18 January 2019
EMA/847661/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/II/0011

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	antidrug antibody
ADR	adverse drug reaction
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
Ara-C	cytarabine arabinoside
AST	aspartate aminotransferase
ATE	average treatment effect
ATT	average treatment effect of the treated
BEST	Biomarkers, Endpoints, and Other Tools
BiTE	bispecific T-cell engager
BSA	body surface area
CD	Cluster of Differentiation
CI	confidence interval
CIF	cumulative incidence function
cIV	continuous intravenous infusion
CNS	central nervous system
CR	complete response/remission
CR1	first complete remission
CR2	second complete remission
CRh*	complete remission with partial hematologic recovery
CSR	clinical study report
Css	steady state concentration
DCAS	direct comparison analysis set
ECOG	Eastern Cooperative Oncology Group
EMA/EMEA	European Medicines Agency
FAS	full analysis set
GMALL	German Multicenter study Group for Adult Acute Lymphoblastic Leukemia
H0	null hypothesis
HSCT	hematopoietic stem cell transplantation
HSCT Sec EP FAS	HSCT secondary endpoint full analysis set
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IPTW	inverse probability of treatment weight
Key Sec EP FAS	Key Secondary Endpoint Full Analysis Set
KM	Kaplan-Meier
LLoQ	lower limit of quantitation

mAbs	monoclonal antibodies
MHC	major histocompatibility complex
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin’s lymphoma
OS	overall survival
PA	primary analysis
PBRER	Periodic Benefit-risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
Prim EP FAS	Primary Endpoint Full Analysis Set
PSUR	Periodic Safety Update Report
RFS	relapse-free survival
RQ-PCR	real-time quantitative polymerase chain reaction
SAS	safety analysis set
SD	standard deviation
sIPTW	stabilized inverse probability of treatment weight
SmPC	Summary of Product Characteristics
TCR	T–cell receptor
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 8 March 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO;
as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and to update the safety information. The Package Leaflet is updated in accordance.
RMP version 4.0 is included in this submission.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

BLINCYTO was designated as an orphan medicinal product EU/3/09/650 on 24 July 2009, in the following indication: Treatment of acute lymphoblastic leukaemia.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0014/2016 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP P/0014/2016 was not yet completed as some measures were deferred

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on 17 December 2009 (EMEA/CHMP/SAWP/788794/2009). The Protocol Assistance pertained to clinical aspects of the dossier

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
Submission date	8 March 2017
Start of procedure:	25 March 2017
Rapporteur's preliminary assessment report circulated on:	24 May 2017
CoRapporteur's preliminary assessment report circulated on:	29 May 2017
Joint Rapporteur's updated assessment report circulated on:	16 June 2017
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 June 2017
MAH's responses submitted to the CHMP on:	13 October 2017
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 November 2017
Scientific Advisory Group (SAG) oncology	22 November 2017
PRAC RMP advice and assessment overview adopted by PRAC	30 November 2017
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	7 December 2017
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	14 December 2017
MAH's responses submitted to the CHMP on:	23 February 2018
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 March 2018
PRAC RMP advice and assessment overview adopted by PRAC	12 April 2018
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	20 April 2018
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	26 April 2018
MAH's responses submitted to the CHMP on:	26 June 2018
PRAC RMP advice and assessment overview adopted by PRAC	12 July 2018
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 July 2018
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	19 July 2018
An Oral explanation took place on:	24 July 2018
CHMP opinion:	26 July 2018

1.3. Steps taken for the re-examination procedure

Appointed re-examination (Co-)Rapporteurs for the Type II procedure:

Filip Jospehson Jorge Camarero

Timetable	Actual dates
Submission date	18 September 2018
Start of procedure:	16 October 2018
Re-examination CHMP Rapporteur Assessment Report	16 October 2018
Re-examination CHMP Co-Rapporteur Assessment Report	18 October 2019
CHMP and PRAC members comments	26 October 2018
Updated Joint Assessment Report	30 October 2018
SAG experts meeting to address questions raised by the CHMP	8 November 2018
CHMP Opinion	15 November 2018

2. Scientific discussion

2.1. Introduction

Blincyto is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. Treatment with Blincyto is associated with a rapid depletion of peripheral B-cells, accompanied by T-cell activation, and a transient increase in cytokine.

Blincyto is currently authorized for the treatment of adults with Philadelphia chromosome- negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL) in USA (2014) and in EU (2015). The initial approval is conditional, based upon a phase 2 single arm study (MT103-211). The Specific Obligation (SO) of this conditional approval, additional efficacy and safety data from the phase 3 study "Post-authorisation efficacy study (PAES): Study 00103311 (TOWER):A Study of BITE antibody Blincyto versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukemia (ALL)." were submitted on November 2016 to re-evaluate the clinical B/R of Blincyto, to better quantity the magnitude of its treatment effect and to help better differentiate between the AEs associated with Blincyto and those associated with cytotoxic chemotherapy.

This type II variation seeks to broaden the existing Blincyto indication for ALL to include all adult patients with minimal residual disease (MRD) positive B-precursor ALL. For the new proposed indication, the pivotal study MT103-203 is an ongoing phase 2, open-label, single-arm study in adults with MRD-positive B-cell precursor ALL (N=116), which is supported by an exploratory phase 2 study MT103-202 (N=21) and historical comparator study in patients with MRD-positive ALL (study 20120148).

ALL is a rare aggressive cancer of the blood and bone marrow with a prevalence of 23 and 27 per 100,000 persons for the US in 2010 and in the EU in 2008 respectively. In the EU, more than 7200 new cases are diagnosed annually with approximately 40% occurring in adults and the majority are B-lineage, Philadelphia chromosome-negative ALL. The 5-year OS rate in adults is around 30-40%. Although up to 90% of newly diagnosed adult patients with ALL achieve an initial CR, up to 50% of patients experience relapse.

For patients achieving CR, persistence of MRD is the strongest prognostic feature for relapse after achieving CR regardless of treatment choice or risk classification system, and patients who are highly responsive to induction chemotherapy and achieve an MRD level below 1 x 10^{-4} (MRD-negative) have a favourable prognosis. Assessment of MRD is commonly used clinically to evaluate the depth of response, categorize the level of risk of relapse, and to aid in treatment decisions.

Available data have shown that MRD negativity at the end of induction therapy is a strong and independent prognostic indicator for relapse risk, as highlighted by NCCN in its recommendation for MRD assessment. However, clinical evidence is still too limited to consider MRD negativity as a validated surrogate primary endpoint of clinical benefit especially in a small single-arm pivotal trail. Indeed, as yet, no randomized and controlled studies had established that a treatment effect on MRD could quantitatively explain a treatment effect in terms of validated endpoints such as EFS or OS**.**

The efficacy of Blincyto in the claimed extension of indication is "treatment of patients with MRD-positive B-cell precursor ALL", is based on data from one pivotal phase 2, open-label, single-arm study (MT103-203) in adult subjects with MRD-positive B-cell precursor ALL (N=116); further supported by Study MT103-202, a phase 2, open-label, single-arm study in adult subjects with MRD-positive B-cell precursor ALL (N=21). Rate of MRD response was the primary endpoint in both the MT103-202 and MT103-203 studies. A patient-level historical comparator study (Study 20120148) and a Propensity Score Analysis were also conducted to substantiate the relevance of the single-arm trial data from Study MT103-203 in adult subjects with MRD-positive B-cell precursor ALL.

There were several scientific advices for Blincyto in the treatment of patients with MRD-positive ALL on clinical aspects (CHMP Protocol assistance EMEA/CHMP/SAWP/788794/2009, 17/12/2009).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Table 1: Overview of Blincyto Clinical and Historical Studies in Adult Subjects With MRD-positive B-cell Precursor ALL

Study Number	Description	Population	Nb of Subjects Enrolled (Planned)	Status
MT103-203	Phase 2, open-label, multicenter single-arm	Adults in complete hematologic remission with MRD from B-cell precursor ALL	116	Treatment Completed: Long-term Follow-up Ongoing (5 year) Primary Analysis: February 2014 Secondary Analysis (18 month follow-up): August 2015 Final Analysis Planned: Quarter 1, 2019

MT103-202[a]	Phase 2, open-label, multicenter single-arm	Adults in complete hematologic remission with MRD from B-cell precursor ALL	21	Study Completed Primary Analysis: April 2010 Final Analysis: November 2014
20120148	Non-interventional, retrospective analysis	Adults in complete hematologic remission with MRD from Ph- B-cell precursor ALL	287	Study Completed
Propensity Score Analysis (203-148)	Non-interventional, retrospective propensity score analysis	Adults in complete hematologic remission with MRD from Ph- B-cell precursor ALL	255	Study Completed

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new dose-response studies have been submitted. For the treatment of MRD-positive ALL, in both studies MT103-203 and MT103-202, Blincyto was administrated as a continuous IV infusion at a body surface area (BSA)-based dose of 15 µg/m2/day for 4 weeks followed by a 2-week infusion-free interval.

The proposed posology is a fixed dose regimen of 28µg/day (4weeks on / 2 weeks off) and patients may receive 1 cycle of induction and 3 additional cycle of Blincyto consolidation treatment.

2.4.2. Main study

Study MT103-203 "A confirmatory multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody Blincyto in adult patients with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukemia"

Methods

This is a pivotal, open-label, multicentre, single arm, uncontrolled phase 2 study to support the efficacy of Blincyto in patient with MRD positive B-precursor ALL. It was conducted at 46 centers in Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Romania, Russia, Spain, and the United Kingdom

A primary analysis CSR for this study was generated on 24 September 2014 (cut-off date: 21 February 2014). Since that time, a secondary analysis was completed and a CSR generated on 28 January 2016 with more mature time-to-event data when all subjects had the opportunity to complete the 18 month follow-up period (cut-off date for the secondary analysis: 05 August 2015). The long-term follow-up of this study is still ongoing; the final analysis is planned after all subjects had the opportunity to be followed for 5 years from the start of Blincyto therapy expected for quarter 1 2019.

Study participants

Key inclusion criteria

1. Patients aged ≥18 years with B–precursor ALL in complete hematological remission defined as less than 5% blasts in bone marrow after at least three intense chemotherapy blocks (e.g., GMALL induction I-II/consolidation I, induction/intensification/consolidation or three blocks of Hyper CVAD)*

2. Presence of MRD at a level of ≥10-3 (molecular failure or molecular relapse) in an assay with a minimum sensitivity of 10-4 documented after an interval of at least 2 weeks from last systemic chemotherapy

3. For evaluation of MRD, patients must have a at least one molecular marker based on individual rearrangements of immunoglobulin or TCR-genes or a flow cytometric marker profile evaluated by a national or local reference lab approved by the Sponsor

4. Bone marrow or peripheral blood specimen from primary ALL diagnosis /diagnosis of ALL relapse (a sufficient amount of DNA or a respective amount of cell material) for clonespecific MRD assessment must be received by central MRD lab and lab must confirm that the sample is available

5. Bone marrow function as defined below: ANC (Neutrophils) ≥ 1,000/µL, Platelets ≥ 50,000/µL (transfusion permitted), HB level ≥ 9g/dl (transfusion permitted)

6. Renal and hepatic function: AST (GOT), ALT (GPT), and AP < 2x upper limit of normal (ULN), Total bilirubin <1,5xULN, Creatinine clearance ≥50mL/min (calculated e.g. according Cockroft & Gault)

7. Negative HIV test, negative hepatitis B (HbsAg) and hepatitis C virus (anti-HCV) test

8. Negative pregnancy test in women of childbearing potential

9. ECOG Performance Status 0 or 1

Key Exclusion Criteria

1. Presence of circulating blasts or current extra-medullary involvement by ALL

2. History of relevant CNS pathology or current relevant CNS pathology (e.g. seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder)

