL, with any of the following:
  - relapsed or refractory after first salvage therapy or
  - relapsed or refractory within 12 months of allogeneic HSCT
- 10% or more blasts in bone marrow
- In case of clinical signs of additional extramedullary disease: measurable disease (at least one lesion ≥ 1.5 cm)

- ECOG performance status ≤ 2
- Age ≥ 18 years
- Ability to understand and willingness to sign a written informed consent
- Signed and dated written informed consent is available.

Exclusion criteria

A patient was not eligible for participation in this study if any of the following criteria applied:

- Patients with Ph positive ALL
- Patients with Burkitt´s leukaemia according to WHO classification
- History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis
- Active ALL in the CNS or testes
- Current autoimmune disease or history of autoimmune disease with potential CNS involvement
- Autologous HSCT within 6 weeks prior to start of blinatumomab treatment
- Allogeneic HSCT within 3 months prior to start of blinatumomab treatment
- Any active acute GvHD, or active chronic GvHD Grade 2 to 4
- Any systemic therapy against GvHD within 2 weeks prior to start of blinatumomab treatment
- Cancer chemotherapy within 2 weeks prior to start of blinatumomab treatment (intrathecal chemotherapy and dexamethasone are allowed until start of blinatumomab treatment)
- Radiotherapy within 2 weeks prior to start of blinatumomab treatment
- Immunotherapy (for example, rituximab) within 4 weeks prior to start of blinatumomab treatment
- Any investigational anti-leukaemic product within 4 weeks prior to start of blinatumomab treatment
- Treatment with any other IMP after signature of informed consent
- Eligibility for allogeneic HSCT at the time of enrolment (as defined by disease status, performance status and availability of donor)
- Known hypersensitivity to immunoglobulins or to any other component of the IMP formulation
- Abnormal laboratory values as defined below:
  - AST (SGOT) and/or ALT (SGPT) and/or AP ≥ 5 x ULN
  - Total bilirubin ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)
  - Creatinine ≥ 1.5 x ULN or Creatinine clearance < 50 mL/min (calculated)
  - Hb ≤ 9 g/dL (transfusion allowed)
- History of malignancy other than ALL within 5 years prior to start of blinatumomab treatment with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix

- Active uncontrolled infection, any other concurrent disease or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator
- Infection with HIV or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)
- Pregnant or nursing women
- Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least 3 months thereafter. Male patients not willing to ensure not to beget a child during participation in the study and at least 3 months thereafter
- Previous treatment with blinatumomab

7.1.1.3. Study treatment

Patients received one to 5 treatment cycles of blinatumomab at a target dose of 28 µg/day. In the first cycle, the initial dose was 9 µg/day for the first seven days of treatment, a dose which was then escalated to 28 µg/day starting from Week 2 of treatment. The target dose of 28 µg/day was also administered in Cycle 2 and the following cycles starting with Day 1 of each cycle.

A cycle consisted of a cIV over 4 weeks followed by a treatment free interval of 2 weeks. Patients who achieved CR or CRh* within 2 cycles of treatment received up to 3 additional cycles of consolidation treatment. Patients with haematological relapse during the follow up period received up to 3 additional cycles of blinatumomab for a maximal total of eight cycles at the investigator´s discretion. Retreatment started with a dose step in the first cycle like the regular treatment (9 µg/day in the first week of treatment followed by 28 µg/day starting from Week 2).

7.1.1.4. Efficacy variables and outcomes

Assessment of efficacy

Bone marrow (BM) was used for haematological assessment and for evaluation of MRD by PCR.

The following samples were obtained for cytomorphological assessment and MRD measurement:

- Cytomorphology: BM smears (slides), at screening, prior to treatment with blinatumomab (in case of pre-phase only), at Day 15 of the first treatment cycle (recommended), at the end of each treatment cycle, and during efficacy follow up. In case of insufficient quality of the aspiration material on Day 29 of the treatment cycle, a core biopsy was performed prior to treatment start in the next cycle or at the end of core study visit, as applicable.
- MRD: Aliquots for PCR, at screening, at Day 15 of the first treatment cycle (recommended), and at the end of each treatment cycle. A screening PCR sample was not required if the patient was registered in Kiel and primers for PCR analysis were available.

If a marrow aspiration was not possible, or the aspirate did not contain any BM, a core biopsy was required.

The degree of bone marrow infiltration defined by the percentage of leukemic blasts in bone marrow was evaluated by local laboratories as per cytological assessment. Bone marrow slides were provided to the designated central laboratories for haematological assessment. The B-precursor phenotype was confirmed by the central laboratory by immunocytochemistry. The following markers analysed as needed: CD3, CD5, CD10, CD13, CD19, CD23, CD33, CD34, CD79A, POX, and TDT.

MRD was assessed by the designated central laboratory by PCR.

Known cytogenetic and molecular aberrations were documented in the CRF

Results of additional tests routinely conducted by the investigators but not required by protocol such as immunophenotypic, cytogenetic or molecular analyses conducted during the study were collected and documented in the CRF.

Definitions of treatment response

The treatment was defined to be efficacious, when the patient was stated to be in CR or in CRh*.

Haematological remissions are defined by the following criteria:

- Complete remission:
  - Less than or equal to 5% blasts in the bone marrow
  - No evidence of disease
  - Full recovery of peripheral blood counts:
    - Platelets > 100,000/µL
    - ANC > 1,000/µL
- Complete remission with only partial haematological recovery:
  - Less than or equal to 5% blasts in the bone marrow
  - No evidence of disease
  - Partial recovery of peripheral blood counts:
    - Platelets > 50,000/µL
    - ANC > 500/µL

Patients who had achieved CR or CRh* within 2 cycles of treatment received up to 3 additional cycles of treatment for consolidation.

- Blast free hypoplastic or aplastic bone marrow:
  - Less than or equal to 5% blasts in the bone marrow
  - No evidence of disease
  - Insufficient recovery of peripheral counts: platelets ≤ 50,000/µL and/or ANC ≤ 500/µL.
- Partial remission:
  - BM blasts of 6 to 25% with at least a 50% reduction from Baseline

The onset of remission was defined by the date of the first aspiration/biopsy on which the remission was documented.

- Progressive disease:
  - An increase of at least 25%, or an absolute increase of at least 5,000 cells/µL (whichever was greater), in the number of circulating leukaemia cells, development of extramedullary disease, or other laboratory or clinical evidence of progressive disease.
- Non-response:
  - None of the above.
- Haematological relapse:
  - Proportion of blasts in bone marrow > 5% or
  - Blasts in peripheral blood after documented CR/CRh*
  - An extramedullary relapse was assessed as haematological relapse.

The relapse was analysed by immunophenotyping to determine whether the criteria for B-precursor ALL were fulfilled. The onset of relapse was defined by the date of the first sample on which relapse was documented.

All haematological assessments of bone marrow were reviewed in a central reference laboratory.

In the event of disease progression or haematological relapse within the treatment period, treatment was terminated.

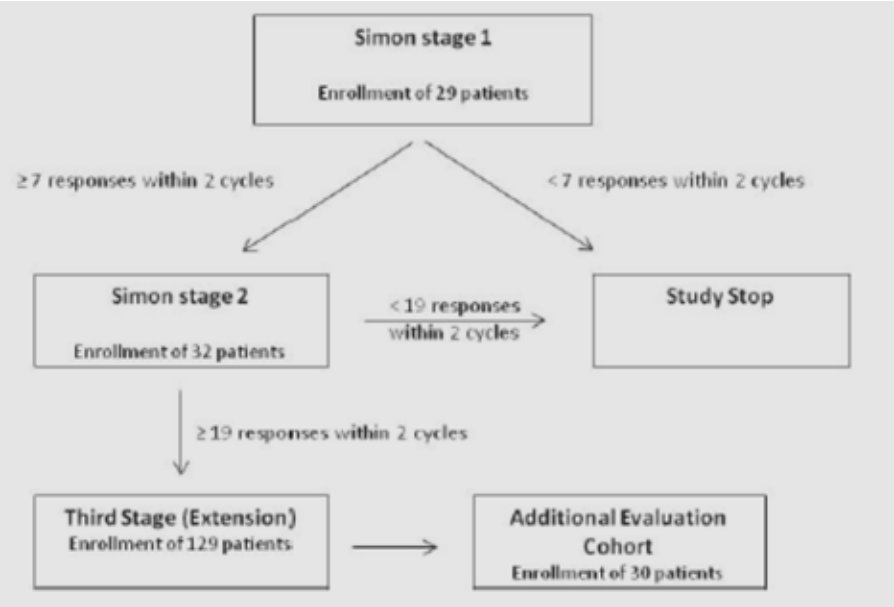
- Extramedullary disease:
  - If clinical signs of extramedullary lesions were present, assessments were performed according to Cheson criteria. If computed tomography (CT) scans were conducted, these were done according to standard clinical practice. If a CT scan had been performed within one month before start of blinatumomab treatment and if no clinical signs of a change of disease state were observed, this assessment was regarded as a screening assessment.
- MRD response:
  - MRD < 10^{-4} measured by PCR.
- MRD complete response:
  - MRD complete response was achieved if no PCR amplification of individual rearrangements of immunoglobulin- or T cell receptor (TCR)-genes were detected. The following minimum technical requirements for the assay must have been fulfilled:
    - sensitivity of at least 10^{-4}
    - quantitative measurement range of at least 10^{-4}
- MRD relapse:
  - Reappearance of individual rearrangements of immunoglobulin or TCR-genes for at least one individual marker measured by an assay with a sensitivity of minimum 10^{-4} in patients who had achieved previous MRD response.
- MRD progression:
  - Increase in the MRD level by one log as compared to the baseline level which was equal to a 10-fold increase in the number of MRD cells.

7.1.1.5. Analysis populations

The study protocol originally used a Simon 2 stage design. The study was subsequently expanded to further evaluate safety and the manufacturing method intended for marketing. The proposed Simon 2 stage design with extension and additional evaluation cohort is provided in Figure 19, shown below.

In Stage 1 of the Simon 2 stage design, 29 subjects were enrolled, and 10 subjects achieved remission (CR/CRh*) during the first 2 cycles of treatment; at least 7 responses were needed to continue the study. The goal was met, thus stage 2 was initiated. In Stage 2, 37 subjects were enrolled, and 17 CR/CRh* responses were achieved during the first 2 cycles of treatment. Thus, a total of 27 responses were achieved during Stages 1 and 2. At least 19 of 61 responses were needed to continue the study; this goal was met, thus, a third stage (extension) was initiated leading to the enrolment of 123 additional subjects. An additional 36 subjects were enrolled to evaluate central nervous system (CNS) symptoms (that is, additional evaluation cohort); the data from these subjects will be reported in the secondary analysis CSR.

Figure 19: Simon 2 stage design with third stage (extension) and additional evaluation cohort



Primary analysis set (PAS): The primary efficacy endpoint of this study was the rate of subjects who reached CR/CRh* as best response within the first 2 cycles of treatment with blinatumomab. The primary efficacy endpoint was formally assessed twice: at the end of Simon Stage 2 design (interim analysis) and the end of Stage 3 (primary analysis), which was conducted when the last subject of the primary analysis cohort completed the first 2 cycles of treatment (that is, the primary analysis set (PAS)); data cut-off date 10 October 2013).

Secondary endpoints: All secondary efficacy endpoints were analysed when the last subject had an opportunity to complete the first 2 cycles of treatment.

7.1.1.6. Sample size

Sample size estimation for the primary efficacy endpoint 'rate of subjects who achieve a CR/CRh* within 2 cycles of treatment with blinatumomab' was based on a Simon 2 stage minimax design with the following parameters: $p_0 = 20\%$, $p_1 = 36\%$, a 1 sided type 1 error of 2.5% and a power of 80%. According to these parameters, 61 treated subjects (29 at Stage 1 and 32 at Stage 2) were needed to achieve 80% power. The study would have been stopped at Stage 1 if fewer than 7 out of 29 subjects were observed with CR/CRh* in Stage 1. If at least 19 out of 61 subjects (approximately 31%) showed a CR/CRh* within 2 cycles of treatment with blinatumomab at the end of Stage 2, then H_0 would have been rejected and further development of blinatumomab would have been considered warranted. This was used to propose the continuation of the trial via a third stage of recruitment.

Subject enrolment was to have ended after the one hundred-fortieth subject had started treatment or after the fiftieth subject had started treatment with CTM5 in the first treatment cycle, whichever occurred later.

The combined sample of subjects from all 3 stages, of at least 140 subjects, was used to perform the primary statistical analysis. A sample size of 140 and a $p_1 = 45\%$ provided 96% power to reject H_0 with a type I error of 2.5%.

The addition of the third stage of recruitment also provided an opportunity to estimate safety risks with greater precision. With N = 140, the 95% confidence interval (CI) for adverse events that were not observed would range from 0 to 2.1%, suggesting that unobserved events were unlikely to occur more frequently than in approximately 1 in 50 subjects.

With a sample size of 50 subjects treated with only CTM5 and an assumed remission rate among those subjects of at least 45%, 23 subjects were expected to achieve remission and a 95% CI around the rate of remission for subjects treated with CTM5 was 32% to 61%.

Upon completion of the third stage of the trial, a fourth stage of recruitment of subjects was initiated. For this cohort, 36 subjects were treated. Subjects in this cohort underwent additional MRI and neurological examinations. The neurological examination results were used to test for statistically significant changes from baseline by comparing the number of test items with at least 1 abnormal finding before blinatumomab treatment to the number of test items with at least 1 abnormal finding after blinatumomab treatment. Assuming a mean of 0 abnormal findings at baseline, a mean change from Baseline of 0.5 (follow up minus baseline), a standard deviation (SD) of the mean difference equal to 1.0, and a 1-sided type I error rate of 2.5%, the sample size of 30 subjects provided approximately 80% power to detect a mean change from Baseline that was greater than 0, indicating an increase in abnormal neurologic examination results after blinatumomab use.

The total sample size for enrolment into Stages 1 through 3 was expected to be approximately 170 treated subjects (it was expected to be 140 subjects at a minimum and could have been as high as 190 subjects). For this CSR, data for the PAS are reported (that is, first 189 subjects who had the opportunity to be assessed for at least the first 2 cycles of treatment).

7.1.1.7. Statistical methods

A summary of efficacy analyses is provided in Table 17, below.

Table 17: Summary of efficacy analyses

Endpoint	Methods
CR/CRh* rate within 2 cycles of treatment with blinatumomab and during core study, using the best response	Response rate and the exact 2 sided 95% CI
Relapse free survival	Median, range, first and third quartile with 2 sided 95% CI by Kaplan-Meier
Overall survival	Median, range, first and third quartile with 2 sided 95% CI by Kaplan-Meier
Time to haematological relapse (duration of response) for subjects who experienced CR/CRh*	Median, range, first and third quartile with 2 sided 95% CI by Kaplan-Meier
Proportion of subjects who received an allogeneic HSCT after treatment with blinatumomab	Transplant rate and the respective exact 2 sided 95% CI
Best treatment response by cycle, within the first 2 cycles, and during the core study	Best response rates and the respective exact 2-sided 95% CI
Time-to-response: CR/CRh*, CR	Median, range, first and third quartile with 2-sided 95% CI by Kaplan-Meier (1 Kaplan Meier)

Endpoint	Methods
Event free survival	Median, range, first and third quartile with 2 sided 95% CI by Kaplan-Meier
Landmark analyses of overall survival	Median, range, first and third quartile with 2 sided 95% CI by Kaplan Meier
100 day mortality after allogeneic HSCT	Median, range, first and third quartile with 2 sided 95% CI by Kaplan-Meier and mortality rate along with 95% CI at 100 day by Kaplan-Meier estimate
MRD response	Response rate and the respective exact 2 sided 95% CI
Stratification variables and subgroup analyses for efficacy endpoints	Forest plots containing the point estimates and the corresponding 2 sided 95 CIs

CI = confidence interval; CR = complete remission; CRh* = complete remission with partial recovery of peripheral blood counts; HSCT = hematopoietic stem cell transplant; MRD = minimal residual disease.

7.1.1.8. Participant flow

A total of 267 subjects were screened; 78 subjects were considered screen failures. Overall, 189 subjects were enrolled in the study, received blinatumomab, and were included in the PAS/FAS (see Table 18, below). The PAS was defined as subjects from the first 3 stages of the study who received any infusion of blinatumomab. For this iteration of the CSR, the FAS was identical to the PAS. In a future iteration based on data from all stages of study recruitment, the FAS will differ from the PAS. Overall, 5.3% (10/189) of subjects completed 5 cycles of treatment; for 1.1% (2/189) of subjects treatment was ongoing at the time of the data cut-off date of 10 October 2013. The most common reasons (> 10%) for not completing 5 cycles of treatment included: physician's decision (24.3%; 46/189; for 30 subjects, physician´s decision was for subjects to move on to HSCT, for 16 subjects the decision was not related to HSCT); progressive disease (22.8%; 43/189); adverse events (16.9%; 32/189); and disease relapse (12.2%; 23/189) (Table 19, below). As of the cut-off date, 61.9% (117/189) of subjects had ended the study and 38.1% (72/189) of subjects were ongoing. The most common reason for ending the study was death (60.8%; 115/189). At the time of the data cut off, no subjects had completed the planned 3 year follow up period (see Table 20, below) as the first subject was enrolled in January 2012.

Table 18: Number of subjects in each analysis set

Analysis set	Eligible subjects (N = 189)	
	N =	(%)
Primary analysis set (PAS)	189	(100.0%)
Full analysis set (FAS)	189	(100.0%)
Efficacy set (EFS)	172	(91.0%)
Per protocol set (PPS)	167	(88.4%)

Full analysis set (FAS): all subjects who received any infusion of blinatumomab. Primary analysis set (PAS): subjects from the first 3 stages of the study who received any infusion of blinatumomab. Efficacy set (EFS): subjects from the PAS for whom at least 1 evaluable response assessment was available after start of treatment Per protocol set (PPS): subjects from the EFS who did not have any major protocol deviation.

Table 19: Disposition of subjects at the end of core study

	PAS/FAS (N = 189)		EFS (N = 172)		PPS (N = 167)	
	N =	(%)	N =	(%)	N =	(%)
Status [a]						
Core study ongoing	2	(1.1%)	2	(1.2%)	2	(1.2%)
Completed 5 cycles	10	(5.3%)	10	(5.8%)	8	(4.8%)
Did not complete 5 cycles	177	(93.7%)	160	(93.0%)	157	(94.0%)
Reasons for not completing 5 cycles						
Physician decision	46	(24.3%)	45	(26.2%)	39	(23.4%)
Related to HSCT	30	(15.9%)	30	(17.4%)	25	(15.0%)
Not related to HSCT	16	(8.5%)	15	(8.7%)	14	(8.4%)
Progressive disease	43	(22.8%)	43	(25.0%)	40	(24.0%)

	PAS/FAS (N = 189)		EFS (N = 172)		PPS (N = 167)	
	N =	(%)	N =	(%)	N =	(%)
Adverse event	32	(16.9%)	19	(11.0%)	27	(16.2%)
Disease relapse	23	(12.2%)	23	(13.4%)	21	(12.6%)
Lack of efficacy	14	(7.4%)	14	(8.1%)	13	(7.8%)
Death	7	(3.7%)	6	(3.5%)	7	(4.2%)
Withdrawal by subject	7	(3.7%)	5	(2.9%)	7	(4.2%)
Protocol violation	2	(1.1%)	2	(1.2%)	1	(0.6%)
Other	3	(1.6%)	3	(1.7%)	2	(1.2%)

EFS = Efficacy Set; FAS = Full Analysis Set; HSCT = haematopoietic stem cell transplant; PAS = Primary Analysis Set; PPS = Per Protocol Set; a) Status at the time of the data cut-off date (10 October 2013).

Table 20: Disposition of subjects at the end of study evaluation

	PAS/FAS (N = 189)		EFS (N = 172)		PPS (N = 167)	
	n	(%)	n	(%)	n	(%)
Status [a]						
Study ongoing	72	(38.1%)	72	(41.9%)	62	(37.1%)
Ended study	117	(61.9%)	100	(58.1%)	105	(62.9%)
Reasons for ending study						
Completed (end of follow-up period)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Death	115	(60.8%)	99	(57.6%)	103	(61.7%)
Lost to follow up	1	(0.5%)	1	(0.6%)	1	(0.6%)
Withdrawal by subject	1	(0.5%)	0	(0.6%)	1	(0.6%)

EFS = Efficacy Set; FAS = Full Analysis Set; PAS = Primary Analysis Set; PPS = Per Protocol Set a At the time of the data cut-off date (10 October 2013)

7.1.1.9. Major protocol violations/deviations

Any deviation that was considered to have an impact on the efficacy evaluation led to exclusion of the subject from the PPS. The subject incidence of protocol deviations that led to exclusion from the PPS was 11.6% (22/189). (Note, a subject could have both protocol deviations leading to exclusion from the PPS and deviations not leading to exclusion from the PPS). The most common issue that led to exclusion from the PPS was the presence of < 10% bone marrow blasts at screening by central laboratory assessment for 5.3% (10/189) of subjects. Although this was not considered a protocol deviation if the local laboratory result showed at least 10% bone marrow blasts and the central result was not yet available at the time of treatment start, it led to the exclusion of a subject from the PPS. In addition to the protocol deviations defined in the SAP for determination of inclusion of subjects into the respective analyses sets, adherence to the protocol was also monitored by the clinical research monitors during regular site monitoring visits, and any deviations from the protocol were documented.

7.1.1.10. Baseline data

Demographics and other baseline characteristics are presented in Table 21, below. Overall, most subjects were male (63%; 119/189), white (85.8%; 145/189), and were entering their second or greater salvage therapy (57.1%; 108/189). The median age was 39.0 years (range: 18 to 79 years).

In the PAS/FAS, the median time between the initial disease diagnosis and first blinatumomab treatment was 16.59 months (range: 1.9 to 249.0 months). Of the 173 subjects who were reported as relapsed, the median time between last relapse and the start of treatment was 1.38 months (range: 0.1 to 56.8 months). For subjects who were reported as having 1 prior relapse (N = 23), the median time between the first remission and the first relapse (that is, duration of first relapse) was 7.77 months (range: 1.7 to 11.7 months).

Overall, 33.9% (64/189) of subjects had a prior allogeneic HSCT. The median time since previous allogeneic HSCT and the start of treatment was 9.69 months (range: 3.3 to 40.2 months).

Overall, 76.7% (145/189) of subjects had baseline bone marrow blasts ≥ 50% at baseline based on maximum central and local laboratory assessments; 22.8% (43/189) of subjects had bone marrow blasts ranging from 10% to < 50%, and 0.5% (1/189) of subjects had < 10% bone marrow blasts per maximum central and local laboratory assessments. The median percent bone marrow blast infiltration at Baseline based on maximum central and local laboratory assessments was 87% (range: 4% to 100%).

Medical history and current medical conditions were collected during screening. Medical history included any medical condition that the subject had experienced before the start of the first infusion. Current medical conditions were defined as those conditions that were ongoing at the start of the first infusion. Medical history conditions (occurring in ≥ 15% of subjects) by MedDRA System Organ Class (SOC) were Infections and Infestations (36.5%; 69/189), Gastrointestinal Disorders (21.7%; 41/189), Surgical and Medical Procedures (18%; 34/189), and Blood and Lymphatic Disorders (17.5%; 33/189). The highest incidences of current medical conditions (occurring in ≥ 50% of subjects) by MedDRA SOC were Blood and Lymphatic Disorders (74.1%; 140/189), Investigations (57.7%; 109/189), and Metabolism and Nutritional Disorders (57.1%; 108/189). The most commonly reported current medical condition (high level term) was anaemia (53.4%; 101/189). Prior medications (those that started and stopped before the first blinatumomab infusion) were recorded for most subjects (94.7%; 179/189).

Table 21: Subject characteristics at Baseline (Primary Analysis Set)

Characteristic category	PAS/FAS (N = 189)	EFS (N = 172)	PPS (N = 167)
	n (%)	n (%)	n (%)
Gender			
Male	119 (63.0%)	109 (63.4%)	110 (65.9%)
Female	70 (37.0%)	63 (36.6%)	57 (34.1%)
Geographic region			
Europe	95 (50.3%)	87 (50.6%)	82 (49.1%)
United States	94 (49.7%)	85 (49.4%)	85 (50.9%)
Race			
White	145 (85.8%)	133 (86.4%)	128 (85.3%)
Asian	6 (3.6%)	5 (3.2%)	6 (4.0%)
Black or African American	7 (4.1%)	5 (3.2%)	6 (4.0%)
American Indian or Alaska native	1 (0.6%)	1 (0.6%)	1 (0.7%)
Native Hawaiian or other Pacific Islander	1 (0.6%)	1 (0.6%)	1 (0.7%)
Other	9 (5.3%)	9 (5.8%)	8 (5.3%)
Not recorded[(a)]	20	18	17
Age group (years)			
18 to < 35 years	90 (47.6%)	86 (50.0%)	81 (48.5%)
35 to < 55 years	46 (24.3%)	40 (23.3%)	41 (24.6%)
55 to < 65 years	28 (14.8%)	22 (12.8%)	26 (15.6%)
≥ 65 years	25 (13.2%)	4 (14.0%)	19 (11.4%)
Disease stage entry criteria met			
Primary refractory	16 (8.5%)	15 (8.7%)	16 (9.6%)
Relapse ≤ 12 months of alloHSCT	39 (20.6%)	35 (20.3%)	33 (19.8%)
Entering first salvage with first remission duration ≤ 12 months	23 (12.2%)	22 (12.8%)	21 (12.6%)

Characteristic category	PAS/FAS (N = 189)	EFS (N = 172)	PPS (N = 167)
	n (%)	n (%)	n (%)
Entering second or greater salvage therapies	108 (57.1%)	97 (56.4%)	97 (58.1%)
No criteria met	3 (1.6%)	3 (1.7%)	0 (0.0%)
Number of prior relapses			
0	16 (8.5%)	15 (8.7%)	16 (9.6%)
1	107 (56.6%)	100 (58.1%)	95 (56.9%)
2	46 (24.3%)	39 (22.7%)	39 (23.4%)
> 2	20 (10.6%)	18 (10.5%)	17 (10.2%)
Prior alloHSCT and prior relapses			
No prior alloHSCT	125 (66.1%)	115 (66.9%)	113 (67.7%)
No prior relapse	16 (8.5%)	15 (8.7%)	16 (9.6%)
1 prior relapse	84 (44.4%)	77 (44.8%)	75 (44.9%)
2 prior relapses	22 (11.6%)	20 (11.6%)	20 (12.0%)
> 2 prior relapses	3 (1.6%)	3 (1.7%)	2 (1.2%)
Number of prior salvage therapies			
No prior salvage therapy	38 (20.1%)	37 (21.5%)	32 (19.2%)
1 prior salvage therapy	77 (40.7%)	70 (40.7%)	69 (41.3%)
2 prior salvage therapies	42 (22.2%)	38 (22.1%)	40 (24.0%)
> 2 prior salvage therapies	32 (16.9%)	27 (15.7%)	26 (15.6%)

EFS = Efficacy Set; FAS = Full Analysis Set; HSCT = hematopoietic stem cell transplantation; PAS = Primary Analysis Set; PPS = Per Protocol Set; a) Race was not permitted to be collected in France.

7.1.1.11. Results for the primary efficacy outcome

The primary efficacy endpoint of this study was CR/CRh* rate within the first 2 cycles of treatment with blinatumomab. The primary analysis was based on the PAS (subjects from the first 3 stages of the study who received any infusion of blinatumomab). For this iteration of the CSR, the FAS was identical to the PAS. Efficacy analyses based on the EFS and PPS were performed as sensitivity analyses. The overview of the best response rates for the first 2 cycles of treatment and the core study are presented in Table 22, below.

Table 22: Overview of best response rates during the first 2 cycles of treatment and the core study (Primary Analysis Set)

Response	First 2 Cycles of Treatment (N = 189)			Core Study (N = 189)		
	N =	%	95% CI	N =	%	95% CI
CR/CRh*	81	42.9%	35.7% to 50.2%	82[a]	43.4%	36.2% to 50.8%
CR	63	33.3%	26.7% to 40.5	67	35.4%	28.6% to 42.7%
CRh*	18	9.5%	5.7% to 14.6%	15	7.9%	4.5% to 12.8%
Blast free hypoplastic or aplastic bone marrow	17	9.0%	5.3% to 14.0%	17	9.0%	5.3% to 14.0%
Partial remission	5	2.6%	0.9% to 6.1%	5	2.6%	0.9% to 6.1%

CI = confidence interval; CR = complete remission; CRh* = complete remission with only partial haematological recovery; * 1 subject had a haematological response after Cycle 2, however, CD19 + leukaemic blasts were present in the CSF. Per protocol, extramedullary disease was equivalent with haematological disease for response assessments; therefore, treatment should have been discontinued. After Cycle 3, the subject had achieved CR; no more leukaemic blasts were present in the CSF after the subject had received intrathecal therapy on Day 29 of Cycle 2 and Cycle 3 as per protocol.

Results for the primary efficacy endpoint of the best response of CR/CRh* rates within the first 2 cycles of treatment with blinatumomab are presented in Table 23.

The core study was defined as the time from the first infusion through 30 days after the last infusion. The best CR/CRh* rates during the core study are presented in Table 24. In the PAS, the best CR/CRh* rate with blinatumomab treatment was 43.4% (82/189; 95% CI: 36.2% to 50.8%) (CR = 35.4% (67/189; 95% CI: 28.6% to 42.7%); CRh* = 7.9% (15/189; 95% CI: 4.5% to 12.8%)). The response rates for blast free hypoplastic or aplastic bone marrow and partial remission were the same as the first 2 cycles of treatment. Of the nonresponders during the core study, 14.8% (28/189) of subjects had progressive disease, 21.2% (40/189) had not responded to treatment, and 9% (17/189) had no response data.

Table 23: Best response during the first 2 cycles; Primary analysis endpoint

Best Response	PAS/FAS (N = 189)			EFS (N = 172)			PPS (N = 167)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
CR/CRh*	81	42.9%	35.7% to 50.2%	81	(47.1%)	(39.5% to 54.8%)	67	(40.1%)	(32.6% to 48.0%)
Complete remission (CR)	63	33.3%	26.7% to 40.5	63	(36.6%)	(29.4% to 44.3%)	51	(30.5%)	(23.7% to 38.1%)
Complete remission with only partial haematological recovery (CRh*)	18	9.5%	5.7% to 14.6%	18	(10.5%)	(6.3% to 16.0%)	16	(9.6%)	(5.6% to 15.1%)
Blast free hypoplastic or aplastic bone marrow	17	9.0%	5.3% to 14.0%	17	(9.9%)	(5.9% to 15.4%)	16	(9.6%)	(5.6% to 15.1%)
Partial remission	5	2.6%	0.9% to 6.1%	5	(2.9%)	(1.0% to 6.7%)	5	(3.0%)	(1.0% to 6.8%)
Nonresponders during the first 2 cycles									
Progressive disease	27	(14.3%)		27	(15.7%)		25	(15.0%)	
Nonresponse	41	(21.7%)		41	(23.8%)		37	(22.2%)	
No response data	18	(9.5%)		1	(0.6%)		17	(10.2%)	

Table 24: Best response during core study

Best response	PAS/FAS (N = 189)			EFS (N = 172)			PPS (N = 167)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
CR/CRh*	82	(43.4%)	(36.2 to 50.8%)	82	(47.7%)	(40.0 to 55.4%)	68	(40.7%)	(33.2 to 48.6%)
Complete remission (CR)	67	(35.4%)	(28.6 to 42.7%)	67	(39.0%)	(31.6 to 46.7%)	55	(32.9%)	(25.9 to 40.6%)
Complete remission with only partial haematological recovery (CRh*)	15	(7.9%)	(4.5 to 12.8%)	15	(8.7%)	(5.0 to 14.0%)	13	(7.8%)	(4.2 to 12.9%)
Blast free hypoplastic or aplastic bone marrow	17	(9.0%)	(5.3 to 14.0%)	17	(9.9%)	(5.9 to 15.4%)	16	(9.6%)	(5.6 to 15.1%)
Partial remission	5	(2.6%)	(0.9 to 6.1%)	5	(2.9%)	(1.0 to 6.7%)	5	(3.0%)	(1.0 to 6.8%)
Nonresponders during the core study									
Progressive disease	28	(14.8%)		28	(16.3%)		26	(15.6%)	
Nonresponse	40	(21.2%)		40	(23.3%)		36	(21.6%)	
No response data	17	(9.0%)		0	(0.0%)		16	(9.6%)	

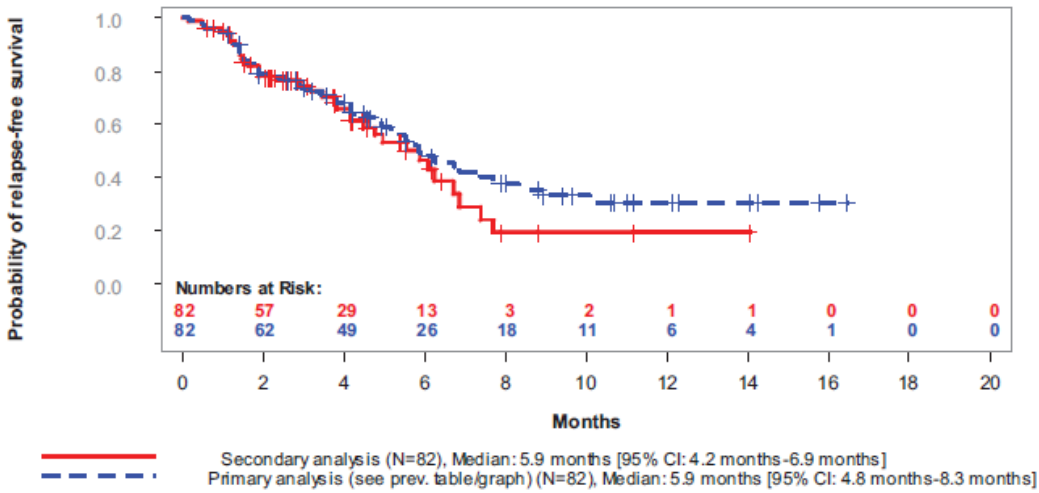
CI = confidence interval; EFS = Efficacy Set; FAS = Full Analysis Set; PAS = Primary Analysis Set; PPS = Per Protocol Set.

7.1.1.12. Results for other efficacy outcomes

Relapse free survival

For the PAS, the median relapse free survival was 5.9 months (95% CI: 4.8 to 8.3 months), with a median observation time of 8.9 months. 37 subjects (45.1%; 37/82) were censored for not having an event (that is, in remission). Median relapse free survival was similar when censoring at the time of HSCT (Figure 20). Relapse free survival was analysed separately for subjects who achieved a best response of CR and those who achieved a best response of CRh*. Based on the best response during the core study, the median relapse free survival for subjects who achieved a CR was 6.9 months (95% CI: 4.2 to 10.1 months) compared with 2.8 months (95% CI: 1.2 to 6.1 months) for subjects who achieved a best response of CRh*. Although relapse free survival was shorter for subjects who achieved CRh* compared with subjects who achieved CR, a benefit to CRh* was observed as 3 subjects who achieved CRh* within the first 2 treatment cycles eventually achieved a CR with additional blinatumomab treatment. For each response category, relapse free survival was similar when censoring at the time of HSCT for those subjects that underwent an HSCT.

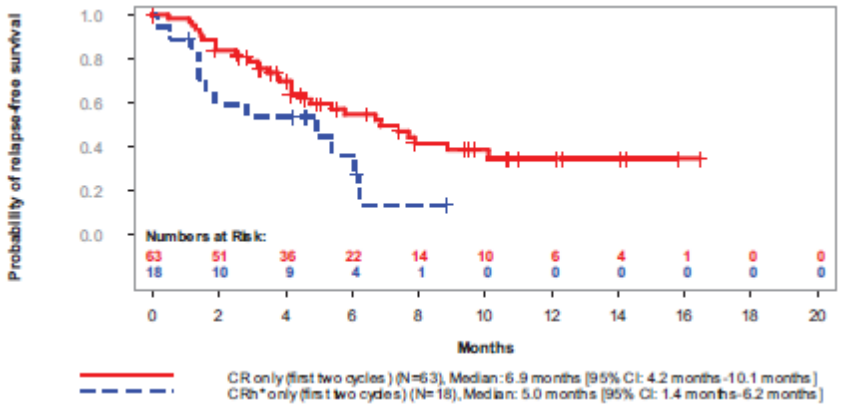
Figure 20: Relapse free survival by Kaplan-Meier method, primary and secondary analyses during the core study (primary analysis set)



Relapse free survival is defined for subjects who reached a CR or CRh* during the core study only Primary analysis: subjects in remission (CR or CRh*) during the core study Secondary analysis: subjects in remission (CR or CRh*) during the core study and were censored for HSCT.

When based on the best response within the first 2 cycles, the median relapse free survival for subjects who achieved a best response of CR was 6.9 months (95% CI: 4.2 to 10.1 months) (N = 63) compared with 5.0 months (95% CI: 1.4 to 6.2 months) for subjects who achieved a best response of CRh* (N = 18) (see Figure 21, below). The median relapse free survival was similar when censored at the time of HSCT for those subjects that underwent an HSCT. The clinical benefit of achieving a CRh* within 2 cycles was apparent, as it could lead to an eventual conversion to CR and a prolonged relapse free survival.

Figure 21: Relapse free survival, estimated by Kaplan-Meier method, separately for subjects who reached the best response of CR or CRh* during the first 2 cycles (Primary Analysis Set)



Relapse free survival is defined for subjects who reached CR or CRh* during the first 2 cycles only.

*Time to haematological relapse (duration of response): Subjects with CR/CRh**

Time to haematological relapse was measured only for subjects in remission (CR/CRh*), and was measured from the time the subject first achieved remission until first documented relapse or death due to disease progression. Subjects without a documented relapse (haematological or extramedullary) and who did not die were censored at the time of their last bone marrow

assessment or their last survival follow-up visit confirming remission. Subjects who died without having reported haematological relapse or without showing any clinical sign of disease progression were censored on their date of death.

For the PAS, the median time to haematological relapse was 6.7 months (95% CI: 5.1 months to not estimable (n.e.)), with a median observation time of 8.0 months. Of the subjects who achieved a CR/CRh* during the core study, 45.1% (37/82) of subjects completed the study in remission (censored). The median time to haematological relapse was approximately 1 month earlier when censoring at the time of HSCT for those subjects who underwent an HSCT.

Haematological relapse was analysed separately for subjects who achieved a best response of CR and those who achieved a best response of CRh*. Based on the best response during the core study, the median time to haematological relapse for subjects who achieved a CR was 7.4 months (95% CI: 4.8 months to n.e.) compared with 6.1 months (95% CI: 1.2 to 6.2 months) for subjects who achieved a best response of CRh*. For each response category, time to haematologic relapse was earlier when censoring at the time of HSCT for subjects who underwent HSCT.

For subjects who achieved CR only within the first 2 cycles of treatment (N = 63), the median time to haematological relapse was 7.7 months (95% CI: 5.4 months to n.e.). For subjects who achieved CRh* only within the first 2 cycles (N = 18), the median time to haematological relapse was 5.0 months (95% CI: 1.4 months to n.e.).

For subjects who achieved CR only within the first 2 cycles and were censored for HSCT, the median time to haematological relapse was 5.4 months (95% CI: 3.8 to 7.4 months). For subjects who achieved CRh* only within the first 2 cycles and were censored for HSCT, the median time to haematological relapse was 5.0 months.

Overall survival

Overall survival was measured for all subjects from the time the subject received the first treatment of blinatumomab until death due to any cause or the date of the last follow-up. Subjects who did not die were censored. An overview of overall survival is presented below in Table 25.

When censored for subjects with HSCT after remission induced by blinatumomab treatment, median overall survival was 5.1 months (95% CI: 4.1 to 7.1 months), with a median observation time of 6.0 months. The Kaplan-Meier curves virtually overlap despite the 1 month difference in estimations (Figure 22).

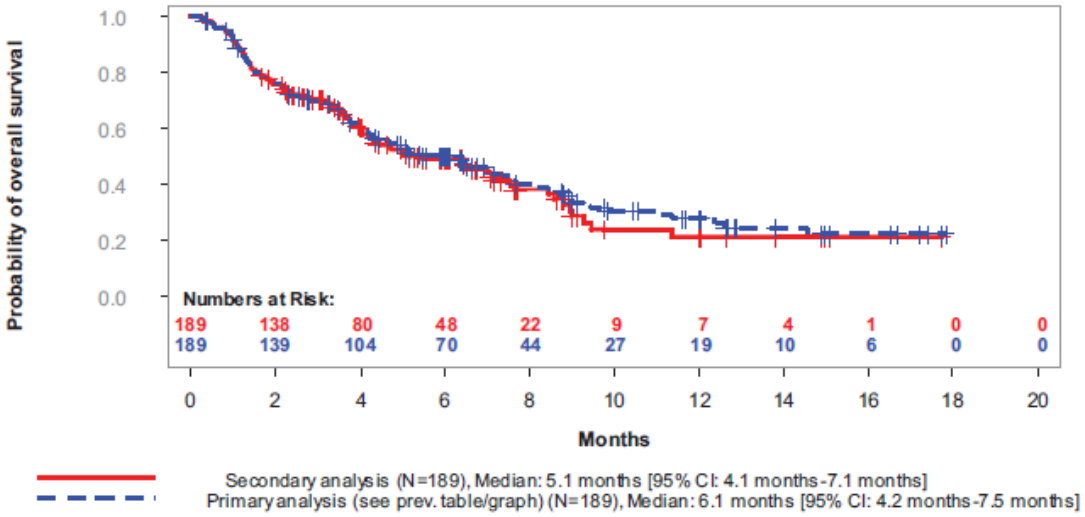
Table 25: Overview of overall survival (Primary Analysis Set)

	N =	Months	
		Median	95% CI
Overall Survival	189	6.1	4.2 to 7.5
Censored for HSCT	189	5.1	4.1 to 7.1
Censoring at the time of first CR/CRh*	189	3.5	2.4 to 3.9
Landmark = 36 days			

	N =	Months	
		Median	95% CI
CR/CRh*	60	11.2	7.8 to n.e.
Nonresponders	101	3.0	2.4 to 4.0
Landmark = 77 days			
CR/CRh*	79	9.9	6.8 to n.e.
Nonresponders	50	2.7	1.6 to 4.5

CI = confidence interval; CR = complete response; CRh* = complete remission with only partial haematological recover; HSCT = haematopoietic stem cell transplant; n.e. = not estimable

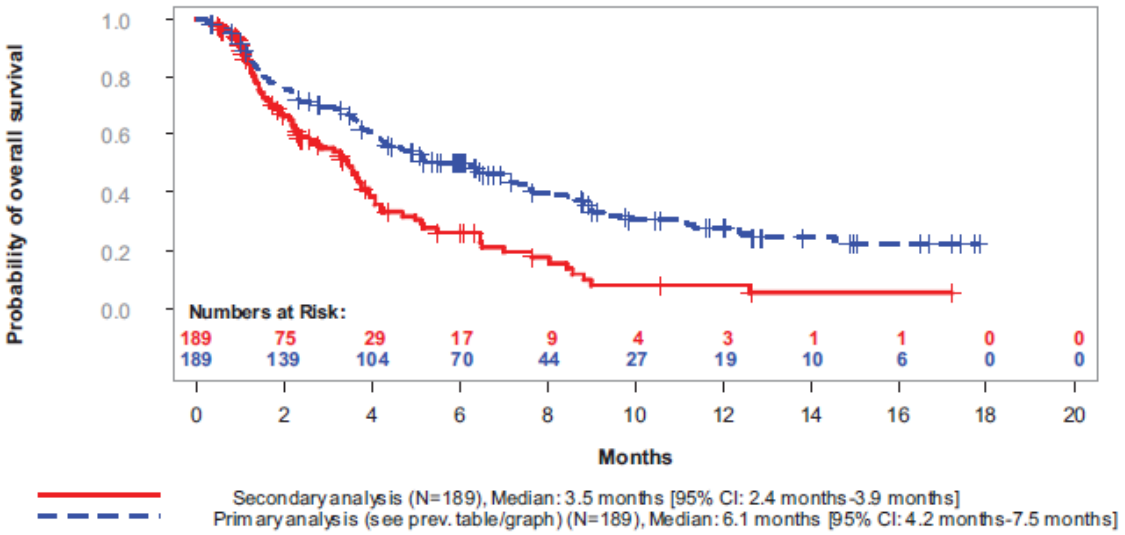
Figure 22: Overall survival, estimated by Kaplan-Meier, secondary analysis censoring subjects with HSCT (Primary Analysis Set)



Primary analysis: subjects in remission (CR or CRh*) during the core study Secondary analysis: subjects in remission (CR or CRh*) during the core study and were censored for HSCT

The clinical benefit of achieving remission was assessed by censoring overall survival at the time CR/CRh* was first achieved and comparing the result to the primary analysis of overall survival. When censored for time of first response, the median overall survival was 3.5 months (95% CI: 2.4 to 3.9 months) as shown below in Figure 23.

Figure 23: Overall survival, estimated by Kaplan-Meier, secondary analysis censoring subjects at the time of first achievement of CR or CRh* (Primary Analysis Set)



Primary analysis: subjects in remission (CR or CRh*) during the core study, Secondary analysis: subjects in remission (CR or CRh*) during the core study and were censored for HSCT.

Overall survival: Landmark analyses

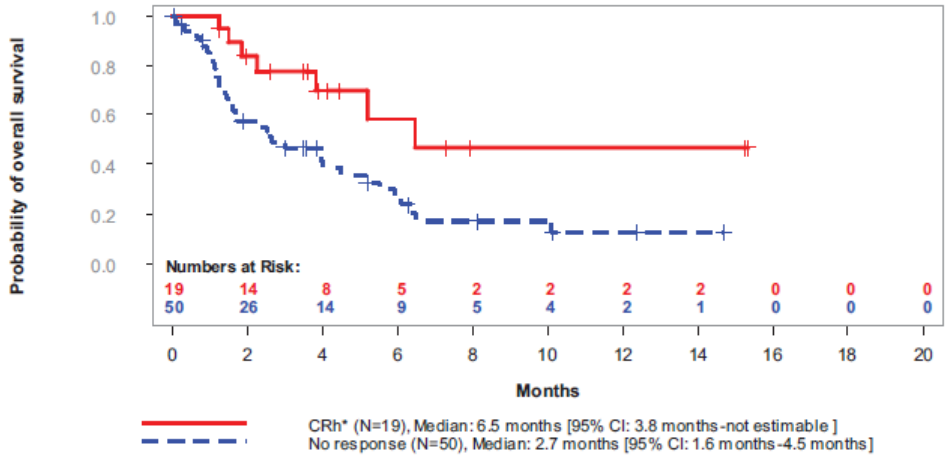
Note, landmark = Day 77 of this study.

Among subjects who were alive by Day 77, median overall survival was 9.9 months (95% CI: 6.8 months to that is,) for subjects who achieved CR/CRh* on or before day 77 (N = 79), and 2.7 months (95% CI: 1.6 to 4.5 months) for nonresponders (N = 50). At the time of the last follow-up for subjects in remission (CR/CRh*), 65.8% (52/79) of subjects were alive (censored) and 34.2% (27/79) of subjects had died; of the nonresponders, 28% (14/50) of subjects were alive (censored) and 72% (36/50) of subjects had died.

To better understand the benefit of CRh* an ad hoc analysis was performed for subjects who were alive and achieved CRh* on or before day 77 (that is,, subjects with CR before day 77 were excluded from the analysis). The median overall survival was 6.5 months (95% CI: 3.8 months to n.e.) for subjects who achieved CRh* (N = 19) compared with 2.7 months (95% CI: 1.6 to 4.5 months) for nonresponders (N = 50). The difference of approximately 4 months observed for this analysis may likely be a benefit of CRh* on survival; however, other factors cannot be ruled out (for example, subject's health). At the time of the last follow-up, 63.2% (12/19) of subjects who achieved CRh* were alive (censored) compared with 28% (14/50) of nonresponders who were alive (censored) (see Figure 24, shown below).

Subjects who died or were censored by Day 77 or had reached best response = CR before Day 77 were excluded from the analysis. CRh* refers to the number of subjects who had reached CRh* at best response by Day 77, 'No response' refers to those subjects who never had reached CRh* by Day 77.

Figure 24: Overall survival, landmark analysis using Kaplan-Meier methods, stratified by CRh* status (excluding subjects with CR before Day 77); Landmark = Day 77 (Primary Analysis Set)

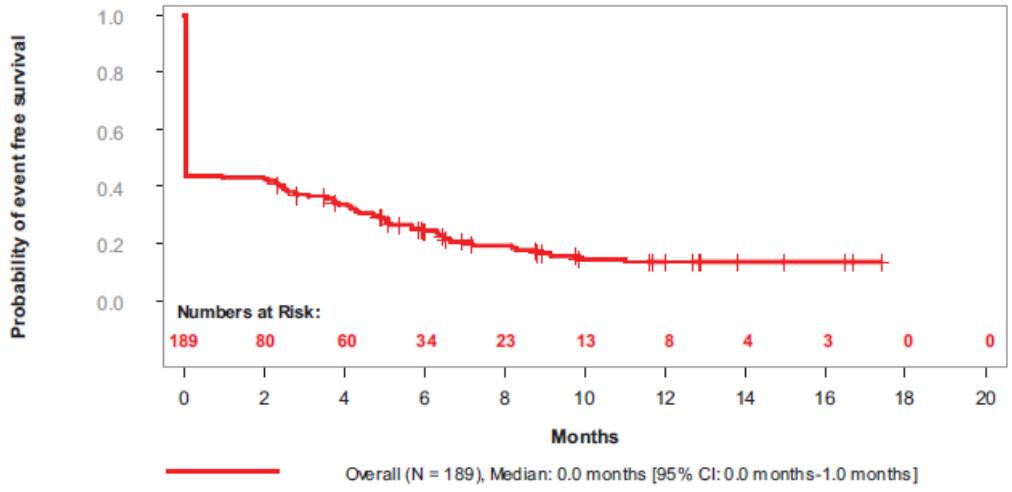


Event free survival

The analysis of event free survival was assessed for all subjects who started treatment with blinatumomab in this study. Event free survival was calculated relative to the start date of blinatumomab infusion in the first treatment cycle. The date of bone marrow aspiration at which haematological relapse was first detected, or the date of diagnosis on which the haematological or extramedullary relapse was documented or the date of start of any new therapy for ALL (excluding HSCT), or the date of death was used as the event date for event free survival, whichever was earlier. Subjects who did not achieve CR/CRh* during the core study were evaluated as having an event on Day 1. Subjects with CR/CRh* who did not experience haematological relapse, did not receive a new therapy for ALL (excluding HSCT), and did not die, were censored on the date of the last available bone marrow aspiration or on the last date of survival follow-up visit, whichever was later.

The estimated median event free survival was not informative since more than 50% of subjects had not achieved remission and were assigned an event free survival of 1 day (see Figure 25, below).

Figure 25: Event free survival, estimated by Kaplan-Meier (Primary Analysis Set)



Time to response analyses

The time to CR/CRh* and time to CR were calculated relative to the start date of blinatumomab infusion in the first treatment cycle until CR/CRh* was documented for the first time during the study. Subjects who did not experience CR/CRh* as best response during the study were censored at the end of core study visit. An overview of the time to response is presented in Table 26, below.

Table 26: Overview of time to response (Primary Analysis Set)

Response	Response rate	Median Time to Response	
		Months	95% CI
CR/CRh*	43.4% (82/189)	2.3	1.7 to 2.3
CR	35.4% (67/189)	2.5	2.3 to 4.1

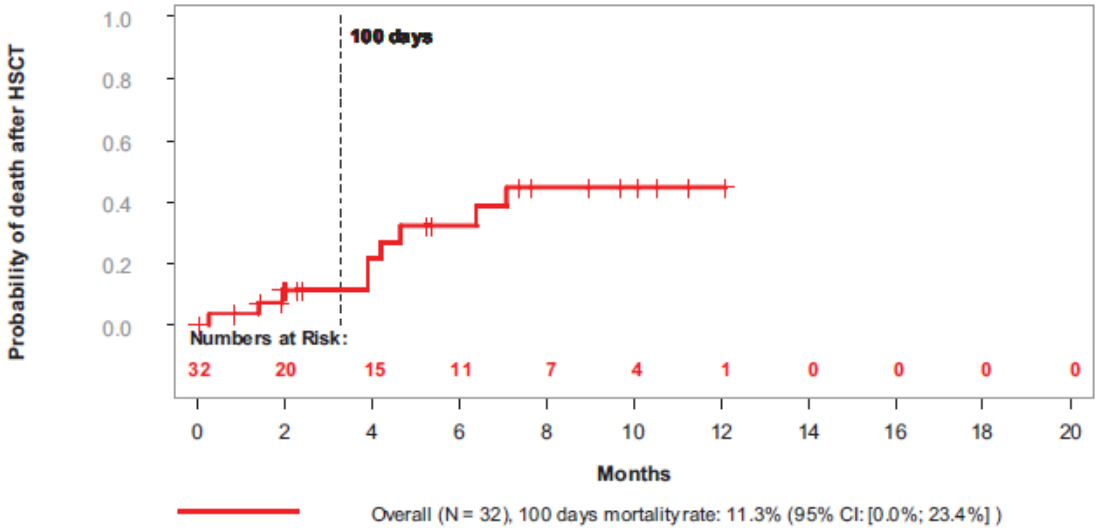
CI = confidence interval; CR = complete remission; CRh* = complete remission with only partial haematological recovery

100 day mortality after allogeneic haematopoietic stem cell transplant

The analysis of 100 day mortality after allogeneic HSCT was assessed for all subjects who received an allogeneic HSCT while in remission (CR/CRh*) following treatment with blinatumomab. 100 day mortality after allogeneic HSCT was calculated relative to the date of allogeneic HSCT.