3. Current infiltration of cerebro-spinal fluid by ALL

4. History of or active relevant autoimmune disease

5. Prior allogeneic HSCT

6. Eligibility for treatment with TKIs (i.e., Philadelphia chromosome-positive (Ph) patients with no documented treatment failure of or intolerance/contraindication to at least 2 TKIs)

7. Systemic cancer chemotherapy within 2 weeks prior to study treatment (except for intrathecal prophylaxis)

8. Radiotherapy, therapy with monoclonal antibodies (rituximab, alemtuzumab) or any investigational product with within 4 weeks prior to study treatment

9. Autologous hematopoietic stem cell transplantation (HSCT) within six weeks prior to study treatment

10. Previous treatment with Blincyto

11. Active infection, any other concurrent disease or medical condition that are deemed to interfere with the conduct of the study as judged by the investigator

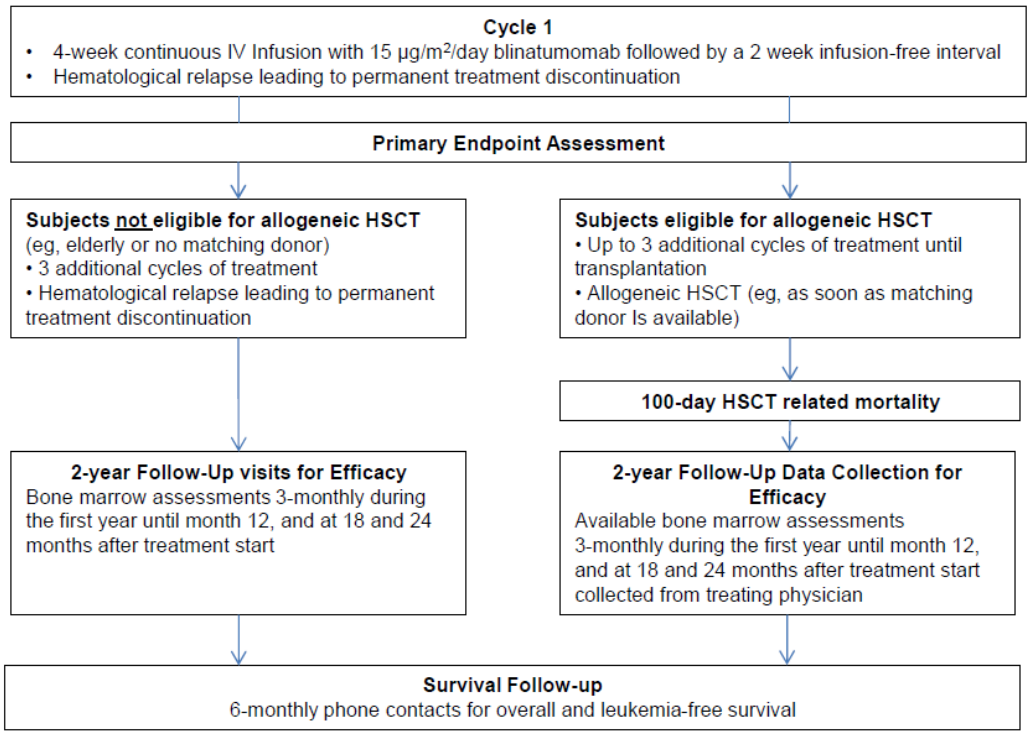
Treatments

Subjects received at least 1 and up to 4 consecutive cycles of Blincyto. A cycle consisted a cIV infusion at a dose of 15µg/m2/day at a constant flow rate over 28 days per treatment cycle followed by an infusion-

free period of 14 days, which may be prolonged for up to 7 days if necessary. Subjects in haematological remission generally were expected to receive 4 cycles of treatment. In the event of haematological relapse within the treatment period, Blincyto was terminated.

Upon completion of 1 cycle of treatment, all subjects were assessed for MRD response. The study design is presented below.

Figure 8-1. Study Design for Study MT103-203



The core study was defined as follows: completing the day 29 visit of 4 cycles for subjects not proceeding to HSCT and completing of at least day 29 of cycle 1 for subjects proceeding to HSCT. Efficacy follow-up visits including bone marrow assessment occurred at months 9, 12, 18 and 24 months after the start of treatment, then survival follow-up visits by phone every 6 months until year 5.

Prior and concomitant therapies

Cerebrospinal fluid (CSF) prophylaxis by intrathecal triple combination (dexamethasone 4mg or equivalent, methotrexate 15mg, cytosine arabinoside 40mg) prior to C1, at the end of C2 and C4; also every 3months after until at least M18 for subject who did not undergo HSCT.

Before the start of each cycle on day1 a corticosteroid (prednisone 100mg IV or equivalent) was given. In case of neurologic event oral dexamethasone was administered at a dose of at least 24mg/day for up to 3days and an appropriate prophylactic anticonvulsant treatment in case of seizure.

Objectives

The primary Objective is to evaluate the efficacy of Blincyto to induce complete MRD response

The key Secondary Objective is to evaluate the effect of Blincyto on hematological relapse for subjects with Ph-negative ALL.

Other Secondary Objectives are:

- to evaluate the overall survival in subjects with ALL treated with Blincyto

- to evaluate the effect of Blincyto on 100-day mortality rate associated with allogeneic HSCT

- to evaluate the safety and tolerability of Blincyto

- to evaluate the effect of Blincyto on duration of MRD negativity

- to evaluate the effect of Blincyto on the kinetics of MRD

- to evaluate subject's quality of life during and after therapy

- to evaluate resource utilization

An exploratory Objective is to assess potential biological predictors of response to Blincyto

Outcomes/endpoints

The primary efficacy endpoint of the study was the proportion of subjects who achieved a complete MRD response defined by the absence of MRD after 1 cycle of treatment with Blincyto evaluated by the central MRD laboratory (University of Kiel, Germany). Evaluation of MRD was performed on bone marrow (BM) aspirate specimens. A second bone marrow sample may have been collected in the case that the first specimen did not clearly reveal a complete MRD response. This second sample was considered confirmatory for the primary endpoint of complete MRD response.

At baseline, subjects were potentially eligible for enrolment based on the finding of MRD at a level of≥ 10-3 at the local laboratory. An aliquot of ≥ 5 mL of BM was required for the baseline central MRD review.

After each treatment cycle (day 29) and during the efficacy follow-up visits, a BM aspiration/biopsy was performed by the local laboratory to evaluate the degree of BM infiltration defined by the percentage of leukemic blasts in BM (as per cytological assessment). Furthermore, in the event of abnormal blood counts (suggesting leukemic relapse), a BM evaluation should have been performed prior to initiating the subsequent cycle of treatment with Blincyto.

Definitions of Treatment Response Evaluation

Complete MRD: No PCR amplification of individual rearrangements of Ig- or TCR-genes was detected after completion of the first cycle. All subjects with established PCR based MRD assay who had been treated with Blincyto within the first cycle and had a post-treatment BM sample obtained at the end of infusion of cycle 1 were evaluable for MRD response assessment.

MRD Relapse: Reappearance of individual rearrangements of Ig- or TCR-genes ≥ lower limit of quantification (LLOQ) (usually 10-4) for at least 1 individual marker measured by an assay with a sensitivity of minimum 10-4 in subjects who had achieved MRD response.

MRD Progression: The increase in the MRD level by 1 log as compared to the baseline level, which is equal to a 10-fold increase in the number of MRD cells.

Sample size

The sample size estimation for the primary efficacy endpoint "proportion of patients who achieve complete MRD response after one cycle of treatment with Blincyto" was based on Fleming's standard single-stage procedure but using the exact binomial distribution. The following statistical hypotheses for the primary efficacy endpoint was tested in this clinical study: H0: $\pi \leq p0$ vs H1: $\pi \geq p1$

The sample size parameters for this endpoint was p0 = 44%, p1 = 61%, a one-sided type I error of 2.5% and a power of 90%. p0, the MRD response probability, which, if true, meant that Blincyto was not worth

studying further, was estimated to be not higher than 44%. The future use of Blincyto would be of considerable interest if the true MRD response probability (π) was 61% or higher (p1).

According to these parameters, 100 patients were required, i.e. the study had a 90% power of demonstrating that the 97.5% one-sided exact confidence interval for the MRD response rate excluded 44% (p0) if the true unknown response rate was 61% (p1). If the study concluded with at least 55 out of 100 patients (55%) showing a complete MRD response after one cycle of treatment with Blincyto, one was able to reject H0.

EMA scientific advice suggested that recruitment of more patients would be desirable if they could be recruited in the planned time frame. Thus, if the recruitment rate was higher than currently anticipated, up to 130 evaluable patients might be recruited. In case more than 100 evaluable patients were recruited in this study the following parameters would be adjusted for the primary efficacy endpoint:

N=110 patients: H0 could be rejected with 60/110 (=55%) of MRD negative patients

N=120 patients: H0 could be rejected with 64/120 (=53%) of MRD negative patients

N=130 patients: H0 could be rejected with 69/130 (=53%) of MRD negative patients

The sample size determination for the Key Secondary Efficacy Endpoint has been performed based on assumptions of historical data. Currently available historical data of 80 patients showed that 14 out of 80 patients (17.5%) were hematological relapse-free after one year. In a conservative manner this data was used for the estimates of the 18-month time point. A two-sided 95% confidence interval of this rate had an upper limit of 28%. Thus, it was considered clinically meaningful, if patients treated with Blincyto had a probability of at least 28% to be hematological relapse-free after 18 months (i.e. if the lower limit of the 95% confidence interval for the rate of hematological relapse-free patients observed in this study was at 28% or higher).

The statistical concept for analyzing the key secondary endpoint was based on the Kaplan-Meier estimates (product-limit estimator) of hematological relapse at 18 months from start of treatment with Blincyto. The following statistical hypotheses for the key secondary endpoint were tested in this clinical study: H0: $\pi \leq p0$ vs H1: $\pi \geq p1$

Power calculation for the key secondary endpoint with a p0 of 28% and a one-sided type one error of 2.5% was done by simulation based on sampling from an exponential distribution. For rates of patients without hematological relapse after 18 months between 48% and 55% (p1), 10,000 trials were generated with a random drop-out-probability rate of 10% and with varying rates for HSCT (60%, 67% and 75%). If available, the onset of HSCT was simulated after 1.5 months on study from an exponential distribution with a median time to transplant of 1.5 months. This would insure no transplant earlier than 1.5 months after initiation of Blincyto and most of the transplant occurring during the first 6 months. The rate of significant trials among 10,000 repetitions [i.e. trials where the lower boundary of the two-sided 95% Greenwood confidence interval was above 28%] calculated as the power under the respective rates. Accordingly, this study would have a 90% power of demonstrating that the lower boundary of the 95% confidence interval (based on Greenwood's formula, Collett, 2003) for the Kaplan-Meier point estimate of the RFS rate at 18 months excludes 28% (p0) if the true unknown rate of patients without hematological relapse at 18 months is 55% (p1) and if the HSCT availability rate was not >67%. Under these assumptions, if the observed KM rate at 18 months was approximately 43%, one would be able to reject H0.

Randomisation

This was a single-arm, uncontrolled study.

Blinding (masking)

This was an open-label study.

Statistical methods

The primary analysis was performed with all data available at the time when all patients had the opportunity to be evaluated for the primary efficacy endpoint i.e. complete MRD response after the first treatment cycle (cut-off date: 21 February 2014). An updated analysis focusing on the key secondary endpoint was carried out after all subjects had been transplanted, relapsed, died or had 18 months of follow-up (cut-off date: 05 August 2015). The final analysis will be carried out 5 years after the last patient has been enrolled (last patient last visit expected in January 2019).

Analysis Sets were*:*

Analysis of Safety Endpoints (FAS): All subjects who received any infusion of Blincyto (intention-to-treat principle in single-arm open-label studies).

Primary endpoint full analysis set (**Prim EP FAS**): all subjects with an Ig or TCR PCR MRD assay with the minimum required sensitivity of 1 x 10-4 at central lab established at baseline.

Primary endpoint efficacy set (**Prim EP Efficacy Set**): subjects in prim EP FAS above, in hematological complete remission (CR) at treatment start, with MRD level ≥ 1 x 10-3 as per central lab at screening baseline and 1 follow up sample in cycle 1 at central lab available unless samples are not available due to discontinuation because of a Blincyto-related adverse event or disease progression/relapse

Primary endpoint per protocol set (**Prim EP PPS**): subjects in Prim Efficacy Set above and who did not have any major relevant protocol violation which could have an impact on the primary efficacy endpoint (initial and early stage protocol violations)

Key secondary endpoint full analysis set (**Key Sec EP FAS**): all subjects from the FAS excluding Philadelphia-positive subjects and in hematological CR at treatment start

Key secondary endpoint per protocol set (**Key Sec EP PPS**): subjects in Key Sec EP FAS above and who did not have any major relevant protocol violation which could have an impact on the key secondary efficacy endpoint (late stage protocol violations.)

HSCT secondary endpoint full analysis set (**HSCT Sec EP FAS**): all subjects from FAS who underwent HSCT prior to relapse (hematological or extramedullary) excluding Philadelphia-positive subjects

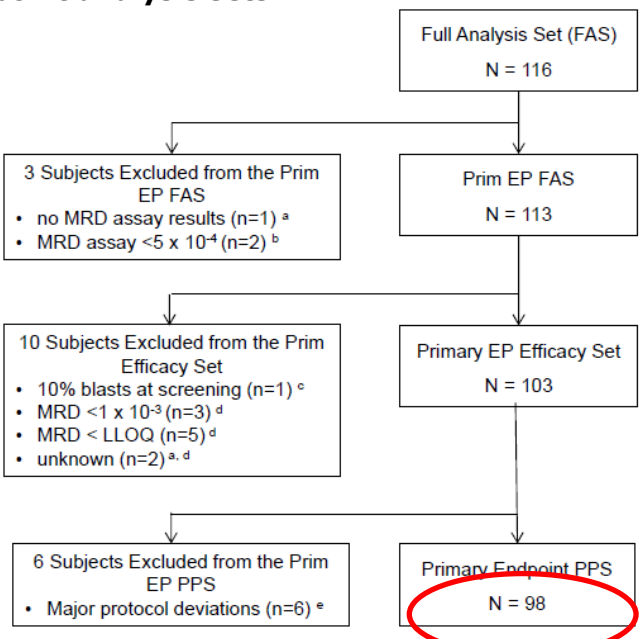
HSCT secondary endpoint per protocol set (**HSCT Sec EP PPS**): as HSCT Efficacy Set above and who did not have any major relevant protocol violation which could have an impact on the key secondary efficacy endpoint (late stage protocol violations)

Secondary endpoint per protocol set (Sec EP PPS): as FAS and in hematological CR at treatment start who did not have any major relevant protocol violation which could have an impact on the key secondary efficacy endpoint (late stage protocol violations)

Results

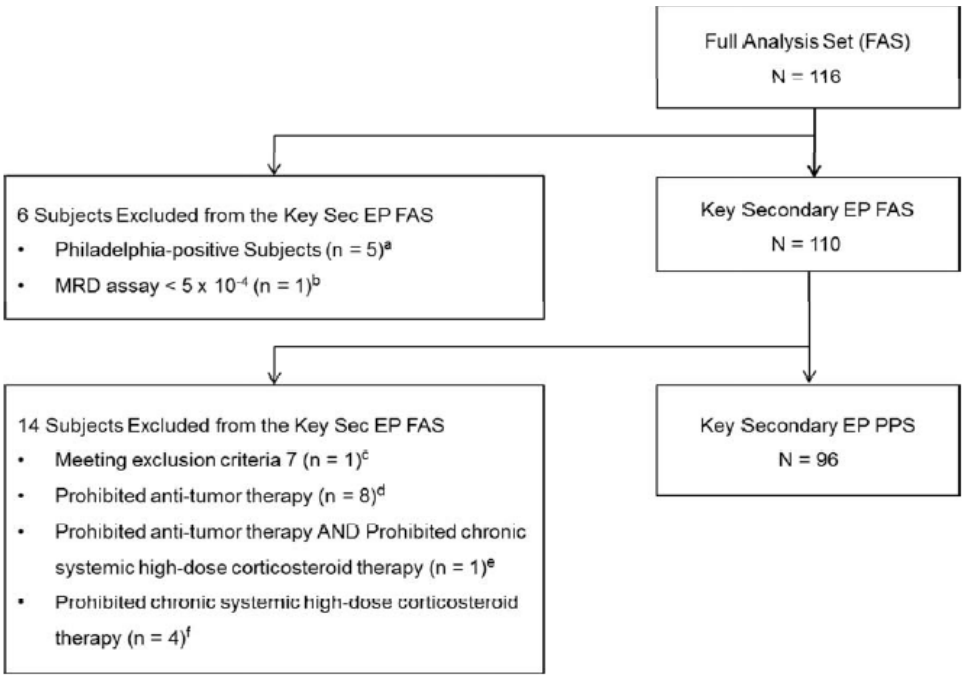
Participant flow

Figure 1: Primary endpoint analysis sets



FAS = full analysis set; EP = endpoint; LLOQ = lower limit of quantification; MRD = minimal residual disease; Prim = primary; PPS = per protocol set
[a] Subject 1311-004
[b] Subject 1301-002 and Subject 1407-005
[c] Subject 1018-002
[d] Table 14-2.2 (MRD level at baseline by central lab)
[e] Listing 16-2.2.3; Subject 1303-005 was already excluded from the Prim Efficacy FAS (MRD < LLOQ)

Figure 2: key secondary endpoint analysis sets



EP = endpoint; FAS = full analysis set; Key Sec = key secondary; MRD = minimal residual disease; PPS = per protocol set

Recruitment

This study was conducted at 46 centers in Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Romania, Russia, Spain, and the United Kingdom.

Date of first subject enrolled: 30 November 2010

Date cutoff date for primary efficacy: 21 February 2014

Conduct of the study

The Applicant stated that the study was conducted in accordance with ICH Guidelines for GCP.

Protocol amendments

The original study protocol was dated on 22 April 2010 and was subsequently amended 6 times. The implemented changes are summarized below:

Table 2: Summary of protocol amendments.

Amendment	Major Changes
Global Protocol Version 1.0 22 April 2010 (1 subject enrolled under this protocol version)	Not applicable
Protocol Version 2.0_DE/Local Amendment 1.0 (Germany) 07 July 2010 (9 subjects enrolled under this protocol version)	• Update exclusion criteria #14 (malignancy) per Paul-Ehrlich-Institute
Global Amendment 1.0 04 February 2011 Implemented in Global Protocol 2.0_global and 3.0_DE (see below)	• Update storage and stability information • Update to labeling information
Global Protocol Version 2.0_DE/3.0 DE/ Global Amendment 2.0 04 July 2011 (45 subjects enrolled under this protocol version)	• Add collection of blinatumomab immunogenicity sample • Update known and potential benefits and risks • Implement prescreening for early detection of MRD • Update MRD assay requirements • Update inclusion criteria #4 (diagnosis of ALL) • Update labeling information • Update storage and stability information • Update preparation of drug product • Update safety follow-up for subjects who undergo HSCT • Update early termination • Update definitions in drug safety • Add information regarding legal and ethical requirements and protocol amendments • Clarify the following: duration of subject participation, intense chemotherapy, informed consent, writing test, examination of CSF, selected sites for ECG and PK assessments • Implement minor administrative changes and update references and contacts
Global Amendment 3.0 17 February 2012	• Add a provision to implement additional urgent safety measures in case of neurologic-related adverse events • Change contact details for drug safety department and safe reporting • Adapt patient information and informed consent form

Global Protocol Version 3.0/4.0_DE/ Global Amendment 4.0 11 July 2012 (61 subjects enrolled under this protocol version)	• Update assessment schedule • Update list of contacts • Update known and potential benefits and risks • Add a provision to restart drug at a lower dose in the case of neurologic-related adverse events • Add C-reactive Protein testing • Clarify the following: retreatment cycles, efficacy assessments, hospitalization, discontinuation criteria, use of premedication, MRD sample requirements, assessment for neurologic-relate adverse events, reporting periods for adverse events, safety reporting procedures
Global Amendment 05 06 March 2014 Amendment after end of recruitment	• Amend the key secondary objective/endpoint
Global Protocol Version 5.0_DE/ Global Amendment 06 13 June 2014 Amendment after end of recruitment	• Harmonize the description of the blinatumomab and its preparation with the Investigator's Brochure and other clinical trials within the blinatumomab clinical development program

ALL = acute lymphoblastic leukemia; CSF = cerebrospinal fluid; ECG = electrocardiogram; HSCT = hematopoietic stem cell transplant; MRD = minimal residual disease; PK = pharmacokinetic

A number of changes were made to the initial SAP including: Clarifications that the key secondary endpoint would be reported after all subjects have been transplanted, relapsed, died, or had 18 months of follow-up; update of analyses sets and the definitions of the primary and key secondary endpoints ; addition of the analysis of HSCT secondary endpoint set ; updates to the planned analyses, protocol violations, type and number of tables, listings, and graphs; addition of definition of a completed cycle and haematological relapse, the covariate of MRD level at baseline, details regarding 100-day mortality, ECG analysis, more details regarding PK analysis, and events of interest (EOIs).

Protocol deviations and treatment compliance

Overall, 46.6% (54/116) of subjects had at least 1 relevant protocol violation during enrollment. Six subjects had protocol violations that led to exclusion from the Prim EP PPS set: 3 subjects received systemic chemotherapy within 2 weeks prior to Blincyto treatment; 2 subjects received a prohibited, chronic, systemic high-dose corticosteroid before an MRD assessment; 1 subject received a prohibited anti-tumor therapy before an MRD assessment.