Among eligible subjects, 39.5% (32/81; 95% CI: 28.8% to 51%) received an allogeneic HSCT while in remission induced by blinatumomab and without any other subsequent anti-leukemic medication (excluding conditioning regimens). The 100 day mortality rate for these subjects was 11.3% (95% CI: 0% to 23.4%) (see Figure 26). Thus, the survival rate was 88.7% at day 100 after transplant.

Figure 26: 100 day mortality after allogeneic hematopoietic stem cell transplant (Primary Analysis Set)



7.1.1.13. Exploratory efficacy endpoints

Rate of MRD response during the first 2 cycles of treatment

An overview of MRD response rates during the first 2 cycles of treatment is presented below in Table 27. The overall MRD and complete MRD response rates during the first 2 cycles were 34.4% and 28%, respectively. For subjects who achieved CR/CRh* within the first 2 cycle response rates improved to 74.1% and 63%, respectively. Among those subjects with MRD assessments available, MRD and complete MRD response rates for subjects who achieved a CR were similar to those observed for CR/CRh*, while response rates for subjects who achieved CRh* or blast free hypoplastic or aplastic bone marrow were lower than CR/CRh* and CR response rates.

Table 27: Overview of MRD response rates during the first 2 cycles of treatment (Primary Analysis Set)

Characteristic/Category	MRD Response		
	N =	%	95% CI
Within first 2 cycles with MRD assessments (N = 181)[a]			
MRD response	65	35.9%	-
Complete MRD response	53	29.3%	-
Within first 2 cycles (N = 189)			
MRD response	65	34.4%	(27.6 to 41.6%)
Complete MRD response	53	28.0%	(21.8 to 35.0%)
CR/CRh* within first 2 cycles with MRD assessments (N = 73)[a]			
MRD response	60	82.2%	(71.5 to 90.2%)

Characteristic/Category	MRD Response		
	N =	%	95% CI
Complete MRD response	51	69.9%	(58.0 to 80.1%)
CR/CRh* Within First 2 Cycles (N = 81)			
MRD response	60	74.1%	(63.1 to 83.2%)
Complete MRD response	51	63.0%	(51.5 to 73.4%)
CR within first 2 cycles with MRD assessments (N = 58)[b]			
MRD response	50	86.2%	-
Complete MRD response	43	74.1%	-
CRh* within first 2 cycles with MRD assessments (N = 15)[c]			
MRD response	10	66.7%	-
Complete MRD response	8	53.3%	-
Blast free hypoplastic or aplastic bone marrow within first 2 cycles with MRD assessments (N = 10)[d]			
MRD response	5	50.0%	-
Complete MRD response	2	20.0%	-

CI = confidence interval; CR = complete remission; CRh* = complete remission with only partial haematological recovery; MRD = minimal residual disease; - = not reported. MRD response: MRD < 10-4 measured by PCR; MRD complete response: no PCR amplification of individual rearrangements of immunoglobulin- or TCR genes could be detected. Sensitivity and quantitative measurement range of assay need to be at least 10^{-4}. a) Excludes subjects with no MRD data: n = 8; b) excludes subjects with no MRD data: n = 5; c = excludes subjects with no MRD data: n = 3; d = excludes subjects with no MRD data: n = 7.

7.1.1.14. Conclusions

- Primary endpoint of the study was met with 42.9% (CR 33.3%, CRh* 9.5%) of subjects achieving CR/CRh* within 2 cycles of blinatumomab therapy.
- Primary endpoint was supported by key secondary endpoints including:
  - Median relapse free survival was 5.9 months and nearly 40% of subjects who achieved CR/CRh* proceeded to transplant.
- This study showed a high remission rate in adult patients with heavily pre-treated and/or aggressive relapsed/refractory B-precursor ALL at the target dose of 28 µg/day.

7.1.2. Study MT103-206

An open label, multicentre, exploratory, Phase II study to evaluate the efficacy, safety, and tolerability of the BiTE antibody blinatumomab in adult subjects with relapsed and/or

refractory B-precursor ALL at 2 target dose levels of 15 µg and 30 µg using a Simon's 2-stage design (Figure 27 and Figure 28).

7.1.3. Study design, objectives, locations and dates

This was a double blind, multicentre, randomised, active controlled study conducted in 32 centres in the USA between May 2009 and June 2011.

The primary objective was to evaluate the efficacy of blinatumomab in subjects with relapsed/refractory B-precursor ALL.

The secondary objectives were as follows:

- To evaluate safety and tolerability of blinatumomab in subjects with relapsed/refractory B-precursor ALL
- To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of blinatumomab.

This study is ongoing and will end when the last subject has had the last protocol mandated visit. Results of the primary analysis (conducted when the last subject completed the core study; data cut-off date of 15 October 2012) were presented in the clinical study report.

Figure 27: Study MT103-206 Study design

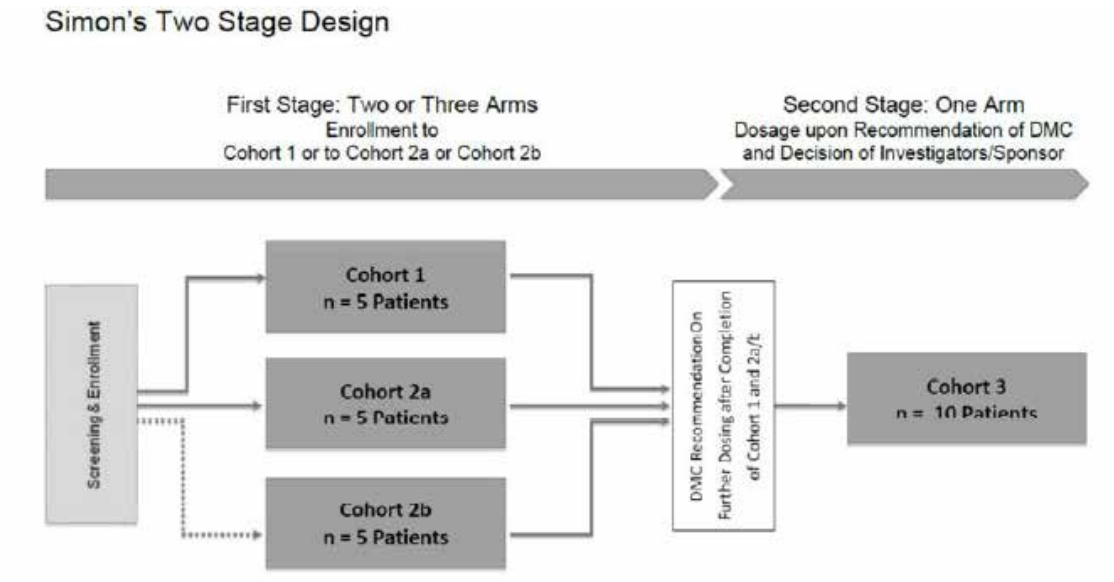
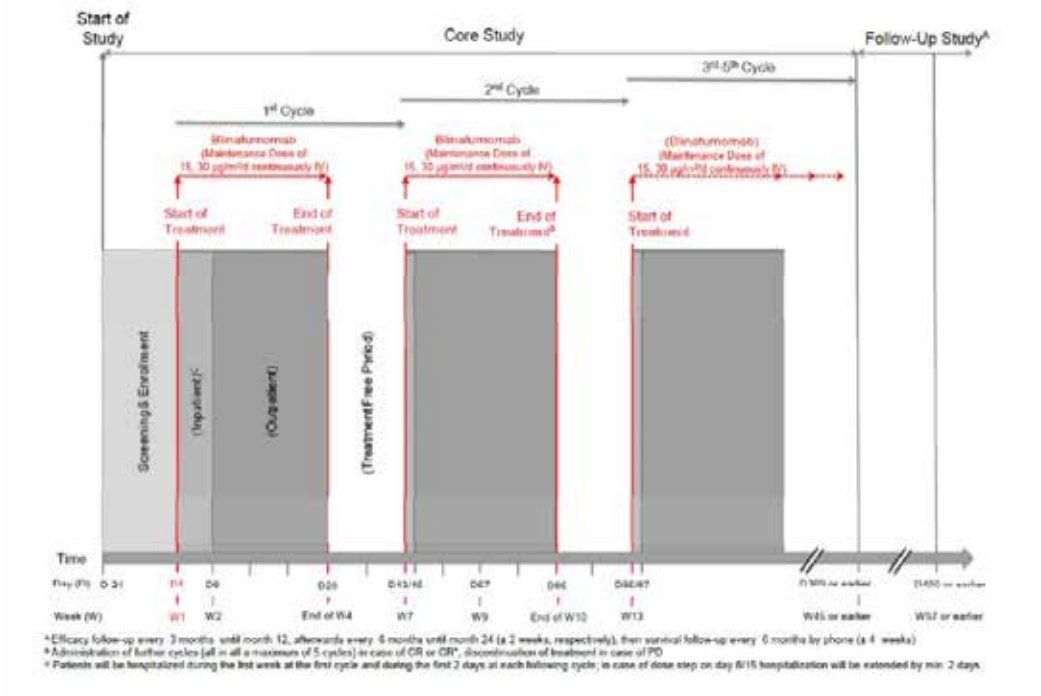


Figure 28: Study schema (visual representation of study periods)



7.1.3.1. Inclusion and exclusion criteria

Inclusion: A subject was eligible for study participation only if all of the following criteria applied:

- Patients with B-precursor ALL relapsed after at least induction and consolidation or having refractory disease:
  - Relapse was defined as reappearance of disease after CR having at least lasted for 28 days
  - Refractory disease was defined as not having achieved CR after induction and/or consolidation I
- More than 5% blasts in bone marrow
- ECOG performance status ≤ 2
- Age ≥ 18 years
- Life expectancy of ≥ 12 weeks
- Ability to understand and willingness to sign a written informed consent
- Signed and dated written informed consent was available

Exclusion: A subject was not eligible to participate in this study, if any of the following criteria applied:

- History or presence of clinically relevant central nervous system (CNS) pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis
- Infiltration of cerebrospinal fluid (CSF) and/or testis by ALL
- History of autoimmune disease with potential CNS involvement or current autoimmune disease

- Autologous HSCT within 6 weeks prior to start of blinatumomab treatment
- Allogeneic HSCT within 3 months prior to start of blinatumomab treatment
- Eligibility for allogeneic HSCT at the time of enrolment (as defined by disease status, performance status and availability of donor)
- Active Graft-versus-Host Disease (GvHD)
- Immunosuppressive therapy against GvHD within 1 week prior to start of blinatumomab treatment
- Patients with Philadelphia positive (Ph+) ALL eligible for treatment with dasatinib or imatinib
- Cancer chemotherapy within 2 weeks prior to start of blinatumomab treatment and tyrosine kinase inhibitors (TKIs) within 72 hours (hrs) prior to start of blinatumomab treatment (intrathecal prophylaxis and/or steroids (≤ 24 mg/day) were allowed until start of blinatumomab treatment.
- Radiotherapy within 4 weeks prior to start of blinatumomab treatment
- Immunotherapy (for example, rituximab) within 4 weeks prior to start of blinatumomab treatment
- Any investigational anti-leukemic product within 4 weeks prior to start of blinatumomab treatment
- Treatment with any other investigational product after signature of informed consent
- Known hypersensitivity to immunoglobulins or to any other component of the study drug formulation
- Presence of human anti-murine antibodies (HAMA)
- Abnormal laboratory values as defined below:
  - Aspartate aminotransferase (AST; SGOT) and/or alanine aminotransferase (ALT; SGPT) and/or alkaline phosphatase (AP) ≥ 5 x upper limit of normal (ULN)
  - Total bilirubin ≥ 1.5 x ULN
  - Creatinine clearance < 50 ml/min (calculated)
  - Hb ≤ 9 g/dl (transfusion allowed)
- Pathological findings of international normalised ratio (INR) or partial thromboplastin time (PTT) > 1.5 x ULN
- Symptoms or signs of disseminated intravascular coagulation (DIC)
- History of malignancy other than ALL within 5 years prior to start of blinatumomab treatment with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix
- Active infection, any other concurrent disease, or medical condition that is deemed to interfere with the conduct of the study as judged by the investigator
- Infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)
- Pregnant or nursing women

- Women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least 3 months thereafter. Male subjects not willing to ensure not to beget a child during participation in the study and at least 3 months thereafter
- Previous treatment with blinatumomab.

7.1.3.2. Study treatments

The planned dosing schedule by cohort is described in Table 31. The decision regarding the cohort 3 dosing schedule was made after the completion of cohort 1 and 2a/b and was designated as the same dosing regimen as cohort 2a; thus, because of an additional cohort for dose evaluation, the number of subjects in this study who were treated with blinatumomab was 36.

Table 28: Planned dosing schedule

Cohort	Evaluable subjects	Initial dose Week 1	Dose Week 2	Target dose level
1	5	15 µg/m^2/day	15 µg/m^2/day	15 µg/m^2/day
2a	5	5 µg/m^2/day	15 µg/m^2/day	15 µg/m^2/day
2b	5	5 µg/m^2/day	15 µg/m^2/day	30 µg/m^2/day
3	10	5 µg/m^2/day	15 µg/m^2/day	15 µg/m^2/day

7.1.3.3. Efficacy variables and outcomes

Primary endpoint

CR and complete response/remission with partial recovery of peripheral blood counts (CRh*) rate within the first 2 cycles of treatment with blinatumomab. CR was defined by the following criteria: less than or equal to 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/µL, haemoglobin (Hb) ≥ 11 g/dL, and absolute neutrophil count (ANC) > 1,500/µL). CRh* was defined by the following criteria: ≤ 5% blasts in the bone marrow, no other evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/µL, Hb ≥ 7 g/dL, and ANC > 500/µL).

Secondary endpoints

- CR rate
- CRh* rate
- Partial response/remission rate
- Rate of MRD response (defined as MRD < 10^{-4} blasts/nucleated cells)
- Proportion of patients who undergo allogeneic HSCT after treatment with blinatumomab
- Time to haematological relapse
- Relapse free survival (RPS)
- OS
- Overall incidence and severity of adverse events
- PK parameters: Steady state blinatumomab concentration (C_{ss}) and serum blinatumomab clearance (CL)

- Quantification and characterization of peripheral blood leukocyte subsets and serum cytokine concentrations

7.1.3.4. Sample size

Using the statistical parameters described and under the original Simon's 2 stage study design, the sample size was planned to contain 20 evaluable subjects. Upon modifying the design to add a third Stage 1 cohort, the sample size was planned to contain 25 evaluable subjects. At least 15 subjects treated with the same dose schedule were to be included in the evaluation of the primary endpoint. Any cycle that was discontinued before 14 days of treatment with blinatumomab was defined as not evaluable for efficacy unless the infusion was stopped due to lack of efficacy (progressive disease/haematological relapse). A cycle defined as being not evaluable could be replaced by a later cycle that was evaluable for the purpose of the evaluation of the primary endpoint and for the evaluation of response within each cycle. Treatment cycles with treatment duration of at least 2 weeks were counted and assessed in the same way as cycles with the scheduled treatment duration of 28 days. Evaluable subjects were defined as those subjects with at least 1 evaluable cycle. For ethical and operational reasons, subjects who were already in the screening phase at the time that the 25th potentially evaluable subject started treatment were also treated. Under the original study design, an over running of subject recruitment up to a total of up to approximately 30 evaluable subjects was possible. However, because of the addition of an additional cohort for dose evaluation, the number of subjects in this study who were treated with blinatumomab was 36.

7.1.3.5. Statistical methods

All documented parameters were recorded and adequately evaluated. All relevant data on subjects (CRF data, laboratory data) were listed. The data were summarised per intended dose schedule using suitable descriptive measures; depending on the structure of the data, either sample statistics or frequency tables were applied. Subjects were analysed according to the intended dose schedule. Additional analyses summarised subjects by the actual dose received (in case of dose modifications were performed after treatment start). Demographics and other baseline characteristics were summarised in total and by intended dose schedule by means of summary statistics (number of subjects, number of subjects with missing data, mean, standard deviations, minimum, median, maximum) for continuous variables and by frequencies for categorical variables.

Efficacy analyses

The study efficacy objectives were evaluated using descriptive methods. Confirmatory analyses were not performed. 2-sided 95% confidence intervals (CIs) were calculated for response rates. Time-to-event data were analysed by Kaplan-Meier (K-M) methods. Confidence intervals for the quartiles of the K-M curves were based on the sign test.

Pharmacodynamic analyses

Descriptive statistic summary and graphical presentations were used for analysing the PD markers for example, leukocyte subpopulations, cytokines, granzyme B). Individual data were provided as listings.

Pharmacokinetic data analyses

PK data analyses were performed by the sponsor.

7.1.3.6. Enrolment of subjects

A total of 50 subjects were screened; 36 subjects were enrolled in the study and received blinatumomab, and were included in the SAF (see Table 29, below). Overall, 50% (18/36) of SAF subjects completed the core study and 75% (27/36) of subjects entered long-term follow-up (see Table 30, below).

Table 29: Number of subjects in each analysis set (SAF/FAS, by intended dose cohort schedule)

	Cohort 1 (15 µg/m²/day) (N = 7)		Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)		Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)		Screening failures (N = 14)		Overall (N = 50)	
	N =	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Screened subjects	7		23		6		14		50	
Screening failure	0		0		0		14		14	
Safety set	7	(100.0%)	23	(100.0%)	6	(100.0%)	0	(0.0%)	36	(72.0%)
Full analysis set	7	(100.0%)	23	(100.0%)	6	(100.0%)	0	(0.0%)	36	(72.0%)
Per protocol set	4	(57.1%)	18	(78.3%)	4	(66.7%)	0	(0.0%)	26	(52.0%)

Per protocol set: all patients from the full analysis set, who have reasonably adhered to relevant protocol conditions; FAS: Full Analysis Set; SAF: Safety Analysis Set.

Table 30: Disposition of subjects (SAF/FAS, by intended dose cohort schedule)

	Cohort 1 (15 µg/m²/day) (N = 7)		**Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)**		**Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)**		**Overall (N = 36)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Completed core study	2	(28.6%)	13	(56.5%)	3	(50.0%)	18	(50.0%)
Terminated core study prematurely	5	(71.4%)	10	(43.5%)	3	(50.0%)	18	(50.0%)
Entered long term follow-up	6	(85.7%)	16	(69.6%)	5	(83.3%)	27	(75.0%)
Started retreatment cycles	2	(28.6%)	0	(0.0%)	0	(0.0%)	2	(5.6%)

	Cohort 1 (15 µg/m²/day) (N = 7)		Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)		Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)		Overall (N = 36)	
Reasons for premature termination of core study								
Adverse Event	4	(57.1%)	3	(13.0%)	1	(16.7%)	8	(22.2%)
Subject withdraws informed consent	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subject is lost to follow up	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subject is not compliant	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Haematological relapse subsequent to CR/CRh* on protocol treatment	0	(0.0%)	1	(4.3%)	1	(16.7%)	2	(5.6%)
Failure to achieve CR/CRh* within 2 complete treatment cycles	1	(14.3%)	3	(13.0%)	1	(16.7%)	5	(13.9%)
Investigator's decision	0	(0.0%)	2	(8.7%)	0	(0.0%)	2	(5.6%)
Administration of non-permitted concomitant medication(s)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	1	(4.3%)	0	(0.0%)	1	(2.8%)
Primary reason for study termination								
End of follow-up period (efficacy F/U and safety F/U)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subject died	7	(100.0%)	13	(56.5%)	2	(33.3%)	22	(61.1%)
Subject withdraws informed consent	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subject is lost to follow up	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subject is not compliant	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Investigator's decision	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

	Cohort 1 (15 µg/m²/day) (N = 7)		Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)		Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)		Overall (N = 36)	
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Note: Subjects who entered long-term follow-up includes subjects who had a survival follow-up visit or an efficacy follow-up visit. CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; F/U: follow-up; SAF: Safety Analysis Set

7.1.3.7. Major protocol violations/deviations

Overall, the most frequently reported protocol deviations were major deviations from treatment schedule with respect to efficacy assessments (17%), cerebrospinal fluid (CSF) prophylaxis not administered before start of new blinatumomab cycle (14%), and non-permitted nonsteroidal anti-inflammatory drug (NSAID) concomitant treatment. None of the protocol deviations in this study were expected to influence the efficacy results of this study or affect the safety of any of the study subjects.

7.1.3.8. Baseline data

Demographic and general baseline characteristics are shown in Table 31.

Table 31: Subject characteristics at Baseline (SAF/FAS, by intended dose cohort)

	Cohort 1 (15 µg/m²/day) (N = 7)		Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)		Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)		Overall (N = 36)	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Male	4	(57.1%)	14	(60.9%)	4	(66.7%)	22	(61.1%)
Female	3	(42.9%)	9	(39.1%)	2	(33.3%)	14	(38.9%)
Age group								
≤ 60 years	5	(71.4%)	20	(87.0%)	4	(66.7%)	29	(80.6%)
> 60 years	2	(28.6%)	3	(13.0%)	2	(33.3%)	7	(19.4%)
Relapsed/ refractory status								
Primary Refractory	0	(0.0%)	2	(8.7%)	1	(16.7%)	3	(8.3%)
Relapsed	7	(100.0%)	21	(91.3%)	5	(83.3%)	33	(91.7%)
Number of prior relapses at study entry								

	Cohort 1 (15 µg/m²/day) (N = 7)		Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)		Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)		Overall (N = 36)	
	n	(%)	n	(%)	n	(%)	n	(%)
0	0	(0.0%)	2	(8.7%)	1	(16.7%)	3	(8.3%)
1	5	(71.4%)	15	(65.2%)	3	(50.0%)	23	(63.9%)
2	2	(28.6%)	6	(26.1%)	1	(16.7%)	9	(25.0%)
3	0	(0.0%)	0	(0.0%)	1	(16.7%)	1	(2.8%)
4	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Prior allogeneic HSCT								
Prior allogeneic HSCT	3	(42.9%)	10	(43.5%)	2	(33.3%)	15	(41.7%)
Sibling (last HSCT)	1	(14.3%)	1	(4.3%)	1	(16.7%)	3	(8.3%)
Unrelated	2	(28.6%)	9	(39.1%)	1	(16.7%)	12	(33.3%)
Haploidentical (mother/ father) (last HSCT)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
No prior allogeneic HSCT	4	(57.1%)	13	(56.5%)	4	(66.7%)	21	(58.3%)
B-precursor ALL								
Yes	7	(100.0%)	23	(100.0%)	6	(100.0%)	36	(100.0%)
Pro-B-ALL	4	(57.1%)	2	(8.7%)	3	(50.0%)	9	(25.0%)
C-ALL	1	(14.3%)	14	(60.9%)	1	(16.7%)	16	(44.4%)
Pre-B-ALL	2	(28.6%)	7	(30.4%)	2	(33.3%)	11	(30.6%)

ALL: Acute lymphoblastic leukaemia; C-ALL: common type; FAS: Full Analysis Set; HSCT: hematopoietic stem cell transplantation; Pro-B-ALL: immunophenotypic subtype of adult B-Precursor ALL; Pre-B-ALL: immunophenotypic subtype of adult B-Precursor ALL; SAF: Safety Analysis Set.

7.1.3.9. Results for the primary efficacy outcome

Results for the primary efficacy endpoint of CR and CRh* rate within 2 cycles of treatment with blinatumomab are presented in Table 32, below. The CR + CRh* rate within the first 2 cycles of treatment with blinatumomab was 69% in subjects overall (25/36 subjects; 95% CI: 51.9 to 83.7) (CR = 42% (15/36 subjects; 95% CI: 25.5 to 59.2); CRh* = 28% (10/36 subjects; 95% CI: 14.2 to 45.2%)). In cohort 1, the CR + CRh* rate within the first 2 cycles of treatment with blinatumomab for subjects was 72% (5/7 subjects; 95% CI: 29.0 to 96.3) (CR = 14% (1/7 subjects; 95% CI: 0.4 – 57.9); CRh* = 57% (4/7 subjects; 95% CI: 18.4 to 90.1)). In cohort 2a/3, the CR + CRh* rate within the first 2 cycles of treatment with blinatumomab for subjects was 70% (16/23 subjects; 95% CI: 47.1 to 86.8) (CR = 44% [10/23 subjects; 95% CI: 23.2 to 65.5); CRh* = 26% (6/23 subjects; 95% CI: 10.2 to 48.4)). In cohort 2b, the CR + CRh* rate within the first 2 cycles of treatment with blinatumomab for subjects was 67% (4/6 subjects; 95% CI: 22.3 to 95.7) (CR = 67% (4/6 subjects; 95% CI: 22.3 to 95.7); CRh* = 0% (0 subjects; 95% CI: 0.0 to 45.9)). Similar results for each respective cohort were seen for best response during the first 2 cycles and during the core study across all cycles, indicating that of the subjects who were responders, most achieved their best response during the first 2 blinatumomab treatment cycles.

In subjects overall, at the end of Cycle 1, 38% (12/32) of subjects achieved CR, 16% (5/32) of subjects achieved CRh*, 6% (2/32) achieved partial response/remission, 13% (4/32) had neither remission nor relapse, 0% had haematological relapse, and 28% (9/32) of subjects had hypocellular bone marrow (see Table 33, below). At the end of Cycle 2, 30% (6/20) of subjects achieved CR, 40% (8/20) achieved CRh*, 5% (1/20) achieved partial response/remission, 5% (1/20) had neither remission nor relapse, 0% had haematological relapse, and 20% (4/20) of subjects had hypocellular bone marrow.