Table 3: Summary of relevant protocol violations

	Full Analysis Set (N = 116) n (%)
Number of subjects with at least one relevant protocol violation	54 (46.6)
Other	31 (26.7)
Not fullfilling Inclusion / Exclusion criteria	11 (9.5)
Treatment not administered per protocol	11 (9.5)
Assessment not done	7 (6.0)
Assessment not done per protocol	7 (6.0)
Forbidden medication	5 (4.3)
Visit out of schedule	1 (0.9)

CRF = case report form; N = Number of subjects in the analysis set.
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

Baseline data

Table 4: Baseline demographics

	Full Analysis Set (N = 116)
Sex - n (%)	
Male	68 (58.6)
Female	48 (41.4)
Race - n (%)	
White	102 (87.9)
Asian	1 (0.9)
Other (mixed)	1 (0.9)
Unknown	12 (10.3)
Age (years)	
n	116
Mean	44.6
SD	16.4
Median	45.0
Q1, Q3	29.5, 60.5
Min, Max	18, 76
Age Group - n (%)	
≥ 18 and < 35 years	36 (31.0)
≥ 35 and < 55 years	41 (35.3)
≥ 55 and < 65 years	24 (20.7)
≥ 65 years	15 (12.9)

Table 5: Baseline disease characteristics

	Full Analysis Set (N = 116)
Philadelphia chromosome disease status - n (%)	
Positive	5 (4.3)
Negative	111 (95.7)
Confirmed t(4;11) translocation / MLL-AF4+ ALL - n (%)	
Yes	5 (4.3)
No	88 (75.9)
Unknown	23 (19.8)
Risk Stratification based on local/national standards - n (%)	
Standard	61 (52.6)
Low	2 (1.7)
Intermediate	5 (4.3)
High	36 (31.0)
Very high	5 (4.3)
Unknown	7 (6.0)
Relapse history - n (%)	
Patients in 1st CR	75 (64.7)
Patients in 2nd CR	39 (33.6)
Patients in 3rd CR	2 (1.7)
Subject in CR per Cheson criteria - n (%)	
Patients in CR (BM blast ≤5% & ANC >1,000/mm^3 & Platelets >100,000/mm^3)	85 (73.3)
Patients not in CR per Cheson criteria	31 (26.7)
MRD level at baseline by central lab - n (%)	
≥10xE-1 and <10xE0	9 (7.8)
≥10xE-2 and <10xE-1	45 (38.8)
≥10xE-3 and <10xE-2	52 (44.8)
<10xE-3	3 (2.6)
Below LLOQ	5 (4.3)
Unknown	2 (1.7)

WBC at first diagnosis - n (%)	
≤30,000/mm^3	78 (67.2)
>30,000/mm^3	18 (15.5)
Unknown	20 (17.2)
WBC at screening - n (%)	
≤30,000/mm^3	116 (100.0)
>30,000/mm^3	0 (0.0)
Chemoresistance after the first week of chemotherapy - n (%)	
Yes	8 (6.9)
No	5 (4.3)
Unknown	103 (88.8)
Need of a second induction course (salvage) for complete haematological remission - n (%)	
Yes	38 (32.8)
No	77 (66.4)
Unknown	1 (0.9)
Previous anti-tumor radiotherapies - n (%)	51 (44.0)
Time from last anti-leukaemia treatment to first dose of blinatumomab (months)	
n	116
Mean	5.0
SD	8.9
Median	2.0
Q1, Q3	1.4, 3.7
Min, Max	0, 55
Time from last anti-leukaemia treatment to first dose of blinatumomab - n (%)	
<1 month	7 (6.0)
≥1 – <4 months	81 (69.8)
≥4 – <7 months	12 (10.3)
≥7 months	16 (13.8)
Time from diagnosis to first dose of blinatumomab (months)	
n	116
Mean	20.4
SD	31.0
Median	8.1
Q1, Q3	5.1, 22.9
Min, Max	3, 206

N=Number of subjects in the analysis set. CR=Complete remission. MRD=Minimal residual disease. LLOQ=Lower limit of quantification. WBC=White blood cell.

Table 6: Previous anti-tumour drug treatment

Characteristic Category	Full Analysis Set (N=116)
Maximum line of therapy	
Front line treatment	75 (64.7)
First relapse treatment	39 (33.6)
Second relapse treatment	2 (1.7)
Front line treatment	116 (100.0)
Pre-phase	80 (69.0)
GMALL	44 (37.9)
combination of regimen /other	14 (12.1)
GMALL elderly	11 (9.5)
GRAALL	8 (6.9)
UKALL	7 (6.0)
GIMEMA	6 (5.2)
PETHEMA	5 (4.3)
FLAG-Ida	4 (3.4)
NILG	4 (3.4)
TKI	4 (3.4)
FRAALLE	3 (2.6)
Hyper-CVAD	3 (2.6)
iBFM	3 (2.6)
AIEOP	2 (1.7)
HOVON	2 (1.7)
ALL-2009	1 (0.9)
ALL-2009 elderly	1 (0.9)
EWALL elderly	1 (0.9)
GRAAPH	1 (0.9)
LALA94	1 (0.9)
Romanian Group for ALL	1 (0.9)

The baseline demographics and characteristics for subjects who received an HSCT compared to those subjects that did not receive HSCT are presented in the Table below:

Table 7: Baseline characteristics and HSCT FAS

	Subjects who received HSCT before relapse or never relapsed (N = 76)	Subjects who received HSCT after relapse (N = 14)	Subjects who did not receive HSCT (N = 26)
Sex - n (%)			
Male	47 (61.8)	10 (71.4)	11 (42.3)
Female	29 (38.2)	4 (28.6)	15 (57.7)
Race - n (%)			
White	67 (88.2)	14 (100.0)	21 (80.8)
Asian	1 (1.3)	0 (0.0)	0 (0.0)
Other (mixed)	0 (0.0)	0 (0.0)	1 (3.8)
Unknown	8 (10.5)	0 (0.0)	4 (15.4)
Age (years)			
n	76	14	26
Mean	42.3	39.8	53.8
SD	14.8	16.3	17.9
Median	42.5	36.0	60.5
Q1, Q3	28.5, 56.0	30.0, 54.0	41.0, 67.0
Min, Max	18, 67	19, 68	21, 76
Age Group - n (%)			
≥ 18 and < 35 years	24 (31.6)	6 (42.9)	6 (23.1)
≥ 35 and < 55 years	32 (42.1)	5 (35.7)	4 (15.4)
≥ 55 and < 65 years	16 (21.1)	1 (7.1)	7 (26.9)
≥ 65 years	4 (5.3)	2 (14.3)	9 (34.6)

Table 14-4.7.4. Baseline Disease Characteristics and HSCT
FAS

	Subjects who received HSCT before relapse or never relapsed (N = 76)	Subjects who received HSCT after relapse (N = 14)	Subjects who did not receive HSCT (N = 26)
Philadelphia chromosome disease status - n (%)			
Positive	2 (2.6)	1 (7.1)	2 (7.7)
Negative	74 (97.4)	13 (92.9)	24 (92.3)
Confirmed t(4;11) translocation / MLL-AF4+ ALL - n (%)			
Yes	4 (5.3)	1 (7.1)	0 (0.0)
No	60 (78.9)	11 (78.6)	17 (65.4)
Unknown	12 (15.8)	2 (14.3)	9 (34.6)
Risk Stratification based on local/national standards - n (%)			
Standard	43 (56.6)	7 (50.0)	11 (42.3)
Low	2 (2.6)	0 (0.0)	0 (0.0)
Intermediate	1 (1.3)	1 (7.1)	3 (11.5)
High	22 (28.9)	5 (35.7)	9 (34.6)
Very high	4 (5.3)	0 (0.0)	1 (3.8)
Unknown	4 (5.3)	1 (7.1)	2 (7.7)
Relapse history - n (%)			
Patients in 1st CR	55 (72.4)	4 (28.6)	16 (61.5)
Patients in 2nd CR	21 (27.6)	10 (71.4)	8 (30.8)
Patients in 3rd CR	0 (0.0)	0 (0.0)	2 (7.7)
Subject in CR per Cheson criteria - n (%)			
Patients in CR (BM blast ≤5% & ANC >1,000/mm^3 & Platelets >100,000/mm^3)	56 (73.7)	11 (78.6)	18 (69.2)
Patients not in CR per Cheson criteria	20 (26.3)	3 (21.4)	8 (30.8)
MRD level at baseline by central lab - n (%)			
≥10xE-1 and <10xE0	7 (9.2)	0 (0.0)	2 (7.7)
≥10xE-2 and <10xE-1	27 (35.5)	5 (35.7)	13 (50.0)
≥10xE-3 and <10xE-2	36 (47.4)	8 (57.1)	8 (30.8)
<10xE-3	2 (2.6)	0 (0.0)	1 (3.8)
Below LLOQ	3 (3.9)	1 (7.1)	1 (3.8)
Unknown	1 (1.3)	0 (0.0)	1 (3.8)
WBC at first diagnosis - n (%)			
≤30,000/mm^3	51 (67.1)	6 (42.9)	21 (80.8)
>30,000/mm^3	9 (11.8)	6 (42.9)	3 (11.5)
Unknown	16 (21.1)	2 (14.3)	2 (7.7)
WBC at screening - n (%)			
≤30,000/mm^3	76 (100.0)	14 (100.0)	26 (100.0)
>30,000/mm^3	0 (0.0)	0 (0.0)	0 (0.0)
Chemoresistance after the first week of chemotherapy - n (%)			
Yes	6 (7.9)	1 (7.1)	1 (3.8)
No	3 (3.9)	1 (7.1)	1 (3.8)
Unknown	67 (88.2)	12 (85.7)	24 (92.3)
Need of a second induction course (salvage) for complete haematological remission - n (%)			
Yes	25 (32.9)	6 (42.9)	7 (26.9)
No	50 (65.8)	8 (57.1)	19 (73.1)
Unknown	1 (1.3)	0 (0.0)	0 (0.0)

Previous anti-tumor radiotherapies - n (%)	36 (47.4)	8 (57.1)	7 (26.9)
Time from last anti-leukaemia treatment to first dose of blinatumomab (months)			
n	76	14	26
Mean	4.9	1.8	6.9
SD	7.7	1.0	13.3
Median	2.0	1.7	2.1
Q1, Q3	1.4, 4.3	1.2, 2.5	1.5, 4.8
Min, Max	1, 41	0, 4	1, 55
Time from last anti-leukaemia treatment to first dose of blinatumomab - n (%)			
<1 month	5 (6.6)	2 (14.3)	0 (0.0)
≥1 – <4 months	51 (67.1)	11 (78.6)	19 (73.1)
≥4 – <7 months	8 (10.5)	1 (7.1)	3 (11.5)
≥7 months	12 (15.8)	0 (0.0)	4 (15.4)
Time from diagnosis to first dose of blinatumomab (months)			
n	76	14	26
Mean	22.0	12.5	20.0
SD	36.2	9.0	20.3
Median	7.5	9.6	9.4
Q1, Q3	5.0, 23.2	4.9, 21.9	7.2, 28.9
Min, Max	3, 206	3, 30	3, 69

N=Number of subjects in the analysis set. CR=Complete remission. MRD=Minimal residual disease. LLOQ=Lower limit of quantification. WBC=White blood cell.

Numbers analysed

A total of 211 subjects were screened, 116 subjects received at least 1 infusion of Blincyto and were included in the FAS.

Table 8: Analysis sets

	All Patients Dosed With Blinatumomab (N = 116)
Full analysis set	116 (100.0)
Primary endpoint full analysis set (Prim EP FAS)	113 (97.4)
Primary endpoint efficacy set (Prim EP Efficacy Set)	103 (88.8)
Primary endpoint per protocol set (Prim EP PPS)	98 (84.5)
Key secondary endpoint full analysis set (Key Sec EP FAS)	110 (94.8)
Key secondary endpoint per protocol set (Key Sec EP PPS)	96 (82.8)
HSCT secondary endpoint full analysis set (HSCT Sec EP FAS)	74 (63.8)
HSCT secondary endpoint per protocol Set (HSCT Sec EP PPS)	66 (56.9)
Secondary endpoint per protocol set (Sec EP PPS)	98 (84.5)
PK Analysis Set (as reported in the primary analysis CSR)	33 (28.4)

HSCT = hematopoietic stem cell transplant; N = number of subjects in the analysis set;
PK = pharmacokinetic, CSR = clinical study report
Source: modified from Table 14-1.3

Outcomes and estimation

Primary Efficacy Endpoint:

Table 9: MRD Response Rate within the First Cycle ññ

	Prim EP FAS (N=113)	Prim EP Efficacy Set (N=103)	Prim EP PPS (N=98)
MRD[a] assessment cycle 1 (%)			
Evaluable	112 (99.1)	102 (99.0)	97 (99.0)
Not evaluable	1 (0.9)	1 (1.0)	1 (1.0)
MRD[a] response at cycle 1 (%) (95% exact CI)			
MRD complete response	88 (77.9) (69.1-85.1)	82 (79.6) (70.5-86.9)	77 (78.6) (69.1-86.2)
MRD non-responders	25 (22.1) (14.9-30.9)	21 (20.4) (13.1-29.5)	21 (21.4) (13.8-30.9)
Low-level MRD positivity, non-quantifiable	10 (8.8) (4.3-15.7)	7 (6.8) (2.8-13.5)	7 (7.1) (2.9-14.2)
Quantifiable MRD positivity	14 (12.4) (6.9-19.9)	13 (12.6) (6.9-20.6)	13 (13.3) (7.3-21.6)
No MRD response assessment	1 (0.9) (0.0-4.8)	1 (1.0) (0.0-5.3)	1 (1.0) (0.0-5.6)
MRD level $<10^{-4}$	98 (86.7) (79.1-92.4)	90 (87.4) (79.4-93.1)	85 (86.7) (78.4-92.7)
MRD level $\geq 10^{-4}$	14 (12.4) (6.9-19.9)	12 (11.7) (6.2-19.5)	12 (12.2) (6.5-20.4)
No MRD response assessment	1 (0.9) (0.0-4.8)	1 (1.0) (0.0-5.3)	1 (1.0) (0.0-5.6)

Table 10: changes from MRD response in MRD non-responders from baseline to the end of cycle 1.

	Cycle 1 MRD[2] Value						
Baseline MRD[1]	-5	-4	-3	-2	-1	NA	Total
NA	0	1	0	0	0	0	1
-5	0	0	0	0	0	0	0
-4	0	1	0	0	0	0	1
-3	1	6	2	0	1	0	10
-2	0	4	2	0	1	0	7
-1	1	0	0	0	0	2	3
Total	2	12	4	0	2	2	22

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[1] If multiple MRD measurements were taken at baseline visit, the latest one prior to blinatumomab infusion was used.
[2] If multiple MRD measurements were taken during Cycle 1, the non-missing minimum MRD result was used.

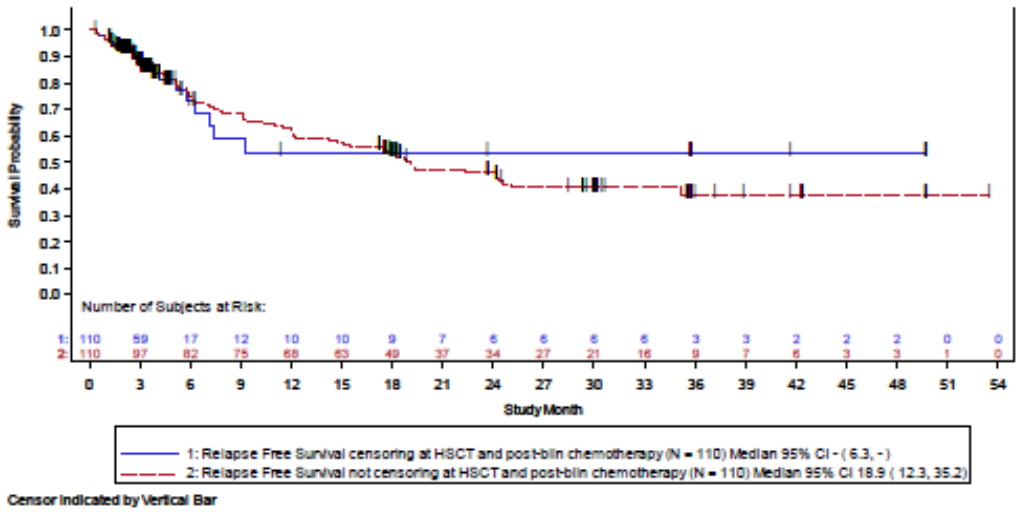
Key Secondary Efficacy Endpoint – Hematological Relapse-free Survival

Table 11: Relapse- free survival

Table 14-4.2.1. Relapse-Free Survival

	Key Sec EP FAS (N=110)	Key Sec EP PPS (N=96)	Key Sec EP FAS Censored at HSCT and Post-blin Chemotherapy (N=110)	Key Sec EP PPS Censored at HSCT and Post-blin Chemotherapy (N=96)
Number of events	62 (56.4)	54 (56.3)	21 (19.1)	20 (20.8)
Relapse	37 (33.6)	33 (34.4)	18 (16.4)	17 (17.7)
Secondary leukemia	1 (0.9)	1 (1.0)	1 (0.9)	1 (1.0)
Deaths	24 (21.8)	20 (20.8)	2 (1.8)	2 (2.1)
Number of censors	48 (43.6)	42 (43.8)	89 (80.9)	76 (79.2)
Kaplan-Meier estimates (95% CI)				
3 months	0.88 (0.81, 0.93)	0.88 (0.79, 0.93)	0.87 (0.79, 0.93)	0.87 (0.78, 0.93)
6 months	0.75 (0.65, 0.82)	0.75 (0.65, 0.82)	0.73 (0.57, 0.84)	0.71 (0.53, 0.83)
12 months	0.61 (0.51, 0.69)	0.60 (0.50, 0.69)	0.54 (0.33, 0.70)	0.51 (0.30, 0.68)
18 months	0.53 (0.44, 0.62)	0.54 (0.43, 0.63)	0.54 (0.33, 0.70)	0.51 (0.30, 0.68)
24 months	0.46 (0.36, 0.55)	0.46 (0.35, 0.56)	0.54 (0.33, 0.70)	0.51 (0.30, 0.68)
Median	18.9 (12.3, 35.2)	18.9 (12.0, 25.1)	NE (6.3, NE)	NE (6.3, NE)
Q1	5.9 (4.5, 9.1)	6.0 (4.2, 9.1)	5.7 (3.7, 7.4)	5.7 (3.7, 7.4)
Q3	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.4, 53.5	0.4, 53.5	0.4, 49.7	0.4, 49.7

Figure 3: haematological relapse-free Survival by Kaplan – Meier



The 18-month KM estimate for RFS were comparable among sensitive analysed in Key Sec EF FAS, Key Sec EF PPS, with or without censoring at HSCT or chemotherapy.

Impact of MRD response on haematological RFS – Day 45 Landmark analysis

The impact of MRD response on RFS was compared via a landmark analysis starting from day 45 by excluding subjects who had an event or were censored before day 45, with a total of 107 subjects included in the analysis. A total of 52.9% (45/85) subjects with complete MRD response at cycle 1 were alive without relapse at the end of the follow-up period, compared with 20.0% (3/15) of subjects who

were MRD non-responders including 9 subjects with quatifiable MRD –positivity and 6 patients with MRD<LLOQ.

The median RFS time was 17.9 months longer for subjects with an MRD complete response at cycle 1 (23.6 months, 95% CI: 17.4 months to n.e.) compared with subjects who were MRD non-responders (5.7 months, 95% CI: 1.6 to 13.6 months). The 18-month KM estimate was 58% (95% CI: 46% to 68%) in subjects with MRD complete response compared with 20% (95% CI: 5% to 42%) in subjects who were MRD non-responders.

Figure 4: RFS from day 45 Landmark analysis: MRD complete responder vs non-responder (subjects in both EP FAS and sey sec EP FAS)

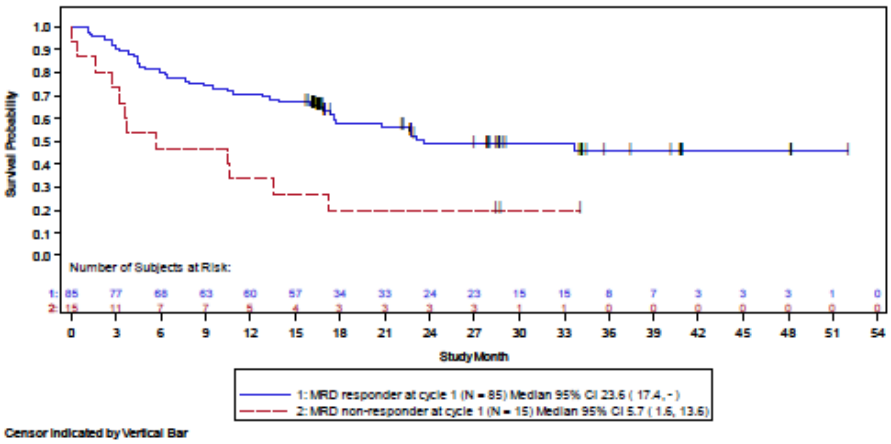


Table 12: RFS by MRD (subjects in both EP FAS and sey sec EP FAS)

	MRD complete responder at Cycle 1 (N=85)	MRD non-responder at Cycle 1 (N=15)	Measurable MRD at Cycle 1 (N=9)	MRD<LLOQ at Cycle 1 (N=6)
Number of events	40 (47.1)	12 (80.0)	7 (77.8)	5 (83.3)
Relapse	23 (27.1)	6 (40.0)	3 (33.3)	3 (50.0)
Secondary leukemia	0 (0.0)	1 (6.7)	0 (0.0)	1 (16.7)
Deaths	17 (20.0)	5 (33.3)	4 (44.4)	1 (16.7)
Number of censors	45 (52.9)	3 (20.0)	2 (22.2)	1 (16.7)
RFS from day 45				
Kaplan-Meier estimates (95% CI)				
3 months	0.91 (0.82, 0.95)	0.73 (0.44, 0.89)	0.78 (0.36, 0.94)	0.67 (0.19, 0.90)
6 months	0.80 (0.70, 0.87)	0.47 (0.21, 0.69)	0.44 (0.14, 0.72)	0.50 (0.11, 0.80)
12 months	0.71 (0.60, 0.79)	0.33 (0.12, 0.56)	0.33 (0.08, 0.62)	0.33 (0.05, 0.68)
18 months	0.58 (0.46, 0.68)	0.20 (0.05, 0.42)	0.22 (0.03, 0.51)	0.17 (0.01, 0.52)
24 months	0.48 (0.36, 0.60)	0.20 (0.05, 0.42)	0.22 (0.03, 0.51)	0.17 (0.01, 0.52)
Median	23.6 (17.4, NE)	5.7 (1.6, 13.6)	5.7 (0.1, NE)	7.1 (0.4, NE)
Q1	8.9 (4.5, 16.0)	2.7 (0.1, 3.7)	3.2 (0.1, 5.7)	1.6 (0.4, 10.5)
Q3	NE (NE, NE)	17.2 (5.7, NE)	13.6 (3.7, NE)	17.2 (1.6, NE)
Min, Max	1.0, 52.0	0.1, 34.0	0.1, 28.7	0.4, 34.0

Impact of relapse history (CR1 or CR2/CR3) on haematological RFS

Subjects in CR1 at the time of treatment with Blincyto, censored at HSCT or post-Blincyto chemotherapy, had a noticeably longer RFS than those in CR2 or CR3 (not estimable [95% CI: 6.3 months to n.e.] versus 7.1 months [95% CI: 4.2 months to 9.3 months], respectively). The results were similar without censoring at HSCT or post-Blincyto chemotherapy.

Table 13: Overview of haematological relapse-free survival rate (censored at HSCT or post-blinatumomab therapy)

	n	RFS events n (%)	Censors n (%)	Months Median	Months (95% CI)
RFS[a] (censored at HSCT or post-blinatumomab chemotherapy)	110	21 (19.1)	89 (80.9)	n.e.	(6.3, n.e.)
Subjects in 1st CR	75	--	--	n.e	(6.3, n.e)
Subjects in 2nd or 3rd CR	35	--	--	7.1	(4.2, 9.3)
RFS[a] (not censored at HSCT or post-blinatumomab chemotherapy)	110	62 (56.4)	48 (43.6)	18.9	(12.3, 35.2)
Subjects in 1st CR	75	36 (48)	39 (52)	24.6	(18.7, n.e.
Subjects in 2nd or 3rd CR	35	26 (74.3)	9 (25.7)	11.0	(6.8, 15.4)
RFS by MRD response at cycle 1[a,b] (Landmark analysis from day 45; not censored at HSCT or post-blinatumomab chemotherapy)					
MRD complete responder	85	40 (47.1)	45 (52.9)	23.6	(17.4, n.e.
MRD non-responder	15	12 (80.0)	3 (20.0)	5.7	(1.6, 13.6)
RFS by HSCT status (Landmark analysis from month 3[a,c])					
HSCT	34	–	--	16.1	(11.3, n.e.
No HSCT	63	–	--	22.1	(12.0, n.e.
RFS by HSCT status (Landmark Analysis from month 6[a,c])					
HSCT	63	–	--	29.2	(13.2, n.e.
No HSCT	19	–	--	n.e.	(4.4, n.e.)
RFS beginning at HSCT[d]	74	38 (51.4)	36 (48.6)	20.9	(14.6, n.e.