Table 32: Best response during the first 2 cycles (SAF/FAS, intended dose cohort schedule)

Best response during the first 2 cycles	Cohort 1 (15 µg/m^2/day) (N = 7)			Cohort 2a/3 (5 to 15 µg/m^2/day) (N = 23)			Cohort 2b (5 to 15 to 30 µg/m^2/day) (N = 6)			Overall (N = 36)		
	n	%	95% CI	n	%	95 % CI	n	%	95% CI	n	%	95% CI
CR/CRh*	5	(71.4%)	(29.0 to 96.3 %)	16	(69.6%)	(47.1 to 86.8 %)	4	(66.7%)	(22.3 to 95.7%)	25	(69.4%)	(51.9 to 83.7%)
CR	1	(14.3%)	(0.4 to 57.9 %)	10	(43.5%)	(23.2 to 65.5 %)	4	(66.7%)	(22.3 to 95.7%)	15	(41.7%)	(25.5 to 59.2%)
CRh*	4	(57.1%)	(18.4 to 90.1 %)	6	(26.1%)	(10.2 to 48.4 %)	0	(0.0%)	(0.0 to 45.9%)	10	(27.8%)	(14.2 to 45.2%)

Best response during the first 2 cycles	Cohort 1 (15 µg/m²/day) (N = 7)			Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)			Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)			Overall (N = 36)		
	n	%	95% CI	n	%	95 % CI	n	%	95% CI	n	%	95% CI
Partial response/ remission	0	(0.0%)	(0.0 to 41.0 %)	2	(8.7%)	(1.1 to 28.0 %)	0	(0.0%)	(0.0 to 45.9%)	2	(5.6%)	(0.7 to 18.7%)
Non-responder during the first 2 cycles												
Hypocellular bone marrow	0	(0.0%)		2	(8.7%)		1	(16.7%)		3	(8.3%)	
Neither remission nor relapse	1	(14.3%)		2	(8.7%)		1	(16.7%)		4	(11.1%)	
Haematological relapse	0	(0.0%)		0	(0.0%)		0	(0.0%)		0	(0.0%)	
Not available	1	(14.3%)		1	(4.3%)		0	(0.0%)		2	(5.6%)	

Blasts were < 5% in all subjects who achieved CR/CRh*. CI: confidence interval; CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; SAF: Safety Analysis Set.

Table 33: Response by cycle (SAF/FAS, by intended dose cohort)

	Cohort 1 (15 µg/m²/day) (N = 7)			Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)			Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)			Overall (N = 36)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
End of Cycle 1	7			23			6			36		
CR		1/5	(20.0%)		9/21	(42.9%)		2/6	(33.3%)		12/32	(37.5 %)

	Cohort 1 (15 µg/m²/day) (N = 7)			Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)			Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)			Overall (N = 36)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
CRh*		2/5	(40.0%)		2/21	(9.5%)		1/6	(16.7%)		5/32	(15.6%)
Partial response/remission		0/5	(0.0%)		2/21	(9.5%)		0/6	(0.0%)		2/32	(6.3%)
Neither remission nor relapse		1/5	(20.0%)		2/21	(9.5%)		1/6	(16.7%)		4/32	(12.5%)
Haematological relapse		0/5	(0.0%)		0/21	(0.0%)		0/6	(0.0%)		0/32	(0.0%)
Hypocellular bone marrow		1/5	(20.0%)		6/21	(28.6%)		2/6	(33.3%)		9/32	(28.1%)
Not available		2			2			0			4	
End of Cycle 2	5			15			3			23		
CR		0/5	(0.0%)		4/13	(30.8%)		2/2	(100.0%)		6/20	(30.0%)
CRh*		5/5	(100.0%)		3/13	(23.1%)		0/2	(0.0%)		8/20	(40.0%)
Partial response/remission		0/5	(0.0%)		1/13	(7.7%)		0/2	(0.0%)		1/20	(5.0%)
Neither remission nor relapse		0/5	(0.0%)		1/13	(7.7%)		0/2	(0.0%)		1/20	(5.0%)
Haematological relapse		0/5	(0.0%)		0/13	(0.0%)		0/2	(0.0%)		0/20	(0.0%)
Hypocellular bone		0/	(0.0%)		4/1	(30.8%		0/	(0.0%)		4/20	(2

	Cohort 1 (15 µg/m²/day) (N = 7)			Cohort 2a/3 (5 to 15 µg/m²/day) (N = 23)			Cohort 2b (5 to 15 to 30 µg/m²/day) (N = 6)			Overall (N = 36)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
marrow		5			3	)		2				0.0 %)
Not available	0			2			1			3		

CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; SAF: Safety Analysis Set.

Results for other efficacy outcomes

Rate of MRD Response

An MRD response at any time during the core study was reached in 69% (25/36; 95% CI: 51.9 to 83.7) of subjects overall, 71% (5/7; 95% CI: 29.0 to 96.3) of subjects in cohort 1, 74% (17/23; 95% CI: 51.6 to 89.8) of subjects in Cohort 2a/3, and 50% (3/6; 95% CI: 11.8 to 88.2) of subjects in Cohort 2b. Of the subjects who achieved haematological remission (CR/CRh*), 88% (22/25) achieved an MRD response.

An MRD response was reached at the end of Cycle 1 in 63% (19/30) of subjects overall, 40% (2/5) of subjects in Cohort 1, in 74% (14/19) of subjects in cohort 2a/3, and 50% (3/6) of subjects in Cohort 2b. At the end of Cycle 2, an MRD response was reached in 79% (15/19) of subjects overall, 100% (5/5) of subjects in Cohort 1, 67% (8/12) of subjects in cohort 2a/3, and 100% (2/2) of subjects in cohort 2b. In MRD responders, MRD relapse at any time after MRD response was reported in 12% (3/25) of subjects overall, 0% (0/5) of subjects in Cohort 1, 12% (2/17) of subjects in Cohort 2a/3, and 33% (1/3) of subjects in cohort 2b. No subjects in the study had MRD progression at any time after MRD response. As of the data cut-off date, there were 2 evaluable subjects in Cohort 3 who had best response of hypocellular bone marrow who also achieved MRD response.

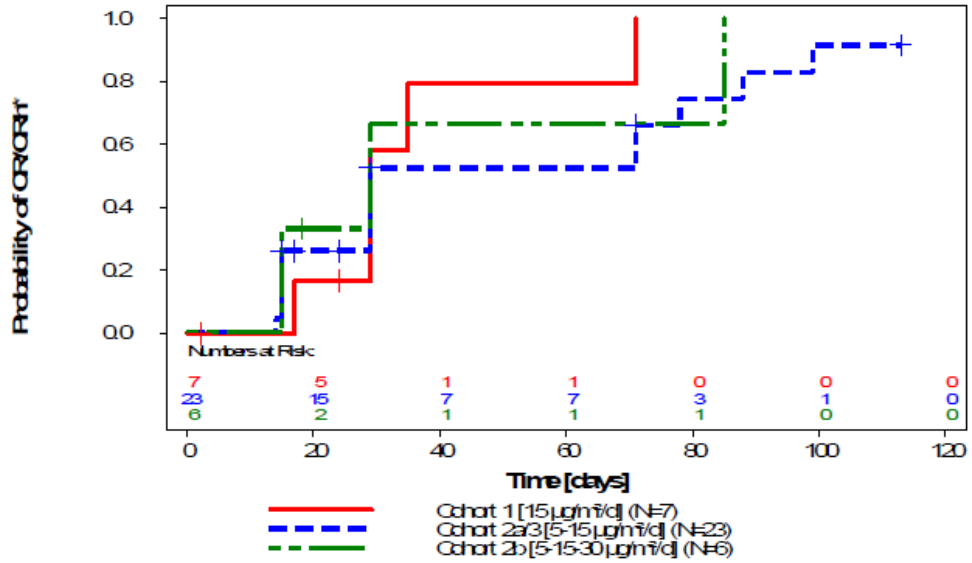
Allogeneic HSCT

Overall, 50% (18/36) of subjects underwent allogeneic HSCT after treatment with blinatumomab. In cohort 1, 43% (3/7) of subjects underwent allogeneic HSCT after blinatumomab treatment including 100% (1/1) of CR subjects and 25% (1/4) of CRh* subjects. In Cohort 2a/3, 61% (14/23) of subjects underwent allogeneic HSCT after blinatumomab treatment including 75% (9/12) of CR subjects, 50% (2/4) of CRh* subjects, 0% (0/2) of partial response/remission subjects, and 100% (3/3) of hypocellular bone marrow subjects. In cohort 2b, 17% (1/6) of subjects underwent allogeneic HSCT after blinatumomab treatment including 0% (0/1) of hypocellular bone marrow subjects. There were 2 subjects who achieved remission and underwent an allogeneic HSCT after relapsing.

*Time to CR/CRh**

The median time to CR/CRh* from the K-M analysis was 29 days in subjects overall and in subjects in Cohorts 1, 2a/3, and 2b (shown in Figure 29, below).

Figure 29: Time to CR/CRh* (SAF/FAS, by intended dose schedule; Kaplan-Meier curves stratified)



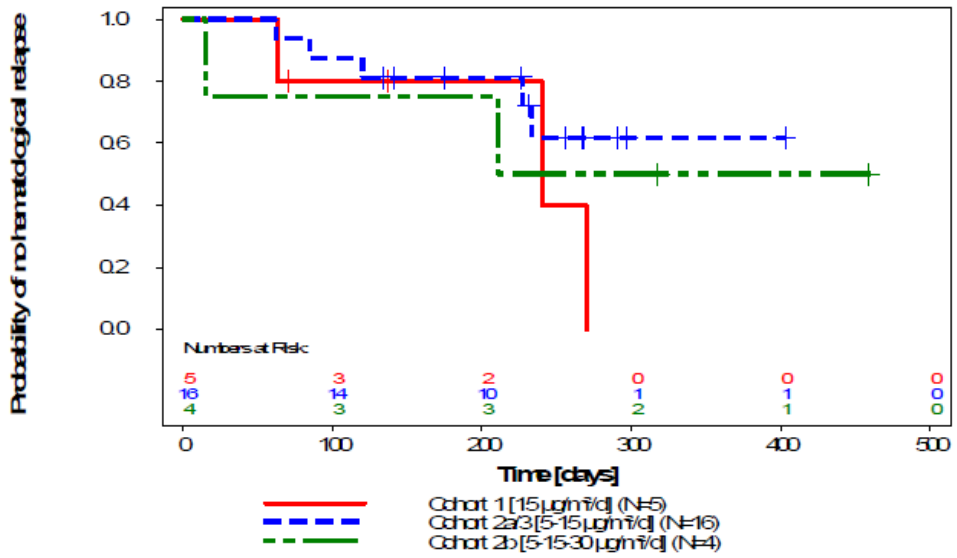
Note: Results displayed for subjects by intended study cohorts only. Results for subjects overall not displayed. CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; SAF: Safety Analysis Set.

Time to haematological relapse

Time to haematological relapse was measured only for subjects who achieved a CR or CRh* during the core study and was measured from the time the subject first achieved remission until first documented relapse or death due to disease progression. Patients without a documented relapse (haematological or extramedullary) and who did not die were censored at the time of their last bone marrow assessment or their last survival follow-up visit confirming remission. Patients who died without having reported haematological relapse or without showing any clinical sign of disease progression were censored on their day of death.

The median time to haematological relapse was 270 days (8.9 months) in responders overall and 240 days in Cohort 1 responders and was not reached in Cohort 2a/3 and 2b responders. 1 year probability rates were 47% (95% CI: 21.6 to 71.9) in responders overall, 0% for Cohort 1 responders, 62% (95% CI: 34.2 to 89.6) for Cohort 2a/3 responders, and 50% (95% CI: 1.0 to 99.0) for Cohort 2b responders (see Figure 30, below).

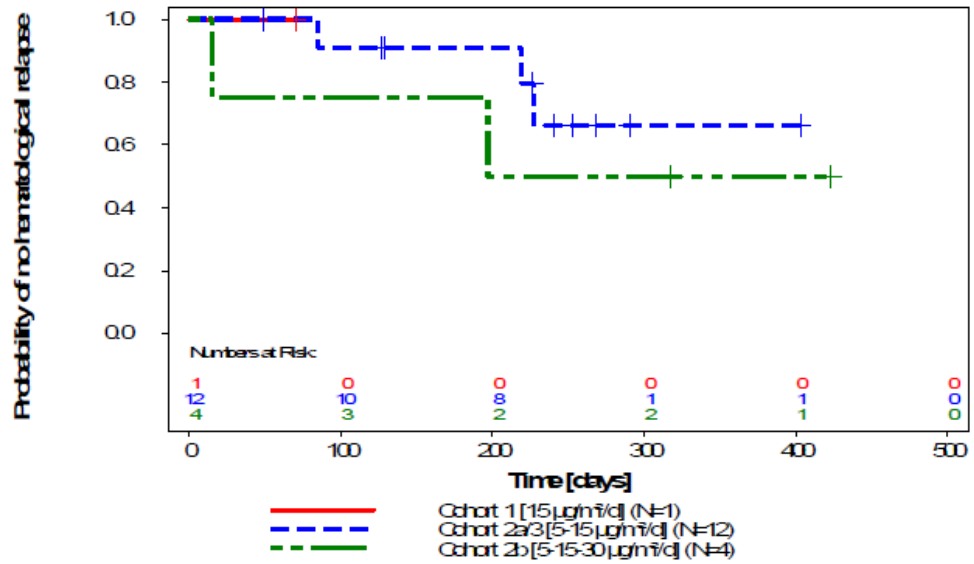
Figure 30: Time to haematological relapse of subjects with CR or CRh* during core study, (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)



Note: Results displayed for subjects by intended study cohorts only. Results for subjects overall not displayed. CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; SAF: Safety Analysis Set

In subjects who achieved CR during the core study, the median time to haematological relapse was not reached in subjects overall (N = 17) nor in Cohorts 1, 2a/3, or 2b. In subjects who achieved CR, 1 year probability rates were 63% (95% CI: 35.9 to 89.2) in subjects overall, not estimable in subjects in Cohort 1, 66% (95% CI: 34.4 to 98.2) in subjects in Cohort 2a/3, and 50% (95% CI: 1.0 to 99.0) in subjects in Cohort 2b (see Figure 31, below).

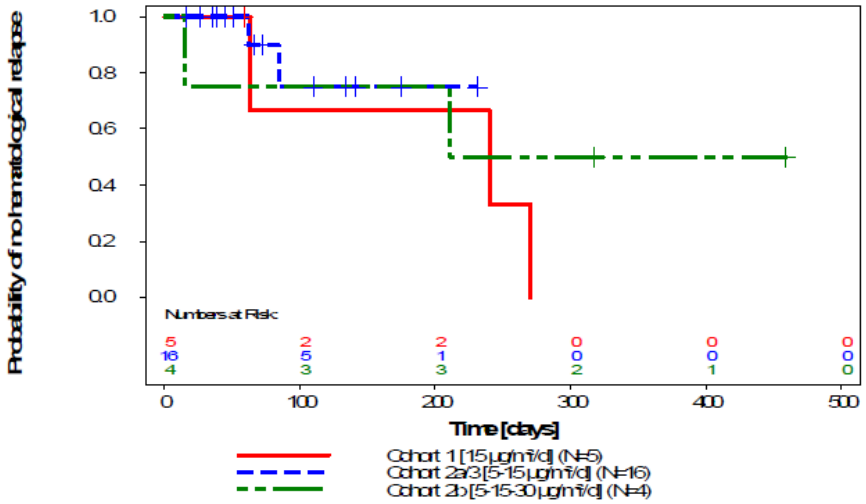
Figure 31: Time to haematological relapse of subjects who reached CR during core study, (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)



Note: Results displayed for subjects by intended study cohorts only. Results for subjects overall not displayed. CR: complete remission; FAS: Full Analysis Set; SAF: Safety Analysis Set.

In subjects with best response of CRh* during the core study, the median time to haematological relapse was 240 days (7.7 months) in subjects overall (N = 8) and in Cohort 1, and was not reached in Cohort 2a/3. No subjects in Cohort 2b had best response of CRh*. In subjects who achieved a CR/CRh* during the core study, the median time to haematological relapse, censoring subjects with allogeneic HSCT at the time of HSCT, was 240 days (7.7 months) in subjects overall (N = 25) and in Cohort 1, and was not reached in cohorts 2a/3 and 2b. One-year probability rates were 32% (95% CI: -2.5 to 66.2) in subjects overall who achieved a CR/CRh*, was 0% in Cohort 1, was not estimable in Cohort 2a/3, and was 50% in Cohort 2b (see Figure 32, below). Censoring subjects who underwent an HSCT resulted in shorter times to haematological relapse compared to the primary analysis results.

Figure 32: Time to haematological relapse of subjects with CR/CRh* during core study censoring subjects with allogeneic HSCT at time of HSCT (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)

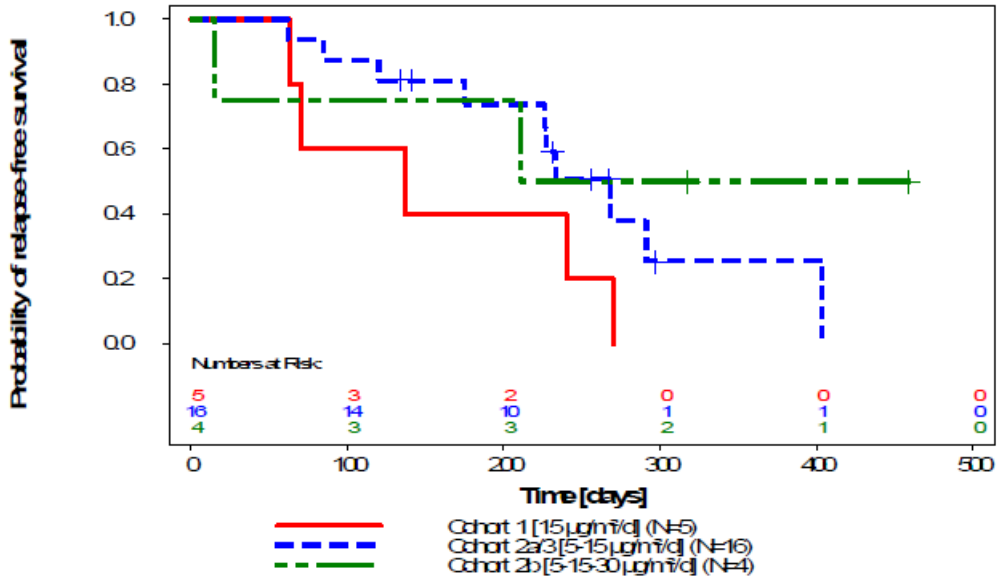


Only allogeneic HSCT as consolidation of CR induced by blinatumomab treatment are considered CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; HSCT: hematopoietic stem cell transplantation; SAF: Safety Analysis Set.

Relapse free survival was measured only for subjects who achieved a CR or CRh* during the core study and was measured from the time the subject first achieved remission until first documented relapse or death due to any cause. Subjects without a documented relapse (haematological or extramedullary) or who did not die were censored at the time of their last bone marrow assessment or their last survival follow-up visit confirming remission.

The median relapse free survival of subjects with CR or CRh* during core study in subjects overall was 233 days (7.6 months; 1 year probability rate = 25%), 137 days (4.6 months; 1-year probability rate = 0%) in Cohort 1, 268 days (8.8 months; 1 year probability rate = 25%) in Cohort 2a/3, and not estimable (1 year probability rate = 50%) in Cohort 2b (see Figure 33, below).

Figure 33: Relapse free survival of subjects with CR or CRh* during core study (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)

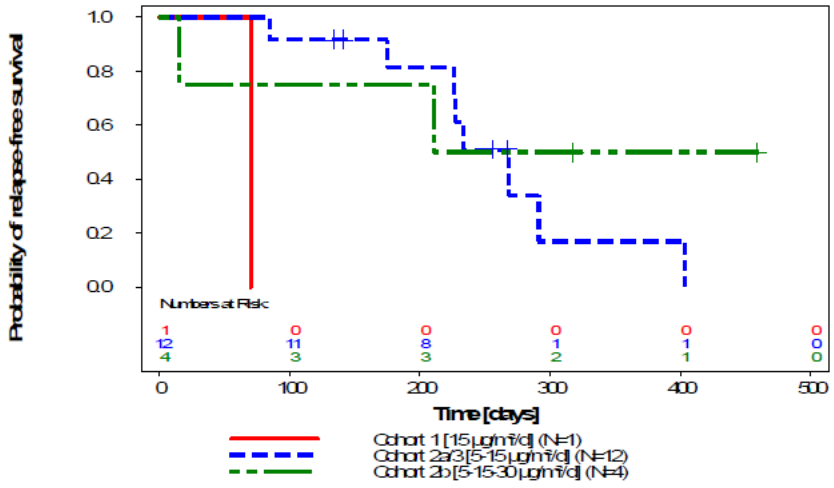


CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; SAF: Safety Analysis Set

The median relapse free survival of subjects with CR during core study was 233 days (7.6 months; 1 year probability rate = 29%) in subjects overall, 70 days (2.3 months; 1 year probability rate = 0%) in Cohort 1, 268 days (8.8 months) (1 year probability rate = 17%) in Cohort 2a/3, and not estimable (1 year probability rate = 50%) in Cohort 2b (see Figure 34, below).

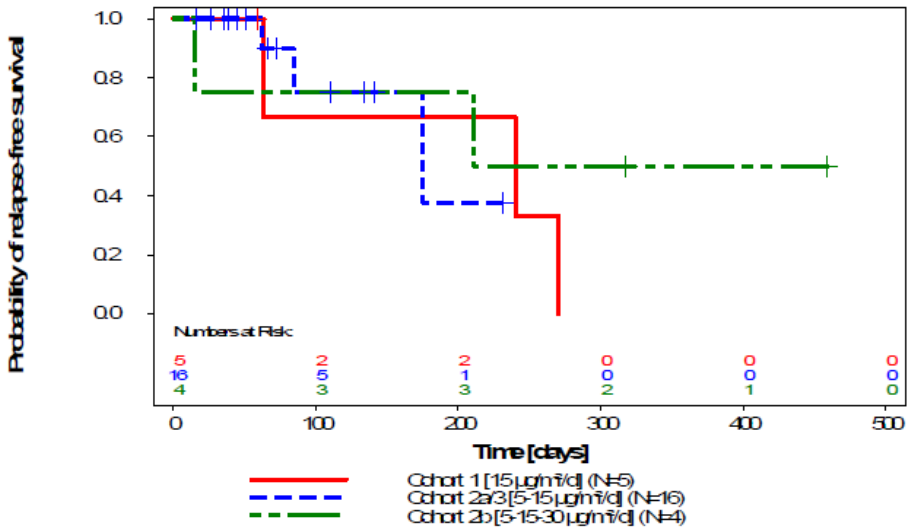
The median relapse free survival of subjects with CR/CRh* during core study censoring subjects with HSCT at time of HSCT was 240 days (7.7 months; 1 year probability rate = 27%) in subjects overall, 240 days (7.7 months; 1-year probability rate = 0%) in Cohort 1, 175 days (5.7 months) (1 year probability rate = not estimable) in Cohort 2a/3, and not estimable (1 year probability rate = 50%) in Cohort 2b (see Figure 35, below). Results of censoring subjects for HSCT were similar to the primary analysis results for relapse free survival.

Figure 34: Relapse free survival of subjects with CR during core study (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)



CR: complete remission; FAS: Full Analysis Set; SAF: Safety Analysis Set.

Figure 35: Relapse free survival of subjects with CR/CRh* during core study censoring subjects with allogeneic HSCT at time of HSCT (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)



Only allogeneic HSCT as consolidation of CR induced by blinatumomab treatment are considered CR: complete remission; CRh*: Complete response/remission with partial recovery of peripheral blood counts; FAS: Full Analysis Set; HSCT: hematopoietic stem cell transplantation; SAF: Safety Analysis Set.

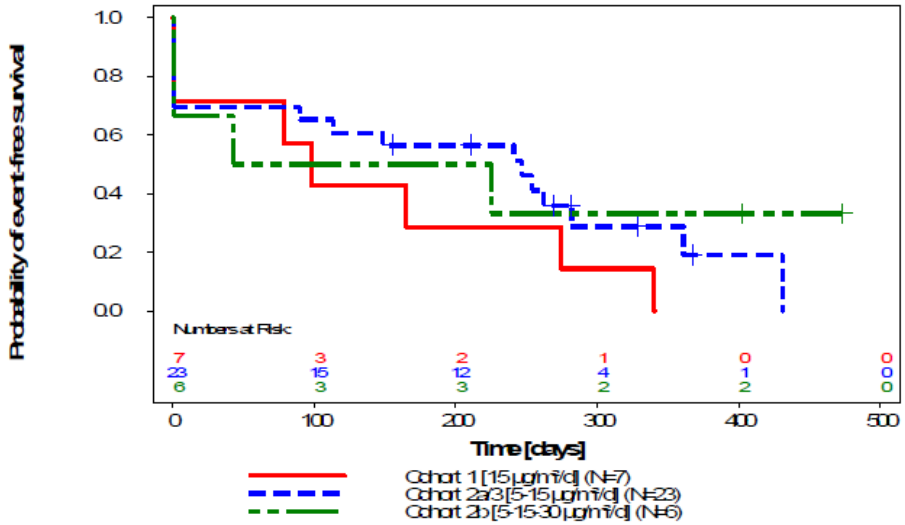
Event free survival

The analysis of event free survival was carried out for all patients who started therapy with blinatumomab in this study. Event free survival was calculated relative to the start date of blinatumomab infusion in the first treatment cycle. The date of bone marrow aspiration at which haematological relapse was first detected or the date of diagnosis on which the haematological or extra medullary relapse was documented or the date of start of any new therapy for ALL (excluding HSCT) or the date of death was used as the event date for relapse free survival, whichever is earlier. Patients who did not achieve CR or CRh* during the core study were evaluated as having an event on Day 1.

Patients with CR or CRh* who did not experience haematological relapse, did not receive a new therapy for ALL (excluding HSCT), and did not die were censored on the date of the last available bone marrow aspiration or on the last date of survival follow-up visit, whichever was later.

The median event free survival of subjects was 165 days (5.4 months; 1 year probability rate = 18%) in subjects overall, 98 days (3.3 months; 1 year probability rate = 0%) in cohort 1, 247 days (8.1 months; 1 year probability rate = 19%) in Cohort 2a/3, and 134 days (4.6 months; 1 year probability rate = 33%) in Cohort 2b (see Figure 36, below).

Figure 36: Event free survival of all subjects (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)

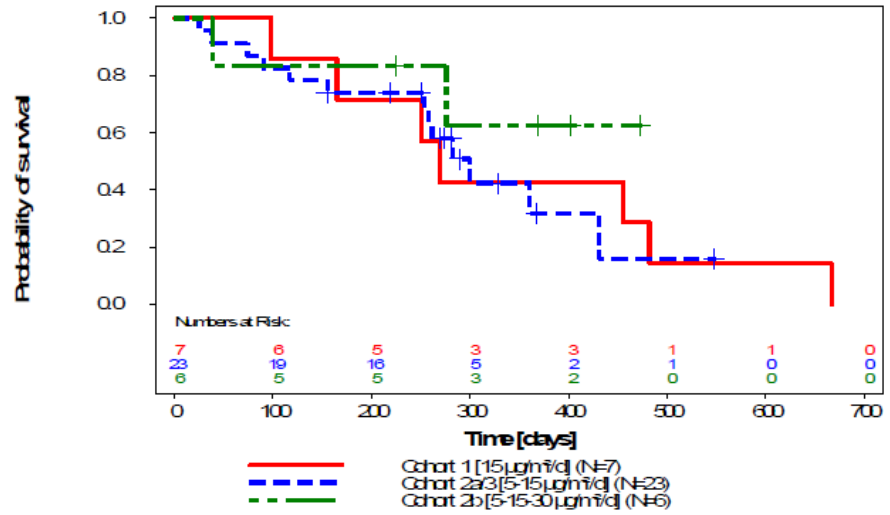


FAS: Full Analysis Set; SAF: Safety Analysis Set.

Overall survival

Overall survival was measured for all patients from the date of first infusion of blinatumomab until the date of death due to any cause. Patients who did not die were censored on the last documented visit date. The median OS of subjects was 300 days (9.8 months; 1 year probability rate = 42%) in subjects overall, 269 days (9.0 months; 1 year probability rate = 43%) in Cohort 1, 300 days (9.8 months; 1 year probability rate = 32%) in Cohort 2a/3, and not estimable (1 year probability rate = 63%) in Cohort 2b (see Figure 37, below).

Figure37: Overall Survival (SAF/FAS, by intended dose schedule; Kaplan-Meier curves, stratified)



FAS: Full Analysis Set; SAF: Safety Analysis Set

7.1.3.10. Conclusions

- Results from Study MT103-206 showed an improved safety profile at a starting dose of 5 µg/m^2/day with escalation to 15 µg/m^2/day after 1 week of treatment as compared with a constant dosing of 15 µg/m^2/day.

- A similar haematological CR + CRh* rate with the 3 dosing algorithms in adult patients with relapsed/refractory ALL.
- Blinatumomab showed single-agent activity in subjects with relapsed/refractory B-precursor ALL.

Comment: The study population in Study MT103-206 is not directly comparable with Study MT103-211. The 2 differences in the Study MT103-206 study population compared to the pivotal Study MT103-211 were the inclusion of 4 Ph+ B-precursor ALL patients and 6 patients who had had late-relapses, of which the second group generally have a more favourable outcome.

7.2. Other clinical studies in acute lymphoblastic leukaemia

The sponsor has provided additional data from 2 Phase II studies in adult subjects with minimal residual disease (MRD) positive B-precursor ALL (Study MT103-202; Study MT103-203, based on interim data) and data from the Phase I/II Study MT103-205 in paediatric subjects (based on interim data) with relapsed/refractory ALL.

7.2.1. Study MT103-202

This was an open label, multicentre Phase II 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 leukaemia (ALL).

7.2.1.1. Objectives:

Primary objective:

- To assess the efficacy of blinatumomab as defined by the effect on minimal residual disease (MRD)

Secondary objectives:

- To assess the effect of blinatumomab on duration of complete haematological remission
- To assess the impact of blinatumomab on the level of MRD
- To assess the effect of blinatumomab on duration of MRD negativity
- To evaluate the safety and tolerability of blinatumomab
- To evaluate the pharmacodynamics (PD) of blinatumomab
- To evaluate the pharmacokinetics (PK) of blinatumomab

Study period

January 2008 (first subject enrolled; first subject was treated May 2008) to January 2010 (data cut-off date for primary analysis; follow-up part of the study is ongoing).

7.2.1.2. Diagnosis and main criteria for eligibility

Adult patients with B-precursor ALL in complete hematologic complete remission (CR) were eligible if their ALL was either molecularly refractory (that is, had never achieved an MRD negativity status before blinatumomab) or was in a molecular relapse (that is, became MRD positive after having been MRD negative) with quantifiable MRD load of ≥ 1×10^{-4} starting at any time point after established standard induction/consolidation therapy of ALL.

7.2.1.3. Duration of treatment

Blinatumomab was administered as a continuous intravenous infusion at a dose of 15 µg/m^2/day over 4 weeks followed by a treatment free period of 2 weeks; nonresponders

could have had their dose increased to blinatumomab 30 µg/m^2/day if at least 1 subject did not respond within the first 4 cycles or at least 1 subject relapsed after MRD response within 2 years after completion of treatment. The duration of core study participation for each subject was up to 62 weeks: a 2 week screening period, followed by a maximum of 10 x 6 week cycles. In addition, after the end of the last treatment cycle, subjects were to be followed-up at regular intervals until haematological relapse but not longer than 5 years after the subject finished the last treatment cycle with blinatumomab in a post study segment. The core study ended at the date of the end of study visit (2 weeks after last infusion of the last treatment cycle) of the last subject undergoing the study.

7.2.1.4. Study endpoints

The primary endpoint was MRD response rate, which was defined by the incidence of MRD negativity within 4 cycles of treatment with blinatumomab. MRD negativity was defined as bcr/abl and/or t(4;11) translocation below detection limit and/or by individual rearrangements of immunoglobulin or TCR-genes below 10^{-4}.

Secondary endpoints were as follows:

- MRD response rate, defined by the incidence of MRD negativity after any treatment cycle
- Time to haematological relapse
- Time to change in MRD level (MRD progression)
- Time to molecular relapse (MRD relapse)
- Overall incidence and severity of adverse events
- Quantification and characterisation of peripheral blood lymphocytes
- Cytokine serum concentrations.

7.2.1.5. Summary of Results

Subject disposition

32 subjects enrolled; 21 subjects received ≥ 1 infusion of investigational product and were included in the Safety Analysis Set (SAF); 20 subjects also had MRD response assessment data available and were included in the Full Analysis Set (FAS); 50% (10/20) of FAS subjects completed the study.

Efficacy results

MRD response was achieved within the first 4 cycles in 80% (16/20) of subjects in the FAS, with all MRD responses having been observed within Cycle 1. By dose cohort, MRD response was achieved in 88% (15/17) of responders who received a constant dose of 15 µg/m^2/day and in 33% (1/3) of nonresponders after dose increase to 30 µg/m^2/day (Table 37). By baseline genetic alteration, MRD response was achieved in 92% (12/13) of subjects with only rearrangements (immunoglobulin or TCR-genes) and 57% (4/7) of subjects with translocations and rearrangements (that is, translocations with or without rearrangements: bcr/abl and/or t(4;11) genes). By refractory and relapsed MRD, MRD response was achieved in 80% (12/15) of subjects with molecular refractory disease and in 80% (4/5) of subjects with molecular relapse.

By MRD level at screening, MRD response was achieved in 90% (9/10) of subjects with MRD level ≥ 10^{-2}, 83% (5/6) of subjects with MRD level < 10^{-2} to ≥ 10^{-3}, and 50% (2/4) of subjects with MRD level < 10^{-3} to ≥ 10^{-4}. The median duration of MRD response for subjects overall was 107 days. Haematological relapse occurred in 4/20 subjects in the FAS. The median time to haematological relapse was not reached. None of the 4 subjects who had haematological relapse received HSCT and all were receiving a constant dose of 15 µg/m^2/day. MRD progression occurred in 6/20 subjects in the FAS. The median time to MRD progression was 221 days. MRD

relapse occurred in 4/20 subjects in the FAS. The median time to MRD relapse was not reached. MRD response within the first 4 cycles by dose cohort is shown in Table 34, below.

Table 34: MRD response within the first 4 cycles by dose cohort (Full analysis set)

MRD Response	Constant Dose (15 µg/m²/d) (N = 17)					Dose Increase (15/30 µg/m²/d) (N = 3)					Total (N = 20)				
	N =	%	LL[a] (%)	UL[a] (%)	P =	N=	%	LL[a] (%)	UL[a] (%)	P =	N =	%	LL[a] (%)	UL[a] (%)	P =
MRD response within the first 4 cycles	15	88.2	63.6	98.5	0.00	1	33.3	0.8	90.6	0.1426	16	80.0	56.3	94.3	0.00
MRD negativity achieved after Cycle 1	15	88.2	63.6	98.5		1	33.3	0.8	90.6		16	80.0	56.3	94.3	
MRD negativity achieved after Cycle 2	15	88.2				1	33.3				16	80.0			
MRD negativity achieved after Cycle 3	15	88.2				1	33.3				16	80.0			
MRD negativity achieved after Cycle 4	15	88.2				1	33.3				16	80.0			

Note: p-values of 0.000 are p < 0.0001; LL: lower limit; MRD: minimal residual disease; UL: upper limit; a) LL/UL: Lower limit/upper limit of the exact 2-sided 95% Clopper-Pearson confidence interval; P-value from 1-sided exact binomial test for H0: Π ≤ 5%

7.2.2. Study MT103-203

This was a confirmatory multicentre, single arm study to assess the efficacy, safety, and tolerability of the BiTE antibody blinatumomab in adult subjects with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukaemia

7.2.2.1. Objectives

Primary objective

To evaluate the efficacy of blinatumomab to induce complete MRD response.

Key secondary objective

For subjects with Philadelphia (Ph) negative acute lymphoblastic leukaemia (ALL), to evaluate the effect of blinatumomab on haematological relapse.

Other secondary objectives

Other secondary objectives included:

- to evaluate the overall survival in subjects with ALL treated with blinatumomab
- to evaluate the 100 day mortality rate associated with allogeneic haematopoietic stem cell transplant (HSCT)
- to evaluate the safety and tolerability of blinatumomab
- to evaluate the effect of blinatumomab on the duration of MRD negativity
- to evaluate the effect of blinatumomab on the kinetics of MRD
- to evaluate subject's quality of life during and after therapy
- to evaluate resource utilisation.

Exploratory

- To assess the potential biological predictors of response to blinatumomab

Study period

From November 2010 (first subject enrolled) to February 2014 (data cut off date). The clinical study report (CSR) represented the primary analysis for this study. The primary analysis was performed with all data available at the time when all subjects had the opportunity to be evaluated for the primary efficacy endpoint (that is, complete MRD response after the first treatment cycle). The key secondary endpoint will be reported after all subjects have been transplanted, relapsed, died, or had 18 months of follow-up. The final analysis will be carried out 5 years after the last subject is enrolled into the study.

7.2.2.2. Diagnosis and main criteria for eligibility

Adult subjects were eligible for this study if they had a diagnosis of MRD positive B-precursor ALL and were in complete hematologic remission (defined as < 5% blasts in bone marrow after at least 3 intense chemotherapy blocks). Subjects must also have had MRD ≥ 10^{-3} (molecular failure or molecular relapse) in an assay with minimum sensitivity of 10^{-4} with at least 1 molecular marker based on individual rearrangement of immunoglobulin (Ig) or TCR-genes or a flow cytometric marker profile documented after an interval of at least 2 weeks from last systemic chemotherapy, and bone marrow function defined as absolute neutrophil count ≥ 1,000/µL, platelets ≥ 50,000/µL, and haemoglobin level ≥ 9 g/dL (transfusions permitted).

7.2.2.3. Duration of treatment

Blinatumomab was administered as a cIV infusion of 15 µg/m^2/day, at a constant flow rate, for 28 days followed by a 14 day infusion free interval (defined as 1 treatment cycle). Subjects received at least 1 and up to 4 cycles of treatment, unless criteria for treatment discontinuation were met. The duration of 1 cycle was 6 weeks. A safety follow-up occurred 30 days after the last infusion. The efficacy follow up occurred up to 24 months after the start of treatment.

7.2.2.4. Study endpoints

Primary endpoint

Proportion of subjects who achieve complete MRD response defined by absence of MRD after 1 cycle of treatment with blinatumomab.

Key secondary endpoint for subjects with Ph negative ALL

- Haematological relapse free survival rate at 18 months following initiation of blinatumomab (not included in report).

Secondary endpoints

- overall survival (not included in this report)
- mortality rate within 100 days after allogeneic HSCT (not included in this report)
- time to haematological relapse (not included in this report)
- duration of complete MRD response (not included in this report)
- effect on MRD level (not included in this report)
- overall incidence and severity of adverse events
- subject's quality of life during and after therapy (not included in this report)
- resource utilisation (not included in this report).

7.2.2.5. Summary of results

Subject disposition

116 subjects received at least 1 infusion of blinatumomab and were included in the FAS. At the time of the data cut-off date of 21 February 2014 the study was ongoing; 106 subjects ended the core study and 10 subjects continued in the core study.

Efficacy results

For the primary endpoint, complete MRD response was achieved within the first cycle in 77.9% (88/113; 95% CI: 69.1% to 85.1%) of subjects. The complete MRD response rate was demonstrated to be statistically significantly greater than 44%. These results were consistent among the analyses sets.

7.2.3. Study MT103-205

This was a single arm, multicentre, Phase II study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of the BiTE antibody blinatumomab (MT103) in paediatric and adolescent patients with relapsed/refractory B-precursor acute lymphoblastic leukaemia (ALL).

7.2.3.1. Objectives

Phase I (primary)

- To determine the recommended Phase II dose of blinatumomab.

Phase I (secondary)

- To assess the safety, PK, anti-leukemic activity, development of anti-drug antibodies (ADAs), and changes in pharmacodynamic (PD) markers after treatment with various doses of blinatumomab.

Phase II (ongoing; recruitment complete; primary)

- To assess the efficacy of the recommended Phase II dose of blinatumomab in paediatric and adolescent patients with B-precursor ALL who met eligibility criteria.

Phase II (secondary)

- To assess the safety of blinatumomab and the development of ADAs to blinatumomab.

This was a first paediatric study, not a first in human study. This is an open label, combined 2 part multicentre clinical study. Phase I was a dose finding study (rolling 6 design) to investigate the PK, safety, and clinical activity of escalating levels (3.7 to 60 μg/m^2/day) of blinatumomab in paediatric and adolescent patients with relapsed or refractory B-precursor ALL.

Once a recommended dose was selected in the Phase I part of the study, the Phase II part (2 stage, single arm design) was begun to assess the safety and efficacy of the recommended dose level of blinatumomab. The study consisted of a screening period, a treatment period, and an 'End of core study' visit, 30 days after last dose of study medication. After the last treatment cycle all subjects were followed for efficacy and survival up to 24 months after treatment start.

7.2.3.2. Study period

This study is ongoing. The first subject was enrolled in January 2012. Data for the subjects from Phase I dose evaluation Phase (N = 41) who received at least 1 dose of blinatumomab are reported in this CSR (data cut-off date of 10 October 2013). Serious and fatal adverse events from 11 October 2013 to 30 March 2014 are reported for all subjects who received blinatumomab.

7.2.3.3. Diagnosis and main criteria for eligibility

- Children or adolescents < 18 years of age; only children age 2 to 17 enrolled before the identification of the recommended Phase II dose
- Morphologic and immunophenotypic evidence of B-precursor ALL with > 25% blasts in bone marrow (M3) at study enrolment
- Relapsed or refractory disease
- Karnofsky performance status ≥ 50% (subjects ≥ 16 years) or Lansky Performance Status of ≥ 50% (subjects < 16 years)
- Excluded subjects with active acute or extensive chronic graft-versus-host disease (GvHD) including taking immunosuppressive agents to prevent or treat GvHD within 2 weeks before blinatumomab treatment; known or suspected central nervous (CNS) involvement; history of or current relevant CNS pathology; any hematopoietic stem cell transplant (HSCT) within 3 months before blinatumomab treatment; immediately previous cancer chemotherapy, radiotherapy, or immunotherapy.

7.2.3.4. Duration of treatment

Blinatumomab was administered as a continuous intravenous (cIV) infusion at a constant daily flow rate over 4 weeks followed by a treatment free interval of 2 weeks. Doses ranged between 3.75 and 30 µg/m^2/day. Each subject was to participate for up to 34 weeks in the core study including a screening period of up to 2 weeks, a treatment period of up to 30 weeks consisting of up to 5 consecutive cycles of 6 weeks each (4 weeks of blinatumomab cIV infusion followed by a treatment free interval of 2 weeks), and an End of Core Study visit 30 days after last dose of study medication.

7.2.3.5. Study endpoints

Phase I

The primary endpoint was the maximum tolerated dose (MTD) defined by ≤ 1 of 6 subjects experiencing a dose limiting toxicity (DLT) or maximum administered dose (MAD).

Secondary endpoints were the overall incidence and severity of adverse events, quantification and characterisation of PK parameters over time, rate of complete remission (CR, which included complete haematological recovery (CRc) and incomplete hematologic recovery (CR*)), duration of CR with CRc or CR*, relapse free survival (RFS), overall survival (OS), time to haematological relapse (TTR), proportion of subjects who develop ADAs at any time, and quantification and characterisation of cytokine serum concentrations.

Phase II (ongoing)

The primary endpoint is the rate of CR. Secondary endpoints are the overall incidence and severity of adverse events, proportion of subjects who undergo HSCT after treatment with

blinatumomab, rate of CR, TTR, CRc or CR* duration, OS, RFS, and the proportion of subjects who develop ADAs at any time.

7.2.3.6. Summary of Results

Subject disposition

41 subjects were enrolled and received at least 1 infusion of blinatumomab and were included in the Phase I full analysis set. At the time of the data cut-off date, 2 subjects (5%) had completed 5 cycles of treatment; treatment was ongoing for 14 subjects (34%); 27 subjects (66%) had ended the study.

Efficacy results

Efficacy variables were secondary endpoints in Phase I. The endpoint of CR rate included CRc and CR*. An overview of best response rates during the first 2 cycles of treatment in Phase I is presented in Table 35, shown below. 13 subjects (32%) had CRc/CR* during the first 2 cycles of Phase I; 6 subjects (15%) had a partial remission. Most CRs were observed in Cycle 1. The median relapse free survival was 8.3 months (95% CI: 3.0 to 16.0 months). The median observation time was 8.6 months. The median overall survival was 5.7 months (95% CI: 3.3 to 9.7 months). The median observation time was 12.4 months. A total of 18 subjects (44%) received allogeneic HSCT during the study. Among the 13 subjects who achieved a CRc/CR*, 9 received an allogeneic HSCT while in remission induced by blinatumomab. One subject received allogeneic HSCT while not in remission within the first 2 cycles; 8 subjects received allogeneic HSCT without having reached CRc/CR* in the first 2 cycles of treatment. Of the subjects with CRc/CR* with a minimal residual disease (MRD) assessment during the first 2 cycles (N = 12), the MRD response rate was 83% (10/12) and the complete MRD response rate was the same.

Table 35: Best response during the first 2 cycles, primary efficacy endpoint (Phase I Full Analysis Set)

Response	Treatment Cohort														
	5 µg/m²/day (N = 5)			15 µg/m²/day (N = 7)			30 µg/m²/day (N = 5)			15 to 30 µg/m²/day (N = 6)			5 to 15 µg/m²/day (N = 18)		
	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]	n	(%)	95% CI[a]
Best response during the first 2 cycles															
CRc/CR*	1	(20.0)	(0.5 to 71.6)	3	(42.9)	(9.9 to 81.6)	1	(20.0)	(0.5 to 71.6)	2	(33.3)	(4.3 to 77.7)	6	(33.3)	(13.3 to 59.0)
Complete remission with complete haematological recovery (CRc)	1	(20.0)	(0.5 to 71.6)	3	(42.9)	(9.9 to 81.6)	1	(20.0)	(0.5 to 71.6)	1	(16.7)	(0.4 to 64.1)	4	(22.2)	(6.4 to 47.6)
Complete remission with incomplete haematological recovery (CR*)	0	(0.0)	(0.0 to 52.2)	0	(0.0)	(0.0 to 41.0)	0	(0.0)	(0.0 to 52.2)	1	(16.7)	(0.4 to 64.1)	2	(11.1)	(1.4 to 34.7)
Blast free hypoplastic or aplastic bone marrow	0	(0.0)	(0.0 to 52.2)	0	(0.0)	(0.0 to 41.0)	0	(0.0)	(0.0 to 52.2)	1	(16.7)	(0.4 to 64.1)	2	(11.1)	(1.4 to 34.7)
Partial remission	2	(40.0)	(5.3 to 85.3)	1	(14.3)	(0.4 to 57.9)	1	(20.0)	(0.5 to 71.6)	0	(0.0)	(0.0 to 45.9)	2	(11.1)	(1.4 to 34.7)

Response	Treatment Cohort														
	5 µg/m²/day (N = 5)			15 µg/m²/day (N = 7)			30 µg/m²/day (N = 5)			15 to 30 µg/m²/day (N = 6)			5 to 15 µg/m²/day (N = 18)		
Nonresponder during the first 2 cycles															
Progressive disease	0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)		0	(0.0)	
Non-response	2	(40.0)		3	(42.9)		1	(20.0)		1	(16.7)		7	(38.9)	
No response data	0	(0.0)		0	(0.0)		2	(40.0)		2	(33.3)		1	(5.6)	

CI = confidence interval. a) 95% CI: lower and upper limit of 2 sided exact 95% confidence interval for percentage of patients within each response category.

7.3. Historical Comparator Studies in Relapsed/Refractory ALL

7.3.1. Historical comparator Study 20120310

This was an analysis of historical data on haematological remission and survival among adult patients with relapsed or refractory (R/R) B-precursor acute lymphoblastic leukaemia (ALL)

7.3.1.1. Study design

A retrospective pooled analysis of historical data available from 1990 to 2014 that was assembled by combining existing clinical databases from the EU study groups and US study groups.

The study cohort included data from 1139 patients (data was available for CRsg in 694 patients, OS in 1112 patients, RFS in 108 patients, and HSCT in 808 patients) whose initial ALL diagnosis was after 01 January 1990. 2 thirds of the database patients were diagnosed after 2000.

Patients included in the study's weighted analysis had:

- first relapse or salvage treatment after a first remission duration of ≤ 12 months, or
- refractory to initial treatment, or
- relapsed/refractory after first or later salvage; for example, second or later relapse)
- relapsed/refractory within 12 months of allogeneic HSCT.

The primary objective of this study was to estimate the proportion of patients with Philadelphia chromosome negative relapsed/refractory B-precursor ALL who achieved haematological CRsg following salvage treatment, excluding patients with a first remission duration of > 12 months in first salvage (that is, late first relapse). CRsg, as defined in each of the different study groups' data, included patients who experienced complete bone marrow recovery (< 5% blasts) with full peripheral blood count recovery (that is, neutrophils/ANC > 1,000/µL, and platelets > 100,000/µL.

Key secondary objectives included estimating OS, RFS, and the proportion of patients receiving allogeneic HSCT. The impact of various prognostic factors on CRsg and OS were also assessed.

This study was conducted in order to provide a historical comparator to provide a better context for evaluating the treatment effect of blinatumomab in the single arm clinical studies of blinatumomab in adult relapsed/refractory ALL patients.

7.3.1.2. Results

Disposition and demographics

A total of 1139 subjects were included in the primary analysis. Of those, 807 were from study groups or sites that had data available on CRsg; 694 patients had data on CRsg and the age/treatment history variables for inclusion in the weighted analyses. Almost 70% of subjects with CRsg data available for the primary analysis came from one site in the US and the German study group. Among the 1139 subjects, 58% were men, and the median age (range) was 35 years (18 to 83 years).

Overall, more than half of the subjects were in first relapse, 12% were refractory to primary treatment, and 17% had an allogeneic HSCT prior to first relapse or first salvage. Approximately one-third of the subject population was diagnosed with ALL between 1990 and 1999, with the remaining 2 thirds diagnosed in 2000 or later.

Efficacy

The overall CRsg rate, weighted to the Study MT103-211 population, was 24% (95% CI: 20, 27) (see Table 36, below). Additionally, in the US, the overall weighted CRsg rate was 22% (95% CI: 14, 29). In the EU, the overall weighted CRsg rate was 27% (95% CI: 22, 33). The unweighted CRsg rate for the 116 subjects receiving single-agent therapy was 7% (95% CI: 3, 13).

Table 36: Strata-specific and combined weighted estimate of complete remission in Study 20120310 (Philadelphia negative primary analysis set; All regions)

Stratum	Age at treatment	Prior lines of treatment	n/N	Stratum %	N_{na}	CRsg Proportion (95% CI)[a]	Stratum % Observed in Study MT103-211
1	< 35	alloHSCT	14/48	6.9%	16	0.29 (0.17, 0.44)	21.2%
2	< 35	In first salvage	52/119	17.1%	21	0.44 (0.35, 0.53)	5.3%
3	< 35	In second + salvage	27/150	21.6%	5	0.18 (0.12, 0.25)	21.2%
4	≥ 35	alloHSCT	11/41	5.9%	6	0.27 (0.14, 0.43)	12.7%
5	≥ 35	In first salvage	57/187	26.9%	37	0.30 (0.24, 0.38)	10.1%
6	≥ 35	In second + salvage	25/149	21.5%	4	0.17 (0.11, 0.24)	29.6%
Combined/ weighted summary						0.24 (0.20, 0.27)	

Philadelphia-negative primary analysis set: Patients with R/R ALL who relapse within 12 months of initial diagnosis, are refractory to previous treatments, relapsed/refractory within 12 months of alloHSCT, or in

second or greater salvage treatment alloHSCT = allogeneic haematopoietic stem cell transplant; CRsg = complete remission by study group; CI = confidence interval; Nna = patients with missing endpoint data. a) For CRsg corresponding to Stratum 1-6, these proportions are calculated directly from historical data and do not reflect any type of weighting. Combined/Weighted summary is the weighted average of Stratum 1-6 weighted by the proportions in the MT 103-211 study (listed in the last column)

OS estimates (median, 6-month, and 12-month) were calculated from a larger sample (nearly 50% larger) of subjects because sites that did not contribute CRsg information could be included. The weighted median OS in 1112 patients with available data was 3.3 months (95% CI: 2.8, 3.6), where survival time was calculated from the start of the last salvage treatment or the last relapse (if salvage date was unavailable). The weighted 6 month OS rate was 30% (95% CI: 27, 34), and the 12-month OS rate was 15% (95% CI: 13, 18).

Among subjects with CRsg, the weighted median RFS was 5.0 months (95% CI: 1.2, 6.6). However, the interpretability of the RFS data is limited because of missing information and likely underreporting of relapse events. Many countries did not have data on RFS, with only 108 (58%) patients with a CRsg reporting on RFS. In addition, routine medical surveillance for relapses was typically not conducted as systematically as in a clinical trial study. Therefore, underreporting of relapse events that occurred before subjects died may have occurred for many subjects, which could result in an RFS overestimation in the historical dataset. As such, these results should be interpreted cautiously.

Among the 808 subjects with available data on HSCT after salvage therapy, 18% (95% CI: 15, 21) received allogeneic HSCT following the last line of salvage therapy. Among subjects who achieved a CRsg as a result of salvage therapy, 7% (95% CI: 5, 9) received allogeneic HSCT.

7.3.1.3. Conclusions

Key outcomes were CRsg and OS among patients who relapsed within 12 months of initial treatment, were refractory to prior treatment(s), relapsed within 12 months of allogeneic HSCT, or were in second or later relapse (the same population as in MT103-211). Among these subjects, the weighted results (adjusted by age, line of salvage, and prior HSCT in Study MT103-211) reflected a generally poor prognosis in this patient population, with a CRsg rate of 24% (95% CI: 20, 27), a median OS of 3.3 months (95% CI: 2.8, 3.6), and 6 and 12 month survival probabilities of 30% (95% CI: 27, 34) and 15% (95% CI: 13,18), respectively.