CI = confidence interval; CR = complete response, EP = endpoint, FAS = full analysis set; HSCT = hematopoietic stem cell transplant; MRD = minimum residual disease; n.e. = not estimable; RFS = relapse-free survival

Impact of HSCT on haematological RFS

The subject incidence of HSCT after Blincyto treatment was 77.6% (90/116) in the FAS. Of the 90 subjects who had an HSCT, 76 (84.4%) subjects were in CR at the time of HSCT, with 19 (21.1%) subjects being MRD-positive and 57 (63.3%) subjects being MRD-negative, and 14 (15.6%) subjects had hematological relapse prior to HSCT. The median time from 1st dose of Blincyto to HSCT was 3.05 months.

Table 14: Incidence of HSCT

	FAS (N = 116)	HSCT Sec EP FAS (N = 74)
Subjects who had HSCT after starting blinatumomab (%)	90 (77.6)	74 (100.0)
Disease status at the time of HSCT[a]		
In CR after starting blinatumomab	76 (84.4)	74 (100.0)
While MRD positive	19 (21.1)	19 (25.7)
While MRD negative	57 (63.3)	55 (74.3)
Following hematological relapse	14 (15.6)	0 (0.0)
Donor[a]		
Related	26 (28.9)	19 (25.7)
Identical	24 (26.7)	18 (24.3)
Haploident	2 (2.2)	1 (1.4)
Unrelated	62 (68.9)	53 (71.6)
Matched	25 (27.8)	20 (27.0)
Mismatched	29 (32.2)	25 (33.8)
Unknown	8 (8.9)	8 (10.8)
Unknown	2 (2.2)	2 (2.7)
Stem Cell Source[a]		
Blood	72 (80.0)	59 (79.7)
Cord blood	4 (4.4)	4 (5.4)
Marrow	11 (12.2)	8 (10.8)
Unknown	3 (3.3)	3 (4.1)
Experienced graft-versus-host disease[a]		
Yes	23 (25.6)	23 (31.1)
No	60 (66.7)	46 (62.2)
Unknown	7 (7.8)	5 (6.8)
Conditioning regimen[a]		
Intensive/Myeloablative regimen	64 (71.1)	55 (74.3)
Reduced Toxicity/Non-myeloablative regimen	20 (22.2)	14 (18.9)
Unknown	6 (6.7)	5 (6.8)
Time from first dose of blinatumomab to HSCT (Months)		
N	90	74
Mean	3.57	3.25
SD	1.84	1.51
Median	3.10	3.05
Q1,Q3	2.30, 4.20	2.16, 3.93
Min,Max	1.21, 11.31	1.21, 11.31

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N = Number of subjects in the analysis set.
[a] Percentages based on subjects who had HSCT after starting blinatumomab.
Note: The 4 subjects with cord blood had unrelated donors.

Two landmark analyses were performed on the Key Sec EP FAS, with the landmark at 3M and 6M after the first dose of Blincyto in order to compare RFS time in subjects with HSCT with those did not have a transplant. The median RFS from the landmark at 3M was 22.1 months (95% CI: 12.0 months to n.e.) for subjects without HSCT and it was 6M shorter (16.1 months, 95% CI: 11.3 months to n.e.) for subjects who received HSCT. The similar trend was also observed at the 6M landmark analysis, the median RFS was not estimated for subjects without a transplant (n.e. 95% CI: 4.4 months to n.e.), it was 29.2 months (95% CI: 13.2 to n.e.) in subjects who received an HSCT.

Figure 5: RFS Landmark analyses at 3 months: subjects who received HSCT vs subjects without HSCT (key sec EP FAS)

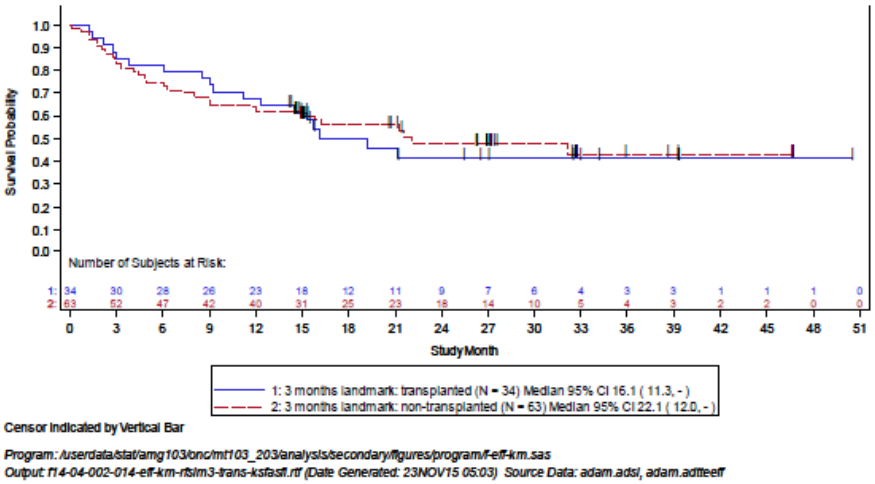
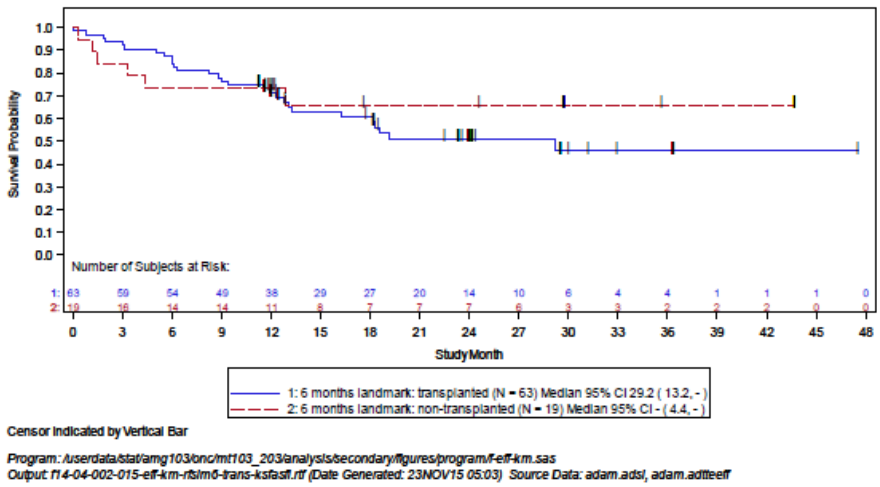


Figure 6: RFS Landmark analyses at 6 months: subjects who received HSCT vs subjects without HSCT (key sec EP FAS)



A total of 74 subjects who underwent HSCT prior to relapse excluding Ph+ subjects comprised the HSCT Sec EP FAS. 51.4% (38/74) of subjects had an RFS event, and 48.6% (36/74) were in remission or otherwise censored. The median RFS for subjects in the HSCT Sec EP FAS was 20.9 months (95% CI: 14.6 months to n.e.). The 18-month KM estimate was 55% (95% CI: 42% to 66%). Not unexpectedly, RFS was longer in subjects with related rather than unrelated donors (NE versus 18.7 months), and in subjects with matched versus mismatched donors (20.8 versus 16.2 months).

Table 15: RFS from HSCT

	HSCT Sec EP FAS (N=74)	HSCT Sec EP PPS (N=66)
Number of events	38 (51.4)	33 (50.0)
Relapse	16 (21.6)	15 (22.7)
Secondary leukemia	0 (0.0)	0 (0.0)
Deaths	22 (29.7)	18 (27.3)
Number of censors	36 (48.6)	33 (50.0)
Kaplan-Meier estimates (95% CI)		
3 months	0.92 (0.83, 0.96)	0.92 (0.83, 0.97)
100 days	0.89 (0.80, 0.94)	0.91 (0.81, 0.96)
6 months	0.81 (0.70, 0.88)	0.82 (0.70, 0.89)
12 months	0.68 (0.56, 0.77)	0.70 (0.57, 0.79)
18 months	0.55 (0.42, 0.66)	0.55 (0.42, 0.67)
24 months	0.45 (0.32, 0.57)	0.44 (0.30, 0.57)
Median	20.9 (14.6, NE)	20.9 (14.9, NE)
Q1	9.3 (3.7, 13.8)	10.2 (4.0, 14.6)
Q3	NE (NE, NE)	NE (NE, NE)
Min, Max	0.6, 50.9	0.6, 50.9

Other Secondary Efficacy Endpoint

Overall Survival

OS was measured for all subjects (FAS) and was defined as the time from treatment start with Blincyto until death due to any cause. At the time of the secondary analysis, a total of 53 deaths (45.7%, 53/116) were reported in the study and 63 subjects (54.3%; 63/116) were alive.

Table 16: Overall Survival

	FAS (N=116)	Sec EP PPS (N=98)	FAS Censored at HSCT and Post-blin Chemotherapy (N=116)	Sec EP PPS Censored at HSCT and Post-blin Chemotherapy (N=98)
Number of events	53 (45.7)	42 (42.9)	5 (4.3)	5 (5.1)
Deaths	53 (45.7)	42 (42.9)	5 (4.3)	5 (5.1)
Number of censors	63 (54.3)	56 (57.1)	111 (95.7)	93 (94.9)
Kaplan-Meier estimates (95% CI)				
3 months	0.97 (0.92, 0.99)	0.97 (0.91, 0.99)	0.97 (0.90, 0.99)	0.96 (0.89, 0.99)
6 months	0.88 (0.80, 0.93)	0.88 (0.79, 0.93)	0.97 (0.90, 0.99)	0.96 (0.89, 0.99)
12 months	0.75 (0.66, 0.82)	0.77 (0.67, 0.84)	0.83 (0.55, 0.94)	0.82 (0.52, 0.94)
18 months	0.65 (0.55, 0.73)	0.66 (0.56, 0.75)	0.83 (0.55, 0.94)	0.82 (0.52, 0.94)
24 months	0.55 (0.45, 0.64)	0.58 (0.47, 0.68)	0.83 (0.55, 0.94)	0.82 (0.52, 0.94)
Median	36.5 (19.2, NE)	40.4 (19.2, NE)	NE (NE, NE)	NE (NE, NE)
Q1	12.0 (7.3, 15.9)	12.3 (7.5, 17.5)	NE (6.6, NE)	NE (6.6, NE)
Q3	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.7, 53.5	0.7, 53.5	0.4, 49.7	0.7, 49.7

Without censoring for HSCT or chemotherapy, the KM estimated OS rate at 18 months (FAS) was 65% (95% CI: 55, 73), with a median OS of 36.5 months (95% CI: 19.2, not estimable). When with censoring for HSCT or after Blincyto chemotherapy, OS rate at 18 months was 83% (95% CI: 55, 94); the median OS was not estimable (KM curves).