Comment: One third of subjects included in the analysis received treatment between 1990 and 2000. With the exception of hyperCVAD, the majority of currently used salvage therapies were not available during this time period: FLAG-Ida was in use after 2000, R hyperCVAD after 2006, BFM 2000 and GMALL 2003. A comparison of CR and OS survival should be made using current standard therapies for R/R ALL.

7.4. Model based meta-analysis

7.4.1. MBMA Studies 118427 and 119834

An MBMA (Mandema et al, 2011) was conducted to evaluate the proportion of CR, DCR, and OS in adult patients with relapsed/refractory ALL receiving existing salvage therapies using data from the literature (Study 118427). The treatment benefit with blinatumomab relative to existing salvage therapies was estimated in Study 119834.

The MBMA dataset for Study 118427 was constructed based on a systematic review of all published English language studies reporting on clinical outcomes in adult patients with relapsed/refractory ALL. Studies were included if they met pre-specified criteria (a peer-reviewed publication of at least 30 adults with B-precursor refractory or relapsed ALL published between January 1995 and December 2012). The final dataset included 24 studies and a total of 4,058 patients.

Established models were used to project the proportion of CR, DCR, and OS with existing salvage therapies for a population similar to that in blinatumomab Study MT103-211. These projections accounted for uncertainty in parameter estimation (due to the sample size of the studies included in the meta-analysis) and heterogeneity across studies.

Study 1193834 estimated the magnitude of the treatment effect with blinatumomab relative to existing salvage therapies on proportion of CR, DCR, and OS for a population similar to the population enrolled in Study MT103-211. The summary prognostic factors for Study MT103-211 were used in the meta-analysis models to compute the proportion of CR, median DCR, and median OS as a projection of the efficacy of existing salvage therapies. Using the resampled efficacy endpoints from Study MT103-211 and the projected efficacy endpoints of existing salvage therapies, the odds ratio of CR as well as the hazard ratio for the DCR and OS of blinatumomab vs existing salvage therapies were calculated, and the associated 95% CI were reported.

For adult relapsed/refractory ALL patients treated with existing salvage therapies and having the same summary prognostic factors as those identified in Study MT103-211, the projected (95% CI) proportion of CR was 0.121 (0.041 to 0.341), median DCR was 4.9 months (2.5 to 9.2), and median OS was 3.9 months (3.0 to 4.7).

For adult relapsed/refractory ALL patients having the same summary prognostic factors as those identified in Study MT103-211, treatment with blinatumomab compared with existing salvage therapies is expected to have an odds ratio for proportion of CR of 3.50 (95% CI: 1.63 to 8.40), hazard ratio for DCR of 0.53 (95% CI: 0.30 to 0.89), and hazard ratio for OS of 0.60 (95% CI: 0.47 to 0.76).

Comment: See comment in the preceding section. A comparison of CR, DCR and OS survival should be made with current standard therapies for R/R ALL, that is, studies after 2000.

7.5. Evaluator's conclusions on clinical efficacy

The sponsors have provided one pivotal Phase II study (Study MT103-211), supported by a second Phase II study (Study MT103-206), one historical comparator study and two model based meta-analysis studies as evidence for the efficacy of blinatumomab for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL. The Phase II study design of both Study MT103-211 and Study MT103-206 presents moderate quality evidence of efficacy, which would have been better provided by a Phase III study design, however protection from bias in selecting patients has to some extent been provided by the inclusion of multiple study sites. In addition, the sponsors have provided a high quantity of evidence with the inclusion of 225 subjects in the 2 clinical studies, 1,139 subjects in the historical comparison study and 4,058 subjects from 24 studies in the MBMA.

The external validity of the studies is high and the results are generalisable to relapsed/refractory ALL patients that would be encountered in typical clinical haematology settings. It is noted that Study MT103-206 included 6 late relapse subjects who all responded to therapy. In comparison to early relapse patients, late relapse ALL patients have a better prognosis and a fraction can be rescued with chemotherapy, whereas early relapse patients can only be rescued with allogeneic haematopoietic stem cell transplantation. It is noted that in the historical comparator and MBMA studies late relapsers have been excluded, however subjects have been appropriately matched to Study MT103-211, which also excludes late relapsers. It is also noted that the historical comparator and MBMA included analyses of subjects treated before the development of current standard of care salvage therapies.

Valid sample size calculations have been performed for Studies MT103-211 and MT103-206 and the ability of both studies to determine that increased CR/CRh* with durable remission rate was caused by blinatumomab treatment is high.

The consistency of results from both Phase II studies was high. In Study MT103-211, CR/CR* with durable remission after 2 cycles of treatment was 42.9% and median OS was 6.1 months, and in Study MT103-206, CR/CRh* with durable remission after 2 cycles of treatment was 69% and median OS was 9.8 months.

The quality of the directness of evidence is moderate. The main objective of both Phase II studies was to demonstrate activity against ALL and consequently the end point, which is common to Phase II studies, was response rates. However, the sponsor argues that while OS is the universally accepted direct measure of clinical benefit in randomised relapsed/refractory ALL studies, CR and CRh* with durable remission, MRD response, and bridge to allogeneic HSCT can predict clinical benefit and are medically relevant. At present, allogeneic HSCT is the only curative option for early relapse/refractory ALL, and patients must be in a haematological CR/CRh* to proceed to transplant. Furthermore, it is becoming increasingly recognised that MRD < 10^{-4} is predictive of relapse following allogeneic HSCT. Consequently, CR and CRh* with durable remission, MRD response and duration of response or time to haematological relapse, to allow time to proceed to allogeneic HSCT are valid surrogate endpoints.

The magnitude of effect is significant when compared to results from the MBMA, with OR 3.5 for proportion of CR and the median OS 3.9 months for the MBMA compared to 6.1 months for Study MT103-211. In addition, there was evidence from the PK/PD analyses that a dose response gradient existed, with B-cell depletion rate increasing with increasing C_{ss}, which suggested that higher drug levels were associated with faster elimination of peripheral B cells.

While it would have been ideal to have considered the final results of a Phase III study, there is sufficient strength to the efficacy data presented in this submission to approve the requested indication of blinatumomab for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL.

8. Clinical safety

8.1. Studies providing evaluable safety data

The primary analysis of safety is based on pooled analyses of the adult relapsed/refractory ALL population, which consisted of 225 subjects in Studies MT103-211 (N = 189) and MT103-206 (N = 36). This analysis is supported by pooled analyses of the program wide pooled population (also referred to more generally as the pooled population), which consisted of 475 subjects treated at various dose levels of blinatumomab in 7 ongoing and completed studies: 225 subjects in the Studies MT103-211 and MT103-206, 41 paediatric subjects with relapsed/refractory ALL in Study MT103-205, 114 subjects with MRD positive ALL in Studies MT103-202 (N = 21) and MT103-203 (N = 93), and 95 subjects with relapsed/refractory NHL in Studies MT103-104 (N = 76) and MT103-208 (N = 19). In addition, serious adverse event data were evaluated for recently initiated Studies 20120216 and 00103311. Given that ALL is an orphan disease, the size of the safety database is considered adequate to define the safety profile of blinatumomab at the intended registration dose.

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by collection of adverse events throughout the studies.

- AEs of interest for the blinatumomab program were neurologic events, cytokine release syndrome, tumour lysis syndrome, infusion reactions, elevated liver enzymes, infections, capillary leak syndrome, leukoencephalopathy, decreased immunoglobulins, venous thrombosis and thromboembolic events (including disseminated intravascular coagulation (DIC)), cytopaenias (including neutropaenia/febrile neutropaenia), and medication errors.
- Additionally, minimum critical toxicities (hepatotoxicity, nephrotoxicity, bone marrow toxicity, QT prolongation and other electrocardiogram (ECG) abnormalities, and immunogenicity) were performed at baseline and at prespecified times during the study.

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable

8.1.4. Other studies evaluable for safety only

Not applicable

8.1.5. Clinical pharmacology studies

Not applicable

8.1.6. Pivotal studies that assessed safety as a primary outcome

Not applicable

8.2. Patient exposure

The proposed registration blinatumomab dosing regimen for adult subjects with relapsed/refractory ALL is 9 µg/day for the first 7 days of treatment followed by 28 µg/day starting from Week 2 for the remaining treatment cycles. A cycle consists of blinatumomab continuous IV infusion at a constant flow rate over 4 weeks followed by a treatment free interval of 2 weeks. In the adult relapsed/refractory studies, subjects were to be hospitalised at least during the first 9 days (1 week plus 2 days following dose step) of the first cycle and the first 2 days of the following cycle. The hospitalisation time depended on the investigator's judgment as well as the safety and tolerability of blinatumomab. For Cycle 3 and beyond, subjects were to be hospitalised for 8 hours of outpatient observation followed by daily outpatient follow-ups during the subsequent 2 days. If dose interruptions lasted longer than 4 hours, re-start of the infusion was to be performed in the hospital under supervision of the investigator.

Study MT103-211 was the first study that used a fixed blinatumomab dose, based on pharmacokinetic analyses that concluded BSA has no effect on blinatumomab clearance. In the other studies included in the pooled safety analyses, including Study MT103-206, dosing was based on the subject's BSA. The fixed starting dose of 9 µg/day, is equivalent to 5 µg/m^2/day for an average person with a BSA of 1.8 m^2, and the target dose of 28 µg/day is equivalent to 15 µg/m^2/day for an average person with a BSA of approximately 1.8 to 1.9 m^2.

In the adult relapsed/refractory population, 225 subjects (189 in Study MT103-211 and 36 in Study MT103-206) were exposed to blinatumomab. The median exposure duration (range) was 42.2 days (1.2 to 150.1 days) in Study MT103-211, and 55.6 days (24.2 to 77.3 days) across dose groups in Study MT103-206. The longest median duration of exposure was 75.2 days (6 subjects) in the 5/15/30 µg/m^2/day dose group in Study MT103-206.

Of the 225 subjects in the adult relapsed/refractory ALL population, 70.4% (133/189) of subjects in Study MT103-211 and 69.4% (25/36) of subjects in Study MT103-206 started and

completed at least 1 cycle of treatment. In Study MT103-211, the mean number of started treatment cycles was 2.0 (SD 1.2) and the mean number of completed treatment cycles was 1.4 (SD 1.4). In Study MT103-206 the mean number of started treatment cycles was 2.5 (SD 1.7), and the mean number of completed cycles was 1.6 (SD 1.5).

In the program-wide pooled population, 475 subjects were treated with blinatumomab at doses ranging from 0.5 to 90 µg/m^2/day, including 436 subjects treated with the proposed registration target dose of 28 µg/day or the approximately equivalent target dose of 15 µg/m^2/day.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

Table 37 (shown) below provides an overview of the incidence of adverse events for the adult relapsed/refractory ALL population. Almost all subjects experienced at least 1 adverse event; the majority of subjects experienced Grade ≥ 3 adverse events, 64.9% of subjects experienced serious adverse events, and 19.6% of subjects permanently discontinued study treatment due to adverse events. Fatal adverse events (that were treatment emergent and occurred up to 30 days after the last dose) were reported for 34 subjects; all but 1 fatal adverse event occurred in the setting of active disease. One subject who was in remission induced by blinatumomab died due to infection/septic shock following allogeneic HSCT. The most common fatal adverse events included sepsis, disease progression, and pneumonia. None of the deaths were due to adverse events that would be unanticipated in patients with haematologic malignancies.

Overall, the overview of adverse event data was consistent across indications in the program-wide pooled population.

8.3.1.2. Other studies

Pooled analyses of the program-wide pooled population consisted of 475 subjects treated at various dose levels of blinatumomab in 7 ongoing and completed studies: 225 subjects in the Studies MT103-211 and MT103-206, 41 paediatric subjects with relapsed/refractory ALL in Study MT103-205, 114 subjects with MRD positive ALL in Studies MT103-202 (N = 21) and MT103-203 (N = 93), and 95 subjects with relapsed/refractory NHL in Studies MT103-104 (N = 76) and MT103-208 (N = 19). In addition, serious adverse event data were evaluated for recently initiated Studies 20120216 and 00103311.

Table 37: Summary of subject incidence of treatment emergent adverse events; adult relapsed/refractory ALL Studies (Full analysis set)

	MT103-211	MT103-206				Total (N = 225)
	9/28 µg/d (N = 189)	15 µg/m^2/d (N = 7)	5/15 µg/m^2/d (N = 23)	5/15/30 µg/m^2/d (N = 6)	Total (N = 36)	
All treatment emergent adverse events; n (%)	188 (99.5)	7 (100.0)	23 (100.0)	6 (100.0)	36 (100.0)	224 (99.6)
Grade ≥ 3	155 (82.0)	7 (100.0)	15 (65.2)	5 (83.3)	27 (75.0)	182 (80.9)

	MT103-211	MT103-206				Total (N = 225)
	9/28 µg/d (N = 189)	15 µg/m²/d (N = 7)	5/15 µg/m²/d (N = 23)	5/15/30 µg/m²/d (N = 6)	Total (N = 36)	
Grade ≥ 4	84 (44.4)	6 (85.7)	9 (39.1)	2 (33.3)	17 (47.2)	101 (44.9)
Serious	121 (64.0)	6 (85.7)	14 (60.9)	5 (83.3)	25 (69.4)	146 (64.9)
Fatal	28 (14.8)	1 (14.3)	4 (17.4)	1 (16.7)	6 (16.7)	34 (15.1)
Leading to study drug discontinuation	34 (18.0)	4 (57.1)	5 (21.7)	1 (16.7)	10 (27.8)	44 (19.6)
Serious	27 (14.3)	4 (57.1)	4 (17.4)	1 (16.7)	9 (25.0)	36 (16.0)
Fatal	10 (5.3)	0 (0.0)	1 (4.3)	1 (16.7)	2 (5.6)	12 (5.3)
Leading to study drug interruption	63 (33.3)	3 (42.9)	6 (26.1)	3 (50.0)	12 (33.3)	75 (33.3)
Serious	47 (24.9)	2 (28.6)	5 (21.7)	3 (50.0)	10 (27.8)	57 (25.3)
Fatal	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Treatment-related treatment-emergent adverse events - n (%)	166 (87.8)	7 (100.0)	23 (100.0)	6 (100.0)	36 (100.0)	202 (89.8)
Grade ≥ 3	105 (55.6)	7 (100.0)	12 (52.2)	4 (66.7)	23 (63.9)	128 (56.9)
Grade ≥ 4	42 (22.2)	5 (71.4)	6 (26.1)	1 (16.7)	12 (33.3)	54 (24.0)
Serious	69 (36.5)	4 (57.1)	9 (39.1)	4 (66.7)	17 (47.2)	86 (38.2)
Fatal	3 (1.6)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.8)	4 (1.8)
Leading to study drug discontinuation	18 (9.5)	2 (28.6)	3 (13.0)	0 (0.0)	5 (13.9)	23 (10.2)
Serious	15 (7.9)	2 (28.6)	3 (13.0)	0 (0.0)	5 (13.9)	20 (8.9)
Fatal	2 (1.1)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.8)	3 (1.3)

	MT103-211	MT103-206				Total (N = 225)
	9/28 µg/d (N = 189)	15 µg/m²/d (N = 7)	5/15 µg/m²/d (N = 23)	5/15/30 µg/m²/d (N = 6)	Total (N = 36)	
Leading to study drug interruption	43 (22.8)	2 (28.6)	5 (21.7)	3 (50.0)	10 (27.8)	53 (23.6)
Serious	29 (15.3)	1 (14.3)	4 (17.4)	3 (50.0)	8 (22.2)	37 (16.4)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Severity Graded using CTCAE version 4.0

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies and program-wide pooled population

In the adult relapsed/refractory ALL population, 75 subjects (33.3%) experienced a treatment interruption due to an adverse event. The system organ class (SOC) with the highest subject incidence leading to treatment interruption was Nervous System Disorders (13.3%). The most frequently reported adverse events leading to treatment interruptions (≥ 2% subject incidence) were confusional state (3.6%), encephalopathy (3.1%), tremor (2.7%), convulsion (2.2%), and pyrexia (2.2%).

Dose delays due to adverse events may cause efficacy concerns in anti-cancer therapies due to the possibility of allowing the cancer to progress during the treatment interruption. However, subjects who interrupted blinatumomab treatment due to an adverse event before achieving remission and then restarted treatment had equally high rates of remission (CR/CRh*) as the study population overall (39.6% versus 42.9% overall in Study MT103-211 and 72.7% versus 69.4% overall in Study MT103-206). Similarly, remission rates (CR/CRh*) in subjects with treatment interruptions due to neurologic adverse events were similar to remission rates overall (42.1% versus 42.9% overall in Study MT103-211 and 66.7% versus 69.4% overall in Study MT103-206). Similar results were observed in subjects who interrupted blinatumomab due to Grade ≥ 3 adverse events and Grade ≥ 3 neurologic adverse events occurring before achieving remission.

In the adult relapsed/refractory population, 44 subjects (19.6%) permanently discontinued study treatment due to adverse events. The SOCs with the highest subject incidence of adverse events were Infections and Infestations (5.3%), with sepsis (1.8%) being the most frequently reported adverse event in this SOC, and Nervous System Disorders (4.4%), with encephalopathy (2.2%) being the most frequently reported adverse event in this SOC. All other adverse events leading to permanent treatment discontinuation were reported with a subject incidence of less than 2%.

Overall, the types of adverse events leading to treatment interruptions and permanent treatment discontinuations reported in the adult relapsed/refractory ALL population were consistent with those reported in the program wide pooled population.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies and program-wide pooled population

Serious adverse events

In the adult relapsed/refractory population, 64.9% of subjects experienced serious adverse events. The most frequently reported serious adverse events (subject incidence ≥ 2%) were febrile neutropaenia (7.6%), pyrexia (6.2%), pneumonia (4.9%), sepsis (4.4%), encephalopathy (3.6%), tremor (3.6%), neutropenia (3.1%), device related infection (3.1%), infection (2.7%), overdose (2.2%), and confusional state (2.2%). All other reported SAEs were reported with a subject incidence of less than 2%.

Overall, the types of serious adverse events reported in the adult relapsed/refractory ALL population were consistent with those reported in the program-wide pooled population. Additionally, in the ongoing and recently initiated studies (Studies MT103-211, MT103-202, MT103-205, MT103-208, 00103311, and 20120216), the types of serious adverse events reported after the primary analysis data cut-off date (10 October 2014) through 30 March 2014 were consistent with those reported in the program-wide pooled population. Across blinatumomab studies, serious adverse events that were observed (such as neutropaenia, febrile neutropaenia, sepsis, and device related infections) reflect events that are common in patients with hematologic malignancies and who have received prior combination chemotherapies. Cytopaenias (including neutropaenia/febrile neutropaenia), infections, medication errors (including overdose), and neurologic events are among the adverse events of interest with blinatumomab and are discussed elsewhere.

Fatal adverse events

In the program wide pooled population, fatal adverse events (that were treatment emergent and occurred up to 30 days after the last blinatumomab dose) were reported for 47 subjects during the blinatumomab studies. Consistent with the background diseases, the subject incidence of fatal adverse events was higher in the adult and paediatric relapsed/refractory populations (15.1% (n = 34) in adult relapsed/refractory ALL and 19.5% (n = 8) in paediatric relapsed/refractory ALL), and lower in the MRD positive ALL and relapsed/refractory NHL populations (1.8% (n = 2) in MRD positive ALL and 3.2% (n = 3) in relapsed/refractory NHL).

In the adult relapsed/refractory ALL population, all but 1 fatal adverse event (due to infection/septic shock following allogeneic HSCT) occurred in the setting of active disease. The most frequently reported fatal adverse events (occurring in ≥ 2 subjects) were sepsis, septic shock, Fusarium infection, pneumonia, fungal pneumonia, acute lymphocytic leukaemia, and disease progression. In the program-wide pooled population, the most frequently reported fatal adverse events (occurring in ≥ 2 subjects) were sepsis, pneumonia, disease progression, respiratory failure, septic shock, fungal pneumonia, Fusarium infection, and acute lymphocytic leukaemia. None of the deaths were due to adverse events that would be unanticipated in patients with hematologic malignancies.

Across all indications, the SOC with the highest subject incidence of fatal adverse events was Infections and Infestations (5.9%), with sepsis (1.5%) being the most frequently reported fatal adverse event in this SOC. The subject incidence of fatal adverse events in the Infection and Infestations SOC was highest in the adult relapsed/refractory ALL population (10.2%), compared with the paediatric relapsed/refractory ALL population (4.9%), relapsed/refractory NHL population (2.1%), and MRD positive ALL population (0.9%). Seven of the 47 deaths (3 due to sepsis (sepsis, bacterial sepsis, and Escherichia sepsis), 1 due to Pneumocystis jirovecii pneumonia, 1 due to invasive fungal infection (central nervous system infection), 1 due to respiratory failure, and 1 due to candida infection) were considered by the investigator to be possibly related to blinatumomab. Based on its mechanism of action, blinatumomab causes B-cell depletion, resulting in decreased immunoglobulins. However, other confounding factors contribute to immunosuppression in these subjects with haematological malignancies, including

the underlying malignancies (particularly high tumour burden), impaired bone marrow function, and previous therapies.

8.3.4. Adverse events of special interest

Adverse events of special interest were defined for blinatumomab based upon emerging clinical data, the mechanism of action of the product, and potential risks as defined by nonclinical data. In general, adverse events of interest can be described in 4 broad categories as shown below:

- Adverse events that are possibly associated with the pharmacologic activity (mechanism of action) of blinatumomab:
  - Neurologic events
  - Cytokine release syndrome
  - Capillary leak syndrome
  - Decreased immunoglobulins
- Adverse events that are likely secondary effects of blinatumomab treatment due to host or disease factors:
  - Infusion reactions
  - Tumour lysis syndrome
  - Elevated liver enzymes
- Adverse events likely associated with the underlying disease and/or prior therapy exposure:
  - Infections
  - Cytopaenias (including neutropenia and febrile neutropenia)
  - Venous thrombosis and thromboembolic events, including DIC
  - Leukoencephalopathy
- Adverse events related to preparation, administration, and drug delivery system:
  - Medication errors
- Additionally, the following minimum critical toxicities were evaluated:
  - QT prolongation and other ECG abnormalities
  - Hepatotoxicity
  - Nephrotoxicity
  - Bone Marrow Toxicity
  - Immunogenicity.

Neurologic events

In the adult relapsed/refractory ALL population, 33.8% of subjects reported ≥ 2 prior relapses at Baseline. Per protocol guidance, as prophylaxis for CNS relapse, lumbar puncture with intrathecal prophylaxis was to be conducted at regular intervals. If a neurologic adverse event occurred, the subject was to receive immediate treatment with dexamethasone. In case of Grade 3 neurologic adverse events, treatment was to be interrupted for 2 weeks. After resolution of the neurologic adverse event, the subject was to continue treatment at a constant lower blinatumomab dose of 9 µg/day for the remaining treatment period. In case of Grade 4 neurologic adverse events, treatment was to be permanently discontinued.

In early Phase I clinical studies of blinatumomab using short term (2 or 4 hours) IV infusion, neurologic and psychiatric adverse events were observed. This led to subsequent studies utilising a continuous IV infusion method to mitigate neurotoxicity and improve efficacy. Subjects with a history or presence of clinically relevant CNS pathology, such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or active ALL in the CNS were excluded from participation in blinatumomab studies.

In the adult relapsed/refractory ALL population, 52.9% of subjects experienced neurologic adverse events (including psychiatric disorders). These events primarily involved the CNS as opposed to the peripheral nervous system (PNS). The preferred terms reported represented a wide spectrum of neurologic adverse events (including psychiatric disorders). The most frequently reported adverse events (subject incidence ≥ 5%) were tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional state. The majority of events occurred during the first cycle. The median time to onset of the events was 9 days from the start of blinatumomab treatment. The majority of neurologic events (91.6%) were clinically reversible. Of the subjects who experienced a Grade ≥ 3 neurologic adverse event that resolved, the median time to resolution of the event was 3 days. Grade ≥ 4 adverse events were infrequently reported (1.8%), and serious neurologic adverse events were observed in 17.8% of subjects, of which encephalopathy, tremor, and confusional state were reported with a subject incidence > 2%. Approximately 5% of subjects (5.3%) experienced neurologic adverse events that led to study treatment discontinuation, of which encephalopathy accounted for almost half of the discontinuation events. No fatal neurologic adverse events were reported as of the data cut off date (10 October 2013); however, after the data cut-off date, 2 subjects enrolled in Study MT103-211 experienced fatal encephalopathy events (one of which was in the setting of general health deterioration and pneumonia and the other in a subject with a past medical history of encephalopathy and typhlitis). Serious adverse events of encephalopathy, confusional state, and cognitive disorders were reported with a ≥ 5% difference in subjects ≥ 65 years of age compared to subjects ≥ 18 and < 65 years of age.

In the program-wide pooled population, a similar subject incidence of neurologic adverse events (including psychiatric disorders) was observed (52.6%) and was consistent with the adult relapsed/refractory ALL population. In the pooled population, 17.3% of subjects experienced serious neurologic events; the most frequently reported serious events (subject incidence ≥ 2%) were encephalopathy (4.4%), tremor (3.8%), aphasia (2.7%), and convulsion (2.7%). Less than 10% of subjects in the program-wide pooled population discontinued study treatment due to neurologic events, such as encephalopathy (2.9%), aphasia (1.9%), tremor (1.7%), and convulsion (1.5%).

With regard to psychiatric adverse events, consistent with the adult relapsed/refractory population, confusional state (6.7%) was the only commonly reported adverse event with a subject incidence ≥ 5% in the program wide pooled population.

Cytokine release syndrome

As would be anticipated based on the mechanism of action, cytokine release occurring with a specific T cell engager such as blinatumomab can result in an exaggerated systemic immune response involving the release of inflammatory mediators/cellular cytokines, which can have effects (in some cases profound) on blood pressure, vascular integrity, and myocardial, lung, and liver functions. When the symptoms are more severe, it can be defined as cytokine storm. Per protocol guidance, in case of signs of cytokine release during treatment, dexamethasone was to be administered orally or intravenously at a dose of at least 3 x 8 mg per day for up to 3 days, followed by step-wise reduction over a period of up to 4 days.

In the adult relapsed/refractory ALL population, 12.0% of subjects experienced the adverse event of cytokine release syndrome or cytokine storm (preferred terms). The greatest risk of

developing cytokine release syndrome was on day 2 from the start of blinatumomab treatment. Less than 1% of subjects experienced ≥ Grade 4 events, and 1.8% reported serious cytokine release syndrome events. 4 subjects experienced cytokine release syndrome that led to study treatment interruption, and only 1 subject experienced cytokine release syndrome that led to permanent treatment discontinuation. However, when looking broadly across the adult relapsed/refractory ALL studies for signs and symptoms of cytokine release syndrome, 94.7% of subjects experienced adverse events potentially associated with cytokine release syndrome, manifested primarily as pyrexia (63.1%) and headache (36.4%). Additional adverse events reported, such as tachycardia, chills, nausea, vomiting, arthralgia, hypotension, hypertension, and elevated liver enzymes were consistent with the clinical symptoms of cytokine release syndrome.