Figure 7: OS by Kaplan – Meier (FAS)

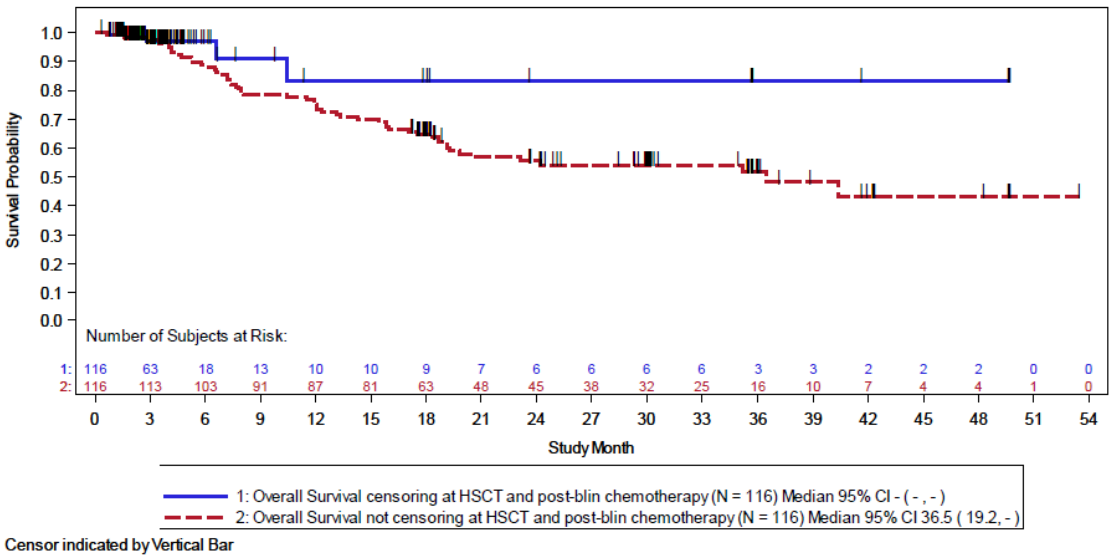
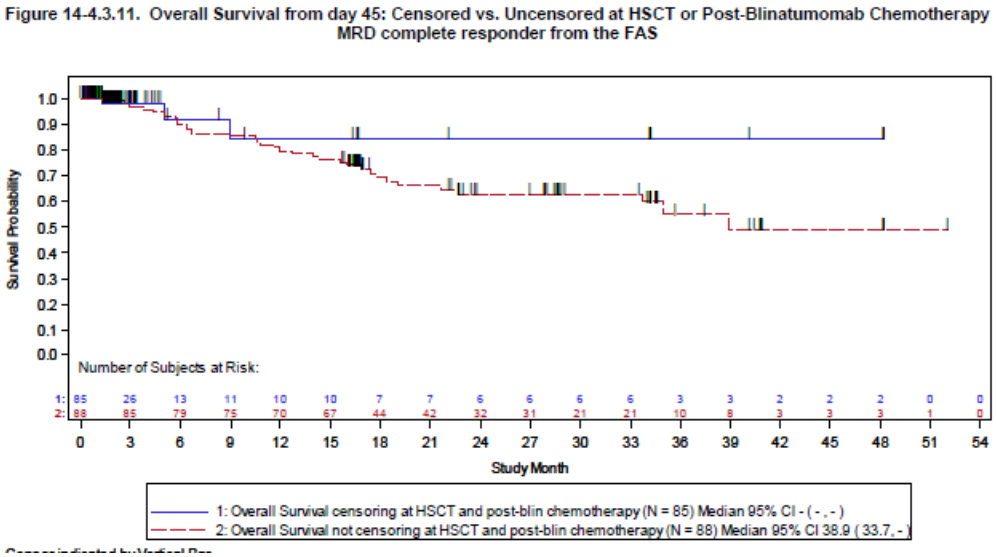


Figure 8: landmark analysis of OS from D45 in MRD responders with or without censoring at HSCT or post-Blincyto chemotherapy.



Impact of MRD response on OS – Day 45 Landmark analysis

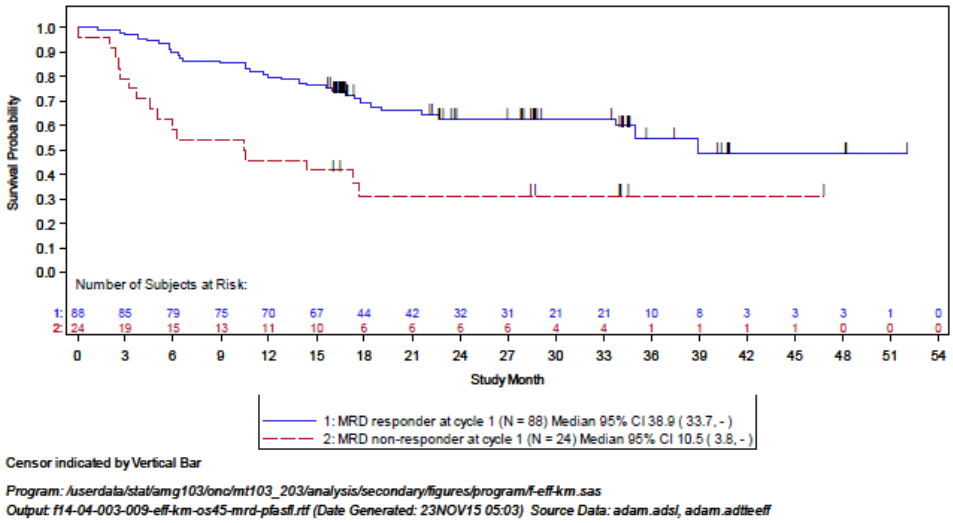
The impact of MRD response on OS was compared via a landmark analysis starting from day 45 in Prim EP FAS subjects (N = 112). The analysis excluded subjects who died or were censored before day 45. In the subgroup of subjects achieving complete MRD response at C1, 62.5% (55/88) of subjects were alive at the end of FU period (and censored), compared with 33.3% (8/24) of subjects who did not have complete MRD response. The median OS time (from day 45) was 28.4 months longer for subjects who had a complete MRD response at cycle 1 (38.9 months, 95% CI: 33.7 months to n.e.) compared with subjects who were MRD non-responders (10.5 months, 95% CI: 3.8 months to n.e.). The 18M KM for OS was 69% (95% CI: 58% to 78%) in subjects who had MRD complete response compared with 31% (95% CI: 14% to 51%) in subjects who were MRD non-responders.

Table 17: OS by MRD response Prim EP FAS

	MRD complete responder at Cycle 1 (N=88)	MRD non-responder at Cycle 1 (N=24)	Measurable MRD at Cycle 1 (N=14)	MRD<LLOQ at Cycle 1 (N=10)
Number of events	33 (37.5)	16 (66.7)	12 (85.7)	4 (40.0)
Deaths	33 (37.5)	16 (66.7)	12 (85.7)	4 (40.0)
Number of censors	55 (62.5)	8 (33.3)	2 (14.3)	6 (60.0)
OS from day 45				
Kaplan-Meier estimates (95% CI)				
3 months	0.97 (0.90, 0.99)	0.79 (0.57, 0.91)	0.71 (0.41, 0.88)	0.90 (0.47, 0.99)
6 months	0.90 (0.81, 0.95)	0.58 (0.36, 0.75)	0.43 (0.18, 0.66)	0.80 (0.41, 0.95)
12 months	0.80 (0.70, 0.87)	0.46 (0.26, 0.64)	0.29 (0.09, 0.52)	0.70 (0.33, 0.89)
18 months	0.69 (0.58, 0.78)	0.31 (0.14, 0.51)	0.14 (0.02, 0.37)	0.56 (0.20, 0.81)
24 months	0.63 (0.51, 0.73)	0.31 (0.14, 0.51)	0.14 (0.02, 0.37)	0.56 (0.20, 0.81)
Median	38.9 (33.7, NE)	10.5 (3.8, NE)	5.5 (2.6, 14.4)	NE (2.4, NE)
Q1	15.8 (10.5, 21.6)	3.5 (0.1, 6.0)	2.7 (0.1, 5.0)	10.4 (2.4, NE)
Q3	NE (NE, NE)	NE (14.4, NE)	14.4 (5.0, NE)	NE (17.2, NE)
Min, Max	1.3, 52.0	0.1, 46.8	0.1, 28.7	2.4, 46.8

N = Number of subjects in the analysis set. CI=Confidence Interval. NE=not estimable.
Note: only subjects alive at day 45 are included in this analysis.
Note: One subject had no post-baseline MRD assessment, so was considered a non-responder but was not included in this analysis.

Figure 9: OS from day 45: MRD complete responder vs non-responder



Censor indicated by Vertical Bar

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Impact of relapse history (CR1 or CR2/CR3) on OS

Subjects in CR1 at the time of treatment with Blincyto had a median OS that was 17.4 months longer than that of subjects in CR2 or CR3: (36.5 months, 95% CI: 20.6 months to n.e. versus 19.1 months, 95% CI: 11.9 months to n.e., respectively)

Figure 10: OS : subjects in 1st CR vs 2nd or 3rd CR (FAS)

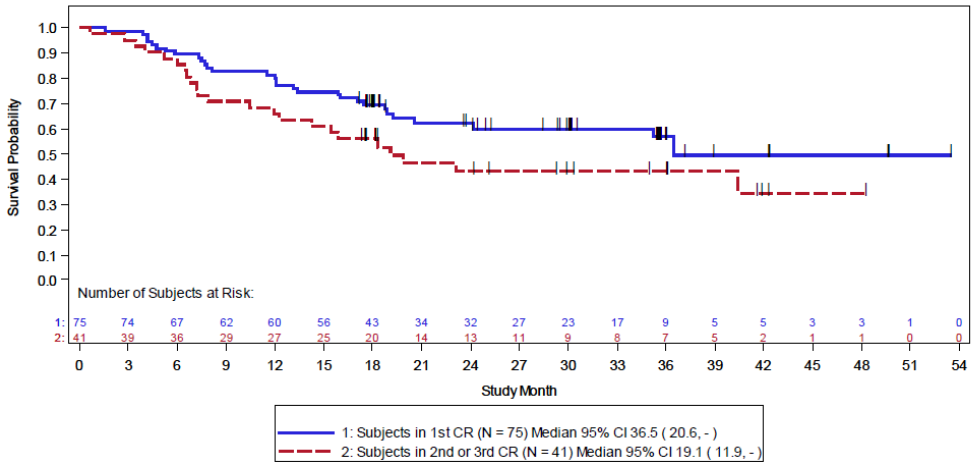


Table 18: Overview of OS analyses

				Months	
	n	Deaths n (%)	Censors n (%)	Median	(95% CI)
OS[a]	116	53 (45.7)	63 (54.3)	36.5	(19.2, n.e.)
Subjects in 1st CR	75	30 (40.0)	--	36.5	(20.6, n.e.)
Subjects in 2nd or 3rd CR	41	23 (56.1)	--	19.1	(11.9, n.e.)
OS by MRD response at cycle 1[b] (Landmark analysis from day 15)					
MRD complete responder	88	33 (37.5)	55 (62.5)	38.9	(33.7, n.e.)
MRD non-responder	24[c]	16 (66.7)	8 (33.3)	10.5	(3.8, n.e.)
OS by HSCT status (Landmark analysis from month 3[a,d])					
HSCT	37	--	--	21.2	(13.0, n.e.)
No HSCT	76	--	--	33.5	(17.6, n.e.)
OS by HSCT status (Landmark analysis from month 6[b,d])					
HSCT	73	--	--	30.5	(14.6, n.e.)
No HSCT	30	--	--	n.e.	(12.9, n.e.)