In the program wide pooled population, the majority of subjects experienced Grade 1 and 2 events of cytokine release syndrome, and < 2% experienced serious adverse events of cytokine release syndrome. Similar to the adult relapsed/refractory ALL population, Grade ≥ 3 and Grade ≥ 4 adverse events were infrequently reported (2.5% and 1.1%, respectively). No fatal adverse events of cytokine release syndrome or cytokine storm were reported in any study.

In the paediatric relapsed/refractory ALL population, 9 subjects experienced adverse events of cytokine release syndrome. One case, which was reported as a serious event of cytokine release syndrome, was also described in the literature as severe toxicity manifested as macrophage activation syndrome (MAS) triggered by the release of cytokines leading to secondary haemophagocytic lymphohistiocytosis (HLH). In addition, one subject reported a non-serious adverse event of HLH; cytokine release syndrome was not reported as a concurrent adverse event.

Capillary leak syndrome

In the adult relapsed/refractory ALL population, one subject (< 1%) experienced an event reported as capillary leak syndrome (study Day 2), which was reported as serious (Grade 4), non-fatal, and led to a temporary interruption of blinatumomab. Following treatment re-initiation approximately 2 weeks later, the subject experienced additional events suggestive of capillary leak syndrome.

Looking broadly across the data for signs and symptoms of capillary leak, in the adult relapsed/refractory population, 44.4% of subjects experienced adverse events suggestive of capillary leak syndrome, and across the program wide pooled population, 41.5% of subjects experienced adverse events suggestive of capillary leak syndrome: 46.3% of subjects were in the paediatric relapsed/refractory ALL population, 53.7% were in the relapsed/refractory NHL population, and 23.7% were in the MRD positive ALL population. The majority of these adverse events were peripheral oedema and hypotension. No fatal adverse events of capillary leak syndrome were reported in any study.

Decreased immunoglobulins

As observed in the adult relapsed/refractory ALL population, decreased immunoglobulins (including adverse events such as hypoglobulinaemia, immunoglobulins decreased, hypogammaglobulinaemia decreased, and other immunoglobulin events) were reported in 14.2% of subjects. The majority of the adverse events were Grade 1 and 2 in severity, with Grade ≥ 3 events reported in 2.2% of subjects and Grade ≥ 4 events reported in < 1% of subjects. The most frequently reported adverse events were decreased immunoglobulins (8.4%), Immunoglobulin G decreased (4.4%), Immunoglobulin A decreased (4.0%), and Immunoglobulin M decreased (3.6%). None of the events were serious or had fatal outcomes. Across the program-wide pooled population, similar findings were observed, with 18.5% of subjects reporting decreased immunoglobulins; the highest subject incidence of decreased immunoglobulins was reported in the relapsed/refractory NHL population (25.3%), as would be expected.

Infusion reactions

In the adult relapsed/refractory population, pyrexia (27%) was the most frequently reported adverse event occurring within the first 48 hours of blinatumomab infusion with a duration ≤ 2 days. Other clinically relevant adverse events with cardiovascular components included hypotension, circulatory collapse, and hypertension, and hypersensitivity-like events included face oedema and swelling face. Other adverse events included tachypnoea and myalgia.

Treatment-related adverse events suggestive of infusion reactions that occurred within 48 hours with any duration and with an underlying cardiovascular component included hypotension, hypertension, tachycardia, sinus tachycardia, bradycardia, supraventricular tachycardia, flushing, and pulmonary oedema. Hypersensitivity-like adverse events included hypersensitivity, face oedema, swelling face, wheezing, erythema, rash, and generalised rash. Other treatment-related adverse events reported within 48 hours of infusion with any duration included tachypnoea, oxygen saturation decrease, dyspnoea, nausea, vomiting, chills, fatigue, asthenia, arthralgia, myalgia, joint swelling, and headache. Clinically relevant treatment related serious adverse events that occurred within 48 hours of infusion with any duration included hypersensitivity (n = 2 subjects), hypotension (n = 2), bradycardia (n = 1), supraventricular tachycardia (n = 1), and arthralgia (n = 1).

Similar to the adult relapsed/refractory population, in the program wide pooled population, pyrexia (38.5%) was the most frequently reported adverse event occurring within 48 hours of blinatumomab infusion with a duration of ≤ 2 days. Additional treatment related adverse events occurring within 48 hours of infusion with any duration in the other populations included hypersensitivity like events, such as periorbital oedema, eyelid oedema, hyperhidrosis, and allergic dermatitis. In the other populations, additional treatment related serious adverse events included infusion-related reaction (preferred term; n = 2 subjects), sinus tachycardia (n = 1), and respiratory failure (n = 1).

Tumour lysis syndrome

In the adult relapsed/refractory ALL population, 4.4% of subjects experienced adverse events of tumour lysis syndrome. None of the events was reported as fatal, 2 subjects (1.0%) experienced serious adverse events, 5 subjects (2.2%) experienced Grade ≥ 3 adverse events, and 1 subject had a Grade ≥ 4 adverse event. One subject permanently discontinued study treatment due to tumour lysis syndrome. The median time to first onset of tumour lysis syndrome was 2 days from the start of blinatumomab treatment.

In the program-wide pooled population, tumour lysis syndrome was reported in 2.7% of subjects, none were fatal, < 1% were reported as serious or Grade ≥ 4 adverse events, and 2 subjects permanently discontinued study treatment due to tumour lysis syndrome. Electrolyte imbalances and abnormal laboratory levels, such as blood urea increased, hyperuricemia, hyperphosphataemia, hyperkalaemia, and hypocalcaemia, and renal events, such as blood creatinine increased, metabolic acidosis, anuria, renal failure, and acute renal failure, were reported in subjects who experienced tumour lysis syndrome.

Elevated liver enzymes

In the adult relapsed/refractory ALL studies, subjects with AST (SGOT) and/or ALT (SGPT) and/or ALP ≥ 5 x the upper limit of normal (ULN) and total bilirubin ≥ 1.5 x ULN (unless related to Gilbert's or Meulengracht disease) were excluded from study participation in the adult relapsed/refractory ALL population, 28.9% of subjects reported elevated liver enzyme adverse events. The most frequently reported events were ALT increased (12.4%), AST increased (11.6%), blood bilirubin increased (7.6%), and GGT increased (7.1%). Other liver abnormalities, such as ascites, hepatomegaly, hepatic steatosis, and prothrombin time prolonged, were infrequently reported. The subject incidence of Grade ≥ 3 and Grade ≥ 4 adverse events was 16.0% and 2.2%, respectively. None of the events were reported with a fatal outcome. Less than 2% of subjects (1.8%) experienced serious adverse events such as ALT increased, AST

increased, and blood bilirubin increased. The median time to onset to the first event was 3 days from the start of blinatumomab treatment. The only hepatic laboratory abnormalities reported as Grade 4 adverse events were ALT increased (0.9%), GGT increased (0.9%), AST increased (0.4%), and blood bilirubin increased (0.4%). Of these abnormal liver enzymes, only AST increased (0.9%) and ALT increased (0.4%) led to permanent study treatment discontinuation.

Twenty-seven subjects met the laboratory criteria of ALT/AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN on any day during study treatment. Upon review of the ALP laboratory values, it was noted that 16 of the 27 subjects also had ALP ≤ 2 x ULN while their ALT/AST and total bilirubin values were increased (ALT/AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN) within one day. However, in all of the cases, plausible, alternative aetiologies were present, such as cytokine release syndrome, severe infection, or concomitant medications known to be associated with the elevations in liver enzymes. The majority of subjects (25 out of 27) were able to be treated through the liver enzyme elevations, with 1 subject requiring temporary treatment interruption and 1 subject permanently discontinuing study treatment.

In the program-wide pooled population, similar findings were observed with regard to liver enzyme elevations as noted in the adult relapsed/refractory ALL population. The most commonly reported hepatic adverse events were ALT increased (14.9%), AST increased (12.0%), GGT increased (9.1%), and blood bilirubin increased (5.9%). Hepatic events that led to permanent treatment discontinuation included AST increased (0.6%), ALT increased (0.4%), GGT increased (0.2%), hepatic enzyme increased (0.2%), hepatic failure (0.2%), and hyperbilirubinaemia (0.2%). The majority of hepatic events reported in the pooled population were reported as Grade of 1 and 2; less than 5% of subjects experienced Grade 4 events.

Infections

In the adult relapsed/refractory ALL population, 64.9% of subjects reported infections, of which pneumonia (4.9%) and sepsis (4.4%) were the most frequently reported serious adverse events. Treatment related infections (per the investigator) were reported in 13.3% of subjects, with pneumonia being the most commonly reported treatment related adverse event. 3 percent (3.1%) of subjects experienced serious device related infections. 10.2% of subjects died due to infections, with sepsis (2.2%) and pneumonia (1.3%) as the most common reason. Other fatal infections included fungal pneumonia, Aspergillosis, Candida sepsis, enterococcal bacteraemia, Escherichia coli sepsis, and Fusarium infection. Overall, 5% of subjects had their infusions interrupted or were permanently discontinued from study treatment due to an infection adverse event, primarily sepsis. Median time to onset of a first infection event was 15 days from the start of blinatumomab treatment. Catheter related infections were observed in 6.7% of subjects.

Immunocompromised individuals are at an increased risk of developing opportunistic infections. Opportunistic infections were observed in 16.4% of subjects and included bacterial infections, such as Klebsiella infection (0.9%), Pseudomonas infection (0.9%), Clostridium difficile colitis (0.9%); fungal infections, such as fungal pneumonia (2.7%), pulmonary Aspergillosis (0.9%), and Aspergillus infection (0.9%); and viral infections, such as cytomegalovirus (CMV) infection (1.8%), herpes zoster (0.9%) and syncytial viral respiratory pneumonia (0.9%). One subject experienced a BK virus infection in the setting of reactivation. One subject diagnosed with encephalopathy was found to be cerebrospinal fluid (CSF)-positive for John Cunningham (JC) virus infection. Initial symptoms included disorientation. Per the investigator's assessment, the subject's clinical presentation and results of the cerebral MRI did not support a diagnosis of progressive multifocal leukoencephalopathy (PML).

In the program wide pooled population, infection rates in the paediatric relapsed/refractory ALL population (48.8%), MRD positive ALL population (48.2%), and relapsed/refractory NHL population (51.6%) were less than those observed in the adult relapsed/refractory ALL population. Of note, the subject incidence of fungal opportunistic infections in the paediatric

relapsed/refractory ALL and adult relapsed/refractory populations were similar (7.3% and 7.1%, respectively) but were lower in the MRD positive ALL and relapsed/refractory NHL populations (1.8% and 3.2%, respectively). The median time to any infection in the paediatric relapsed/refractory ALL population was 10.5 days versus 29 days in the MRD positive ALL studies. No clear pattern emerged with respect to aetiology of these opportunistic infections; however, the rate of infections observed may be associated with the underlying disease. A univariate analysis of time to first onset of infections using Cox proportional hazard models suggest that ECOG PS and general condition at baseline played an important role in the frequency of infections following the treatment. The lower rates of infection in the MRD positive ALL population (48.2%) compared to the adult relapsed/refractory ALL population (64.9%) also suggest that the underlying population's medical status is more of a risk factor for the development of infections.

Blinatumomab is to be prepared under a clean aseptic environment in a laminar airflow hood and subsequently administered via a pump as a continuous IV infusion. As blinatumomab infusion solution does not contain a preservative, a study was conducted to assess whether the prepared infusion solution can support growth of representative microorganisms. Blinatumomab infusion solution incubated at 20°C to 25°C supported the growth of Pseudomonas aeruginosa, Escherichia coli, and Pseudomonas aeruginosa, but not Staphylococcus aureus, Micrococcus luteus, or Candida albicans. None of the test organisms showed growth at 2°C to 8°C, the storage specification for blinatumomab infusion solution prior to administration.

To understand the potential impact of blinatumomab administration as it relates to the risk for microbial contamination on the frequency of infections, the incidence of relevant infections in subjects who were eligible to receive more frequent IV bag changes was compared with those eligible to receive less frequent IV bag changes in Study MT103-211 (IV bag changes occurred at intervals of up to every 48 hours in the US and at intervals of up to 96 hours in the EU). For relevant infections (sepsis, septic shock, bacteraemia, and device-related infections), adverse events were reported in 20% of subjects in the US (more frequent bag changes) and 21% in the EU (less frequent bag changes), and Grade ≥ 3 adverse events were reported in 18% of subjects in the US and 16% of subjects in the EU. For related relevant infections (per the investigator), adverse events were reported in 3% of subjects in the US and 3% of subjects in the EU, and Grade ≥ 3 adverse events were reported in 3% of subjects in the US and 3% of subjects in the EU. This analysis shows that an increase in relevant infections was not observed with less frequent bag changes. Importantly, the incidence of relevant infections in this study was not higher than the incidence of relevant infections in the general population of adult patients with relapsed/refractory ALL.

Cytopaenias

In the adult relapsed/refractory ALL population, the most commonly reported red-cell line abnormality was anaemia (17.8%), of which one event was reported as serious. Similar rates of anaemia were reported in the program-wide pooled population (15.8%), and one subject experienced a non-serious, Grade 3 event of aplastic anaemia.

As would be anticipated in adult relapsed/refractory ALL population, the most frequently reported abnormalities of the white-blood cell line were febrile neutropaenia (24.4%) and neutropaenia (15.1%). Consistent with the mechanism of action of blinatumomab, 2.2% of subjects experienced lymphopaenia and 1.3% experienced lymphocyte count decreased. There were no fatal outcomes associated with events of lymphopaenia, and only one event of lymphopaenia was reported as serious.

In the program-wide pooled population, 76 subjects (16.0%) experienced events of lymphopenia, with the majority of subjects reporting these events in the relapse/refractory NHL studies. The higher rate of lymphopenia reported in the relapsed/refractory NHL population

most likely reflects different reporting requirements between the studies (based on the Phase I nature of Study MT103-104, all laboratory abnormalities were reported as adverse events regardless of clinical relevance).

Platelet count abnormalities such as thrombocytopenia were reported in 12.4% of subjects in the adult relapsed/refractory ALL population, and 3.6% of subjects reported the adverse event of platelet count decreased. Similar rates of platelet count abnormalities were reported in the program-wide pooled population, with 15.4% of subjects experiencing thrombocytopenia and 3.6% of subjects experiencing platelet count decreased.

Venous thrombosis and thromboembolic events

In the adult relapsed/refractory ALL population, venous thrombosis and thromboembolic events (including DIC) were reported in 10.2% of the subjects and included DIC (6 subjects, 2.7%), device occlusion and deep vein thrombosis (3 subjects each), hemiparesis and embolism (2 subjects each), and splenic infarction, myocardial infarction, infusion site thrombosis, transient ischemic attack, cerebral ischemia, thrombophlebitis, thrombosis, femoral artery occlusion, subclavian vein thrombosis, and venous thrombosis (1 subject each). Serious adverse events were reported in 8 subjects: DIC (2 subjects), device occlusion (2 subjects), and hemiparesis, embolism, femoral artery occlusion, and subclavian vein thrombosis (1 subject each). One fatal adverse event was reported as embolism.

In the program-wide pooled population, 10.7% of subjects experienced venous thrombosis, thromboembolic, or DIC events. Similar to the adult relapsed/refractory population, DIC was the most frequently reported adverse event (2.9%); the one fatal adverse event of DIC was reported in a paediatric subject in the setting of a CNS fungal infection (reported as not related to blinatumomab). Serious adverse events were reported in 4% of subjects in the program-wide pooled population; serious adverse events reported in 2 or more subjects were DIC (3 subjects) and device occlusion, thrombosis in device, hemiparesis, deep vein thrombosis, and thrombosis in 2 subjects each.

As would be expected in these heavily pre-treated populations, DIC was the most frequently reported adverse event, occurring in 2.9% of subjects in the program wide pooled analysis set, with < 1% of the DIC events reported as serious or fatal.

Leukoencephalopathy

Seven subjects in the adult/relapsed/refractory ALL population experienced serious adverse events associated with changes in either brain MRI or brain CT: confusional state (2 subjects), tremor (1 subject), cognitive disorder (1 subject), encephalopathy (1 subject), convulsion (1 subject), and leukoencephalopathy (1 subject). 5 of the 7 subjects had past medical histories, such as chronic ischemia and micro haemorrhage, prior cranial irradiation, and progression of underlying disease. One subject diagnosed with encephalopathy was found to be CSF-positive for JC virus infection. Initial symptoms included disorientation. Study treatment was permanently discontinued approximately one week from the onset of encephalopathy, and the subject recovered on the same day. Per the investigator's assessment, the subject's clinical presentation and results of the cerebral MRI did not support a diagnosis of PML. The remaining subject experienced a serious adverse event of confusional state, and broad white matter hypodensity changes were reported as related to study treatment by the investigator. The subject's past medical history was significant for mental status changes; however, the subject continued on blinatumomab and a repeat CT results showed stable periventricular white matter hypodensity.

In the program-wide pooled population, MRI/CT changes were noted in 4 subjects: 2 subjects from the MRD positive ALL study (Study MT103-203), 1 subject from the relapsed/refractory NHL study (Study MT103-104), and 1 subject from the paediatric relapsed/refractory ALL study (Study MT103-205). Out of the 2 subjects from the MRD positive ALL study, one subject experienced a convulsion and MRI findings consistent with a haemorrhage in the left cerebellar

hemisphere, and the second subject, with a history of radiation therapy and pre-existing MRI findings, experienced tremors and leukoencephalopathy based on MRI results that showed subtle signal enhancement in the white matter of the brain. The leukoencephalopathy was reported as resolved following withdrawal of blinatumomab. One subject with relapsed/refractory NHL and a history of microangiopathic leukoencephalopathy experienced encephalopathy and speech and fine motor function impairment 4 days after blinatumomab administration. MRI results were reported as unspecific microangiopathic leukoencephalopathy with regression of the subgaleal tissue deposits. One paediatric subject with relapsed/refractory ALL experienced confusional state and died due to sepsis with infection, intracranial haemorrhage, and respiratory insufficiency. The CT results were consistent with intracranial haemorrhage.

Across the blinatumomab studies, in these heavily pretreated patient populations, leukoencephalopathy has been infrequently reported, and to date, there have been no reports of PML.

Medication errors

Reporting requirements for medication errors have evolved during the blinatumomab clinical program. Protocols MT103-211 (Version 2) and MT103-205 (Version 2) required that an overdose of > 10% of the intended dose be reported as a serious adverse event. Protocols MT103-104, MT103-202, MT103-203, MT103-206, MT103-208, as well as Version 1 of Protocols MT103-205 and MT103-211, required reporting of all overdoses as serious adverse events. More recently initiated studies (Studies 20120216 and 00103311) require only the reporting of adverse events and serious adverse events associated with an overdose. The continuous infusion of blinatumomab in the clinical trial setting is provided by programmable pumps. A process to collect information on pump errors, independently from any association with overdose, is under development within ongoing Protocol 00103311.

In the adult relapsed/refractory ALL population, medication errors were reported in 6 subjects (2.7%). Of these 6 subjects, the preferred terms overdose (n = 5) and accidental overdose (n = 2) were reported. One subject experienced 2 medication error events (1 event of overdose and 1 event of accidental overdose). Across the program-wide pooled population, medication errors were reported in 22 subjects (4.6%): overdose (3.6%), accidental overdose (0.8%), and wrong technique in drug usage process (0.4%). The majority of subjects reported no adverse events associated with the overdose; the few adverse events reported (fever, tremors, and headache) were consistent with those reported at the recommended therapeutic dose for blinatumomab in adult patients with relapsed/refractory ALL. One subject experienced encephalopathy, for which he was discontinued from treatment after receiving 12 times the intended blinatumomab dose of 5 $\mu g/m^2$ for 1 day.

The types of medication errors reported have been related to either the preparation or administration steps of blinatumomab use. Increased flow rate of the infusion pump (through malfunction (5 subjects) and accidental increase, including manipulation of the pump by the subject (6 subjects), infusion rate set incorrectly (1 subject), and an error connecting the infusion line to the pump (1 subject)) was the most common cause for overdose in the program-wide pooled population. Overdose also resulted from pharmacy preparation errors relating to the calculation of blinatumomab concentration.

The following measures were introduced to mitigate overdose during the conduct of the clinical trials: correction of pharmacy software and prescription forms, updates to standard operating procedures, and retraining of staff across all sites. A total of 9 medication errors (all overdose) were reported after these measures were implemented (September 2012 through October 2013). In comparison, 15 medication errors (of which 13 were overdose) were reported prior to September 2012 (data on file). Results suggest that while the overall rate of overdose errors (number of incidents per subjects at risk) was similar both before (4.5%; 13 of

291) and after (3.9%; 9 of 232) mitigation efforts, specific errors were not repeated by individual sites after retraining.

8.3.5. Minimal critical toxicities

8.3.5.1. QT prolongation and other ECG abnormalities

In the pooled analysis from Studies MT103-206 and MT103-203, 62 subjects met ECG analysis criteria. The results showed a moderate increase in heart rate, likely attributed to multifactorial aetiology related to both disease state and cytokine release. There was no signal of any effect on AV conduction or cardiac depolarization as measured by the PR and QRS interval durations, respectively. There was no significant effect on cardiac repolarisation as measured by the slight decrease in QTcF and the flat to positive slope for blinatumomab in the pharmacokinetic/pharmacodynamic model. There was only a single subject who developed a new morphological ECG change, which appeared to be of no clinical significance. The results of the pooled analyses from Studies MT103-206 and MT103-203 were nearly identical to the results of Study MT103-206 when analysed alone. In addition, a QT/QTc assessment was prospectively planned for the Phase I NHL Study MT103-104. Based on results of this study, ECG analysis from 88 subjects with various subsets of NHL did not reveal a risk for QTc prolongation associated with blinatumomab treatment.

An analysis of adverse events across the blinatumomab program was conducted per International Conference on Harmonisation (ICH) E14 guidance (ICH E14, 2005). Events listed in the guidance were used to determine the selection of certain Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ). In the adult relapsed/refractory ALL population, one subject experienced a non-serious adverse event reported as electrocardiogram QT prolonged. The event occurred concurrent with the administration of ciprofloxacin, which has a known association with prolonged QT. Ciprofloxacin was discontinued following the development of QT prolongation. Other adverse events identified in the adult relapsed/refractory population included convulsion, epilepsy, syncope, tachycardia, sinus tachycardia, bradycardia, sinus bradycardia, supraventricular tachycardia, arrhythmia, palpitations, atrial fibrillation, ventricular extrasystoles, atrial tachycardia, ventricular fibrillation, and heart rate increased. However, a review of these adverse events did not suggest a potential proarrhythmic aetiology. Of the events with available ECG readings in the adult relapsed/refractory ALL population, no QT prolongation was reported. Additional adverse events reported in the program-wide pooled population (not observed in the adult relapsed/refractory ALL population) that were reviewed for a potential proarrhythmic aetiology included atonic seizures, left bundle branch block, cardiac arrest, sinus arrhythmia, supraventricular extrasystoles, and irregular heart rate. Similar to the adult relapsed/refractory ALL population, a review of these events did not suggest a potential proarrhythmic aetiology. However, there was a paediatric subject who experienced an atonic seizure with ECG results noted as 'QTc increased'. Electrolyte disturbances, mostly Grade 1 and 2, were observed at the time of onset of the seizure.

In conclusion, a review of the data revealed that blinatumomab was associated with a moderate but persistent increase in heart rate, but had no significant effect on cardiac repolarisation or other ECG parameters. The adverse events observed appear to overlap with the systemic effects associated with cytokine release syndrome and tumour lysis syndrome, and the ECG results do not suggest any QT risk in subjects receiving blinatumomab.

8.3.5.2. Nephrotoxicity

In the adult relapsed/refractory ALL population, 4.4% of subjects experienced adverse events of potential nephrotoxicity including renal failure (1.8%), renal failure acute (1.3%), anuria (< 1%), and oliguria (< 1%), with acute renal failure (< 1%), renal failure (< 1%), and blood creatinine increased (< 1%) reported as serious. Acute renal failure and renal failure were reported primarily in the setting of infections and tumour lysis syndrome. None of the events of

potential nephrotoxicity led to study treatment discontinuation or had a fatal outcome. In the program wide pooled population, a similar subject incidence (3.2%), including the type of adverse events and outcome, was observed. Overall, the majority of the events reported were non-serious. Of the serious adverse events reported, there were alternative aetiologies, including dehydration, infection, sepsis, and procedure-related complications.

8.3.5.3. Immunogenicity

A low incidence of neutralising antibodies (< 1%, 3 out of 325 subjects) was observed in the 4 adult studies evaluated (Studies MT103-211, MT103-206, MT103-202, and MT103-104). For subjects that showed positive neutralising ADAs during the monitoring period, decreases in drug concentration were observed. The impact of immunogenicity on safety was evaluated through medical review and assessment of the type and severity of adverse events, potential infusion reactions, and number of doses received while on study for blinatumomab treated subjects.

8.3.5.4. Laboratory tests

In the adult relapsed/refractory ALL population, significant liver function test (LFT) elevations (AST, ALT, and GGT) tended to occur early and may have been associated with cytokine release and T cell activity. There were no fatal events due to LFT elevations and nearly all LFT elevations resolved. Some events resolved with treatment interruption with subjects being successfully rechallenged, while others resolved while treatment continued, suggesting a first-dose effect rather than direct toxicity of blinatumomab.

Serum chemistry abnormalities, including potassium and calcium, were typically mild and generally resolved by the end of the core study periods. Some of these abnormalities are consistent with tumour lysis syndrome, a condition associated with hyperkalaemia, hyperphosphataemia, hyperuricaemia, hyperuricosuria, hypocalcaemia, and potentially causing lethal cardiac arrhythmias and/or renal failure. There were no fatal events of tumour lysis syndrome and no fatal events of cardiac arrhythmias in the adult relapsed/refractory ALL population.

Grade 3 and 4 decreases in platelets, white blood cells, and neutrophils were common; however, they were not always reported as clinically significant adverse events by the investigator. Although blinatumomab is not thought to be directly myelotoxic or myelosuppressive, the majority of adult subjects with relapsed/refractory ALL had high tumour burden (67.6% of subjects had ≥ 50% blasts in the bone marrow at baseline) and had been heavily pretreated, which may have played a role in the decreased blood counts. This is supported by the observation that adult subjects in the MRD positive ALL studies had a substantially lower incidence of Grade 3 and 4 cytopaenias despite receiving the same dose of blinatumomab.

Depletion of B cells and immunoglobulins were observed, which is expected due to the B-cell targeted mechanism of action of blinatumomab. No clinically relevant changes were observed in blood pressure, weight, or body temperature. Modest increases in heart rate were observed but had no significant effect on cardiac repolarisation or other ECG parameters

8.4. Post-marketing experience

Not applicable as product not approved in any market.

8.5. Other safety issues

8.5.1. Safety in special populations

8.5.1.1. Safety in pregnancy and lactation

The safety and efficacy of blinatumomab in pregnant women have not been established. Pregnant or breastfeeding women were excluded from blinatumomab studies.

In a developmental toxicity study conducted in mice using a murine surrogate molecule, there was no indication of maternal toxicity, embryotoxicity, or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but haematological effects were not assessed in fetuses.

It is not known if blinatumomab is present in human milk. Because of the potential for blinatumomab to cause adverse effects in infants, blinatumomab treatment or breastfeeding should be discontinued.

No studies have been conducted to evaluate the effects of blinatumomab on fertility. There were no effects on male or female mouse reproductive organs in 13 week toxicity studies with the murine surrogate molecule.

8.5.2. Safety in paediatric subjects

Paediatric subjects are being evaluated in Study MT103-205, an ongoing, Phase I/II, single arm, dose-finding/efficacy study in subjects < 18 years with relapsed/refractory ALL. The Phase I portion of this study is completed (excluding infants < 2 years).

In the Phase I part of the study (excluding infants < 2 years), a total of 41 subjects were enrolled and received ≥ 1 dose of blinatumomab at various dose levels (5, 15, 30, 15 to 30, or 5 to 15 µg/m^2/day). The safety results in paediatric subjects were consistent with the safety profile of blinatumomab in adult relapsed/refractory ALL studies. As of 10 October 2013 (the primary analysis data cut-off date for the marketing application), the most frequently reported adverse events (subject incidence > 25%) were pyrexia (32 subjects; 78%), headache (15; 36.6%), hypertension (13; 31.7%), nausea (12; 29.3%), and abdominal pain, anaemia, and pain in extremity (11; 26.8% each). Grade ≥ 3 adverse events reported with a subject incidence ≥ 10% were anaemia (10 subjects; 24.4%); pyrexia (9; 22.0%); AST increased (8 subjects; 19.5%); hypokalaemia, ALT increased, and white blood cell count decreased (7; 17.1% each); blood bilirubin increased (6; 14.6%); and febrile neutropenia, cytokine release syndrome, respiratory failure, and neutrophil count decreased (5; 12.2% each). Adverse events leading to permanent treatment discontinuation reported in more than 1 subject overall were cytokine release syndrome (3 subjects; 7.3%), and dyspnoea and respiratory failure (2; 4.9% each). 8 subjects died as a result of adverse events, which included respiratory failure (2 subjects) and cardiac failure, disease progression, DIC, fungal infection, multi-organ failure, and sepsis (1 subject each). One death due to respiratory failure, hypotonia, muscle weakness, and cardiac arrest was considered possibly related to blinatumomab by the investigator. Serious adverse events reported up through the additional safety data cut-off date (30 March 2014) were consistent with those reported as of the 10 October 2013 data cut-off date. A more detailed summary of safety for the Phase I portion of this study is provided in the Study MT103-205 Interim CSR. The Phase II portion is ongoing for evaluation of efficacy and safety in up to 40 subjects at the selected blinatumomab dose of 5 to 15 µg/m^2/day.

Outside of clinical studies, 31 paediatric subjects with relapsed/refractory or MRD positive B-precursor ALL have received blinatumomab on a named patient basis as of 30 March 2014. The safety profile of the subjects treated by named patient access or compassionate use is similar to that seen in paediatric subjects in Study MT103-205.

8.5.3. Other special populations and situations

Subjects with severe renal or hepatic impairment were excluded from blinatumomab studies.

In clinical studies, there was no evidence that blinatumomab exposure was different in subjects who had higher than normal AST and/or ALT values at baseline. Additionally, adverse events related to liver enzyme elevations tended to occur early and may have been associated with cytokine release and T cell activity. The majority of subjects were able to be treated through the liver enzyme elevations, with very few subjects requiring temporary treatment interruption or permanently discontinuing study treatment, and none with a fatal outcome.

There was up to a 2-fold reduction in blinatumomab clearance in subjects who had mild or moderate renal impairment (creatinine clearance > 30 mL/min) at baseline. Due to the large intersubject variability in drug exposure, no clinically meaningful impact of renal function on clinical outcomes is expected, and dose adjustment for patients with mild and moderate renal impairment does not appear to be necessary. Additionally, adverse events of acute renal failure and renal failure were infrequently reported and were primarily in the setting of infections and tumour lysis syndrome. None of the events of potential nephrotoxicity led to study treatment discontinuation or had a fatal outcome. Of the serious events reported, there were alternative aetiologies, including dehydration, infection, sepsis, and procedure related complications.

8.5.4. Safety related to drug-drug interactions and other interactions

A formal drug-drug interaction study was not conducted as blinatumomab is not eliminated via hepatic metabolism and blinatumomab is primarily intended to be administered as a single agent.

Blinatumomab did not affect CYP450 enzyme activities and pharmacokinetic interactions between blinatumomab and drugs metabolised by CYP450 enzymes are not expected.

8.6. Evaluator's overall conclusions on clinical safety

The primary analysis of safety was based on pooled analyses of the adult relapsed/refractory ALL population, which consisted of 225 subjects in Studies MT103-211 (N = 189) and MT103-206 (N = 36). The analysis was supported by pooled analyses of the program wide pooled population, which consisted of 475 subjects including 41 paediatric subjects. In addition, serious adverse event data were evaluated for 2 recently initiated clinical studies. The size of the safety database was considered adequate to define the safety profile of blinatumomab at the intended registration dose.

The most common fatal adverse events, which included sepsis, disease progression, and pneumonia, were anticipated to occur in the relapsed/refractory ALL population.

The majority of serious adverse events that were observed, including neutropenia, febrile neutropenia, sepsis, tumour lysis syndrome and device related infections, would be expected in patients with ALL who have received prior combination chemotherapies. Infections relating to B cell depletion and decreased immunoglobulin levels, cytokine release syndrome, and neurologic events are among the adverse events of interest with blinatumomab.

The most frequent AEs observed were fever, chills, lymphopenia, headache, fatigue, and oedema. These may be partly attributed to the mode of action of blinatumomab, which results in local polyclonal T cell activation, and are similar to symptoms experienced at the onset of a viral disease. Across all adult relapsed/refractory ALL studies, 94.7% of subjects experienced adverse events potentially associated with cytokine release syndrome, manifested primarily as pyrexia (63.1%) and headache (36.4%). Of more concern was the development of a generalised cytokine release syndrome or cytokine storm, however less than 1% of subjects experienced Grade 4 events or greater, and episodes can be managed with corticosteroids. The majority of events were observed in Cycle 1 and in subsequent treatment cycles, cytokine elevations were observed in fewer patients with less intensity, which suggests that availability of target cells is required for pronounced cytokine elevations. In patients with a high tumour burden, pre-Phase treatment with corticosteroids is recommended.

Neurotoxicity was observed in Phase I studies using infusions over 2-4 hours and to mitigate against neurological AEs, and to increase efficacy, subsequent studies used a continuous infusion protocol. The most frequently reported adverse events were tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional state. The majority of neurological events were reversible and all Grade 3 and greater events resolved. In patients who had treatment interruptions due to neurological AEs it is not clear if symptoms recurred on re-starting treatment at the same dose or a reduced dose.

Decreased immunoglobulins were reported in 14.2% of subjects, however in practice, infection in the setting of hypogammaglobulinaemia could be managed using intravenous immunoglobulin replacement therapy.

Similar to other antibody therapies, symptoms of capillary leak occurred in almost half the patients across the program wide pool. The majority of these adverse events were peripheral oedema and hypotension and no fatal adverse events of capillary leak syndrome were reported in any study.

Most other AEs were mild and transient in nature. Overall, blinatumomab at a dose level of up to 28 μg/m^2/24 hours was well tolerated.

9. First round benefit-risk assessment

9.1. Assessment of benefits

The benefits of blinatumomab in the proposed usage are:

- Single agent activity of blinatumomab in Ph-negative relapsed or refractory pre-B ALL patients, with CR/CRh rate 43% (CR 35%), 80% of which occurred after one 28 day cycle.
- MRD to log^{-4} in 61% of CR/CRh responders
- Median OS 6.1 months (95% CI 4.2 to 7.5) in poor risk patients with a historical median OS 3.3 months (95% CI 2.8 to 3.6)
- Durable remissions, with a significant number of patients proceeding to allogeneic HSCT. In the pivotal MT103-211 study, among eligible subjects, 39.5% received an allogeneic HSCT while in remission induced by blinatumomab and without any other subsequent anti-leukaemic medication.

9.2. Assessment of risks

The risks of blinatumomab in the proposed usage are:

- Commonly experienced adverse events associated with T cell mediated cytotoxic activity, including cytokine release, tumour lysis syndrome, infusion reactions, and capillary leak syndrome.
- Neurologic events, including tremor, dizziness, encephalopathy, paraesthesia, aphasia, and confusional states. Approximately 5% of subjects experienced neurologic adverse events that led to study treatment discontinuation, of which encephalopathy accounted for almost half of the discontinuation events.
- B-cell depletion, leading to decreased immunoglobulin levels and increased risk of infections.
- Capillary leak syndrome which can occur in up to 50% of patients and cause hypotension and oedema.

- Requirement for a 28 day continuous infusion per cycle and medication errors related to either the preparation or administration steps of blinatumomab.

9.3. Assessment of benefit-risk balance

The benefit-risk balance of Blincyto, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Based on the clinical data submitted it recommended that the application for Blincyto be approved.

11. Clinical questions

1. Following treatment interruption, did any neurological AEs recur after re-initiating treatment?
2. A third of subjects included in the Study 20120310 analysis received treatment between 1990 and 2000. With the exception of hyperCVAD (mid 1990s), the majority of currently used salvage therapies were not used during this time period: FLAG-Ida was in use after 2000, R hyperCVAD after 2006, BFM 2000 and GMALL 2003. What is the overall CRsg rate and OS for the subgroup which was treated after 2000? Similarly, for the MBMA, what are the CR and DCR rates and OS for studies included after 2000? And how do these compare to results for Study MT103-211?
3. The population PK evaluation by the TGA identified that there is a clear relationship between creatinine clearance and product clearance. The sponsor is requested to justify the lack of recommendation in the PI to dose reduce in patients with renal impairment.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Question 1

Following treatment interruption, did any neurological AEs recur after re-initiating treatment?

12.1.1. Sponsor's response

In patients who interrupted treatment due to neurological events (35 patients), later neurological events (not necessarily the same neurologic event experienced initially) were seen with treatment resumption in 20 patients. Table 38, below, provides a summary of subjects who had interrupted or discontinued treatment due to neurological events, and subjects who had later neurological events.

Table 38: Summary of subjects who had drug interruption/discontinuation due to neurologic events; Adult R/R ALL Studies (Full analysis set)

	MT103-211	MT103-206				Total
	9/28 µg/d (N=189) n (%)	15 µg/m²/d (N=7) n (%)	5/15 µg/m²/d (N = 23) n (%)	5/15/30 µg/m²/d (N=6) n (%)	Total (N=36) n (%)	(N=225) n (%)
Number of subjects who had at least one drug interruption due to a neurologic event - n(%)	29 (15.3)	1 (14.3)	3 (13.0)	2 (33.3)	6 (16.7)	35 (15.6)
Worst Grade of 1 - n(%)[a]	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.7)
Worst Grade of 2 - n(%)[a]	13 (44.8)	0 (0.0)	0 (0.0)	1 (50.0)	1 (16.7)	14 (40.0)
Worst Grade of 3 - n(%)[a]	13 (44.8)	1 (100.0)	3 (100.0)	1 (50.0)	5 (83.3)	18 (51.4)
Worst Grade of 4 - n(%)[a]	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Worst Grade of 5 - n(%)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects who later had neurologic events - n(%)[ab]	15 (51.7)	1 (100.0)	2 (66.7)	2 (100.0)	5 (83.3)	20 (57.1)
Number of subjects who later had drug discontinuation due to neurologic events - n(%)[ab]	3 (10.3)	1 (100.0)	1 (33.3)	0 (0.0)	2 (33.3)	5 (14.3)
Number of subjects who had drug discontinuation due to neurologic events only (without any drug interruption) – n(%)	6 (3.2)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.8)	7 (3.1)

Page 1 of 1

[a]The percentage is based on the number of subjects who had at least one drug interruption due to a neurologic event.
[b]If a subject had multiple drug interruptions due to neurologic events, the first one is used.

12.1.2. Evaluator's response

From the data presented above, a recurrent neurological event was observed in 57% of patients occurring after treatment interruption for a first neurological event. One quarter of the patients with a recurrent event discontinued therapy. The proportion of patients experiencing a recurrent neurological event leading to blinatumomab discontinuation should be reflected in the PI.

12.2. Question 2

A third of subjects included in the Study 20120310 analysis received treatment between 1990 and 2000. With the exception of hyperCVAD (mid 1990s), the majority of currently used salvage therapies were not used during this time period: FLAG-Ida was in use after 2000, R hyperCVAD after 2006, BFM 2000 and GMALL 2003. What is the overall CRsg rate and OS for the subgroup which was treated after 2000? Similarly, for the MBMA, what are the CR and DCR rates and OS for studies included after 2000? And how do these compare to results for Study MT 103-211?

12.2.1. Sponsor's response

The issue of changes in medical practice was carefully considered in designing the historical comparator study. Given the rarity of adult ALL, it was important to include as much historical data that were considered comparable and informative in order to improve the study's statistical precision. The decision on what time period to examine came after consulting with clinical researchers in the European Working Group for Adult ALL and the US. It was their general clinical opinion that no significantly new treatments or improvements for adult relapsed/refractory ALL patients in achieving CR after a relapse had emerged since the 1990s. Approximately 70% of the patients in the historical comparator data were from the Year 2000 and beyond (2000+). It is likely that there have been improvements in supportive care and in recent years, more relapsed/refractory ALL patients are probably receiving hematopoietic stem cell transplantation (HSCT).

There have been improvements in the survival of adults with ALL, primarily due to new protocols for front line ALL therapy and the use of paediatric inspired protocols (in frontline therapy) in younger adults. This improvement in survival trend has been observed in large

population based registries in the US and Germany (Pulte et al 2014[1]). From 2002 to 2006, five-year relative survival estimates increased in Germany and the US by 11.8%and 7.3%, respectively, with overall five-year relative survival being 43.4% in Germany and 35.5% in the US (Pulte et al 2014). However, despite improvements in the front-line treatment setting, at least half of adults who achieve a CR will later relapse, and most adults with relapsed ALL will not respond to currently available therapies (Fielding 2011[2]; Advani 2013[3]). It should be noted that outcomes in relapsed or refractory patients do not inevitably improve over time and can in fact worsen due to improved front line therapy. Paradoxically, the use of improved and aggressive front-line regimens as well as increased use of HSCT may make the remaining relapsed and refractory population more severe and treatment resistant over time. This phenomenon is observed in diffuse large B cell lymphoma (DLBCL) where the front-line addition of rituximab has made the relapsed/refractory population substantially more challenging to treat, with lower response rates (Gisselbrecht et al, 2010[4]).

To address potential changes in complete remission per study group (CRsg) and OS rates over time, several ad-hoc weighted analyses were conducted and are presented in Table 39, below. For CRsg analyses, the original weighted estimate for all data from 1990 to 2013 was 0.24 (95% CI, 0.20, 0.27). When limited to data with patients diagnosed from 2000+, the weighted CRsg was not significantly different at 0.26 (95% CI, 0.21, 0.31). To further evaluate whether there were differences in CRsg over time due to the improvements in treatment over time and not to differences in responses between sites, additional ad-hoc analyses were conducted. In these analyses, the data only included sites that had data in both the earlier and latter time periods (1990 to 1999 and 2000+). In these analyses, no difference in CR between the 2 time periods (CRsg = 0.19 for both time periods) was observed. Thus, the small differences observed in the weighted analyses by time period may be due to improvements in treatment over time, or simply due to differences in sites contributing data over different time periods.

For survival, the weighted median OS for relapsed/refractory ALL patients diagnosed from 2000+ was 3.8 months (95% CI, 3.3 to 4.3 months), compared to 3.3 months (95% CI, 2.8 to 3.6 months) when all data are included.

[1] Pulte d et al 2014 Survival of adults with acute lymphoblastic leukemia in Germany and the United States. PLoS One. 2014;9:e85554

[2] Fielding A 2011 Current therapeutic strategies in adult acute lymphoblastic leukemia. *Hematol Oncol Clin N Am.* 2011;25:1255-1279

[3] Advani A 2013 New immune strategies for the treatment of acute lymphoblastic leukemia: antibodies and chimeric antigen receptors. *Hematology Am Soc Hematol Educ Program*. 2013:131-7

[4] Gisselbrecht et al, 2010 Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010; 28 :4184-4190

Table 39: Weighted analysis of CRsg and OS by calendar period in historical comparator data (Study 20120310)

Study Endpoint	Study Sites Included	Time Period	Outcome Result
CRsg	All sites	1990-2013 (main results)	0.24 (0.20, 0.27)
	Any site with data in 2000+	2000 +	0.26 (0.21, 0.31)
	Limited to sites with data in both study periods (1990-1999 and 2000+)	1990- 1999	0.19 (0.12, 0.27)
		2000 +	0.19 (0.12, 0.25)
Median OS	All sites	1990-2013	3.3 (2.8, 3.6) mon
	Any site with data in 2000+	2000 +	3.8 (3.3, 4.3) mon
	Limited to sites with data in both study periods (1990-1999 and 2000+)	1990-1999	2.4 (1.8, 2.8) mon
		2000+	3.2 (2.7, 3.7) mon

CRsg = complete remission per study group; OS = overall survival

In the weighted analysis of the historical comparator data, a patient's treatment history was categorised into three mutually exclusive groups: patients with a prior history of HSCT, patients with one previous salvage treatment (no HSCT), and patients with 2 or more salvage treatments (no HSCT). The results also emphasise the importance of adjusting for patient severity when comparing historical comparator data results to the results of Study MT103-211. More recent historical comparator data include less severe patients (based on the number of previous salvage therapies received) than earlier historical comparator patient data. The weighted results for recent time periods had CR and OS that were substantially less than the CR and OS observed in the Study MT103-211. It should be noted that even with the weighted results, which accounts for a patient's treatment history as described above, a majority of the recent patients in the historical comparator data had experienced only one line of salvage therapy and only a few patients had three lines or more of salvage therapy whereas in the Study MT103-211 patient population, 39% of subjects received blinatumomab as a third or greater line of salvage therapy. Thus, the full range of the patients' disease severity is not completely accounted for, and some residual confounding remains in the historical comparator analysis that biases estimates of CRsg and OS upwards relative to the experience of Study MT103-211 patients.

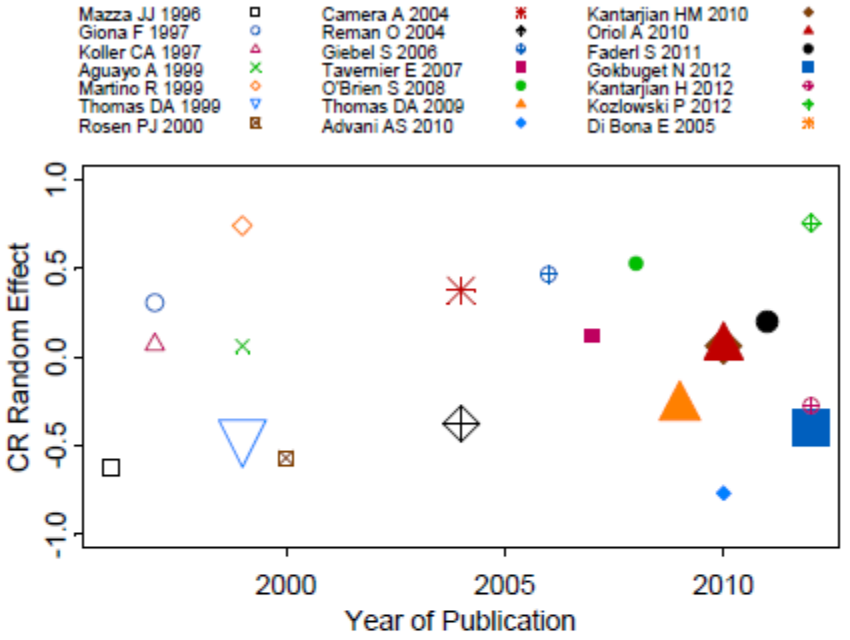
In addition to the evaluation of trends by calendar time periods in the historical comparator data through weighted analyses, as part of the MBMA study (Study 118427), a sensitivity analysis was performed to evaluate the changes in medical practice resulting in improved CR or OS over time. The sensitivity analysis evaluated the unexplained deviation from the predicted CR or OS of each study based on model parameters and patient covariates (that is, the random effect beyond what is explained by the model parameters or differences in patient populations across studies) as a function of publication year (as a result, both the historical comparator study and the MBMA study analysed the impact of the inclusion of studies published in the 90's and early 2000's on CR and OS, and concluded that the impact is not substantial; thus, the current analyses are reasonable (see Figure 38, below)). Within the top panel, CR shows no evidence or trend of improvement in CR with publication year. In the lower panel, OS shows some possible evidence of decreased risk with year, as two recent publications (Kantarjian et al,

2010[5]; Gokbuget et al, 2012[6]) showed the lowest random effect variable. The relapsed patients on first-line chemotherapy in Gökbuget had an unusually high percentage of allogeneic HSCT (75%); significant multivariate covariates for OS included age, time-to-relapse, and salvage response. Otherwise, the salvage treatment plan for Gökbuget subjects was left to the discretion of the investigators. The Kantarjian study subjects were enrolled between 1990 and 2009; no unexpected prognostic factors were identified, and the salvage treatment plan was left to the discretion of the investigators. Allogeneic HSCT in CR was an identified univariate prognostic factor for OS. Overall, the random effect in the OS and CR models across studies is distributed approximately equally above and below 0 demonstrating there is no apparent change in the CR or OS from published studies over time due to improvements in treatment practice. It should be noted that a limitation of this analysis is the publication year is used to reflect the periods of patient treatment, which may be misclassified to some extent in reflecting when patients were actually treated.

As a result, both the historical comparator study and MBMA study analysed the impact of the inclusion of studies published in the 90's and early 2000's on CR and OS, and concluded that the impact is not substantial; thus, when comparing the data from the historical comparator study or from the MBMA study for either the entire time period and from only 2000+, the CR and OS results are still lower than the CR and OS estimates observed in Study MT103-211.

[5] Kantarjian H, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. *Cancer*. 2010;116:5568-5574
[6] Gökbuget N, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors and performance of stem cell transplantation. *Blood*. 2012;120: 2032-2041

Figure 38: Random effects versus year of publication (Study 118427)



Size of the symbol reflects the sample size of the study

12.2.2. Evaluator's response

The evaluator accepts the explanation of the sponsor, the overall effect on the historical comparison is not biased by the inclusion of the earlier studies.

12.3. Question 3

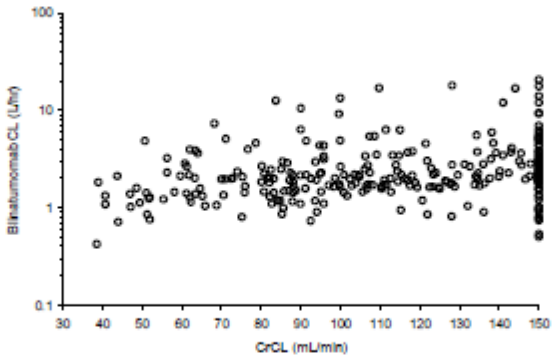
The population PK evaluation by the TGA identified that there is a clear relationship between creatinine clearance and product clearance. The sponsor is requested to justify the lack of recommendation in the PI to dose reduce in patients with renal impairment.

12.3.1. Sponsor's response

Consistent with the population PK evaluation by the TGA, the population PK evaluation conducted by the sponsor also identified creatinine clearance (CrCL) as a significant covariate of blinatumomab clearance (CL). This result is consistent with noncompartmental analysis as presented in the Summary of Clinical Pharmacology.

As described in the SCP, the mean (SD) clearance was 2.92 (2.83) L/h (CV% = 97%) in adult subjects and variability in clearance was substantial over the CrCL range evaluated (see Figure 39, below). No R/R ALL patients with severe renal impairment (CrCL < 30 mL/min) were enrolled in these trials.

Figure 39: Effect of CrCL on blinatumomab CL in subjects with NHL and ALL



Source: Figure 3-13 in the SCP
ALL = acute lymphoblastic leukemia; NHL = non-Hodgkin's lymphoma CL = clearance from non-compartmental analysis;. Creatinine clearance values > 150 mL/min were set to 150 mL/min.

As shown in Figure 39, CL (based on non-compartmental analysis) estimated in subjects with mild and moderate renal impairment (30 mL/min ≤ CrCL < 90 mL/min) were essentially within the range estimated in subjects with normal renal function (CrCL ≥ 90 mL/min). Additionally, based on the population PK analysis, a 50% reduction in CrCL was associated with a 30% reduction in blinatumomab systemic CL. However, the magnitude of the covariate effect is relatively lower than the unexplained between subject variability in blinatumomab pharmacokinetics (up to 96% CV).

Considering that no clinically meaningful impact on efficacy and safety in subjects with moderate renal impairment is expected, dose adjustment for patients with mild and moderate renal impairment is not warranted and posology remains unchanged. There is no information on impact of severe renal insufficiency on the efficacy and safety of blinatumomab in patients with R/R ALL.

12.3.2. Evaluator's response

The clearance mechanism of blinatumomab is not absolutely characterised, but is likely to include proteolysis. The observed effect of creatinine clearance on blinatumomab clearance shown in Figure 39 above is consistent with non-renal clearance and elimination.

However, the evaluator notes the absence of data in patients with severe renal failure.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of blinatumomab in the proposed usage are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of blinatumomab in the proposed usage are unchanged from those identified in the first round assessment of risks.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of blinatumomab, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

It is recommended to the Delegate that blinatumomab be approved for the proposed indication.

15. References

CHMP/EWP/83561/2005 Guideline on Clinical Trials in Small Populations Effective: December 2006

EMA/CHMP/205/95/Rev.4 Guideline on the evaluation of anticancer medicinal products in man Replaces: CPMP/EWP/205/95/Rev.3/Corr (Adopted by TGA June 2006) Effective: 1 April 2014

Mandema J et al. (2011), Model-Based Meta-Analysis for Comparative Efficacy and Safety: Application in Drug Development and Beyond. Clinical Pharmacology & Therapeutics, 90: 766–769.

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