Impact of HSCT on Overall Survival - Landmark Analyses at 3 and 6 Months

Landmark analyses were conducted to compare the OS in subjects who received HSCT (bleu) and those who did not (red). Subjects who died before the landmark date were excluded from the analysis; otherwise subjects were stratified based on whether they received or did not receive HSCT at the landmark date. Landmarks included 3 months and 6 months after the first dose of Blincyto. Among subjects who were alive at 3 months, the median overall survival was 21.2 months (95% CI: 13.0 months to n.e.) in subjects who received HSCT on or before 3 months, and 33.5 months (95% CI: 17.6 months to n.e.) for those who did not receive HSCT. Among subjects who were alive at 6 months, the median OS was 30.5 months (95% CI: 14.6 months to n.e.) in subjects who received HSCT on or before 6 months, and not estimable (95% CI: 12.9 months to n.e.) in those who did not receive HSCT. The OS KM curves at the 3M and 6M landmark analysis were similar between 2 subgroups

Figure 11: OS Landmark analysis at 3 months: HSCT vs not received HSCT - FAS

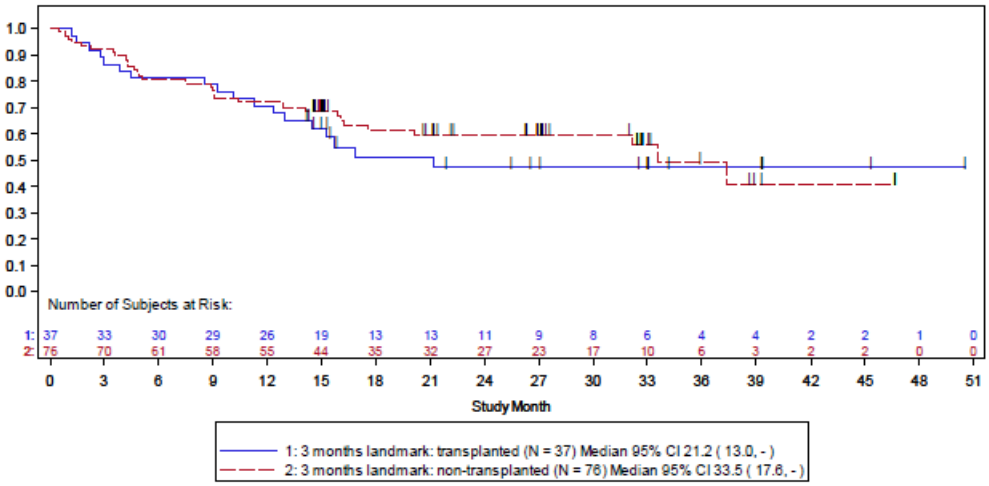


Figure 12: OS Landmark analysis at 6 months: HSCT vs not received HSCT - FAS

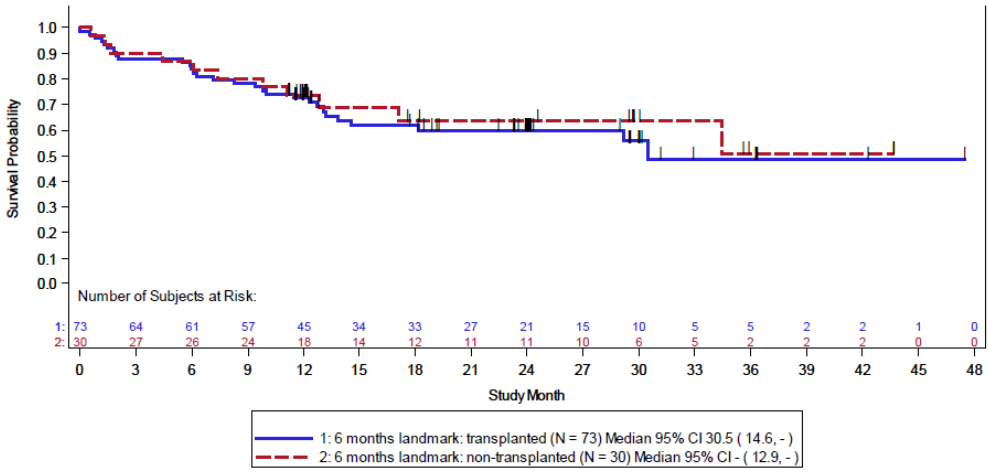


Table 19: Cause of death

	Full Analysis Set (N = 116)
Total number of deaths	53 (45.7)
Death in CR without HSCT - n (%)	3 (2.6)
Death in CR after HSCT - n (%)	23 (19.8)
Death after relapse without HSCT - n (%)	9 (7.8)
Death after relapse pre-HSCT - n (%)	9 (7.8)
Death after relapse post-HSCT - n (%)	9 (7.8)

100-day Mortality Rate Associated with Allogeneic Hematopoietic Stem Cell Transplant

Of 74 subjects in HSCT Sec EP FAS, 31 (41.9%) subjects died, with 5 of 31 (16.1%) deaths occurring during 100 days post-HSCT. The KM estimate of OS rate at 100 days after HSCT was 93% (95% CI: 85% to 97%), therefore the 100-day mortality rate after allogeneic HSCT was 7% (95% CI: 3% to 15%).

Table 20: OS from HSCT

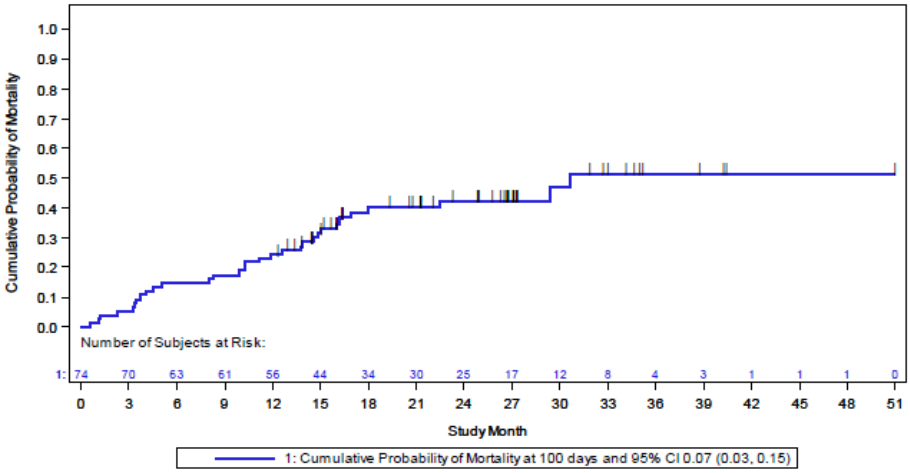
	HSCT Sec EP FAS (N=74)	HSCT Sec EP PPS (N=66)
Number of events	31 (41.9)	26 (39.4)
Deaths	31 (41.9)	26 (39.4)
Number of censors	43 (58.1)	40 (60.6)
Kaplan-Meier estimates (95% CI)		
3 months	0.95 (0.86, 0.98)	0.95 (0.87, 0.99)
100 days	0.93 (0.85, 0.97)	0.95 (0.87, 0.99)
6 months	0.85 (0.75, 0.91)	0.86 (0.75, 0.93)
12 months	0.76 (0.64, 0.84)	0.77 (0.65, 0.86)
18 months	0.60 (0.47, 0.70)	0.61 (0.48, 0.72)
24 months	0.58 (0.45, 0.69)	0.59 (0.45, 0.70)
Median	30.6 (16.9, NE)	NE (16.9, NE)
Q1	12.6 (5.1, 16.1)	13.8 (8.2, 16.9)
Q3	NE (NE, NE)	NE (NE, NE)
Min, Max	0.6, 50.9	0.6, 50.9

Table 21: Post HSCT mortality

	HSCT Sec EP FAS (N = 74)	HSCT Sec EP PPS (N = 66)	FAS patients who received HSCT (N = 90)
Number of deaths post-HSCT	31 (41.9)	26 (39.4)	41 (45.6)
Number of deaths in ≤ 100 days post-HSCT [a]	5 (16.1)	3 (11.5)	9 (22.0)
Donor[a]			
Related	7 (22.6)	5 (19.2)	11 (26.8)
Identical	7 (22.6)	5 (19.2)	11 (26.8)
Haploident	0 (0.0)	0 (0.0)	0 (0.0)
Unrelated	23 (74.2)	20 (76.9)	29 (70.7)
Matched	8 (25.8)	7 (26.9)	11 (26.8)
Mismatched	11 (35.5)	11 (42.3)	14 (34.1)
Unknown	4 (12.9)	2 (7.7)	4 (9.8)
Unknown	1 (3.2)	1 (3.8)	1 (2.4)
Stem Cell Source[a]			
Blood	25 (80.6)	20 (76.9)	33 (80.5)
Cord blood	1 (3.2)	1 (3.8)	1 (2.4)
Marrow	4 (12.9)	4 (15.4)	6 (14.6)
Unknown	1 (3.2)	1 (3.8)	1 (2.4)
Experienced graft-versus-host disease[a]			
Yes	8 (25.8)	8 (30.8)	8 (19.5)
No	21 (67.7)	17 (65.4)	30 (73.2)
Unknown	2 (6.5)	1 (3.8)	3 (7.3)

N = Number of subjects in the analysis set.
[a] Percentages based on subjects who died after HSCT.

Figure 10-10. Cumulative Probability of Mortality Beginning at HSCT (HSCT Sec EP FAS)



Censor indicated by Vertical Bar
C.P.M = Cumulative Probability of Mortality

Time to Haematological Relapse

Time to hematological relapse was measured from the start of Blincyto infusion until the subject experienced hematological or extramedullary relapse. Subjects who died or received HSCT or post-Blincyto chemotherapy after Blincyto were censored at their last hematological assessment prior to death or HSCT or post-Blincyto chemotherapy (whichever occurred first).

In the Key Sec EP FAS (N = 110), a total of 82.7% (91/110) of subjects were censored as of the data cutoff and 17.3% (19/110) subjects had events: 16.4% (18/110) had a relapse and 0.9% (1/110) had secondary leukemia. The 18-month KM estimate for TTHR, censored at HSCT or post-Blincyto chemotherapy, was 55% (95% CI: 34% to 72%); the median TTHR was not estimable (95% CI: 7.1 months to n.e.),

Table 22: time to relapse

	Key Sec EP FAS (N=110)	Key Sec EP PPS (N=96)	Key Sec EP FAS Censored at HSCT and Post-blin Chemotherapy (N=110)	Key Sec EP PPS Censored at HSCT and Post-blin Chemotherapy (N=96)
Number of events	39 (35.5)	35 (36.5)	19 (17.3)	18 (18.8)
Relapse	37 (33.6)	33 (34.4)	18 (16.4)	17 (17.7)
Secondary leukemia	1 (0.9)	1 (1.0)	1 (0.9)	1 (1.0)
Death due to Disease Progression	1 (0.9)	1 (1.0)	0 (0.0)	0 (0.0)
Number of censors	71 (64.5)	61 (63.5)	91 (82.7)	78 (81.3)
Kaplan-Meier estimates (95% CI)				
3 months	0.90 (0.82, 0.94)	0.89 (0.81, 0.94)	0.90 (0.81, 0.94)	0.90 (0.81, 0.94)
6 months	0.81 (0.72, 0.87)	0.81 (0.71, 0.87)	0.75 (0.58, 0.86)	0.73 (0.55, 0.85)
12 months	0.71 (0.61, 0.79)	0.70 (0.59, 0.78)	0.55 (0.34, 0.72)	0.52 (0.31, 0.70)
18 months	0.67 (0.57, 0.76)	0.67 (0.56, 0.76)	0.55 (0.34, 0.72)	0.52 (0.31, 0.70)
24 months	0.62 (0.51, 0.71)	0.62 (0.50, 0.72)	0.55 (0.34, 0.72)	0.52 (0.31, 0.70)
Median	NE (24.3, NE)	NE (22.3, NE)	NE (7.1, NE)	NE (6.3, NE)
Q1	9.1 (5.7, 18.7)	9.0 (5.1, 18.7)	5.7 (4.2, 9.3)	5.7 (3.7, 7.4)
Q3	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.4, 53.5	0.4, 53.5	0.4, 49.7	0.4, 49.7

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N = Number of subjects in the analysis set. CI=Confidence Interval. NE=not estimable

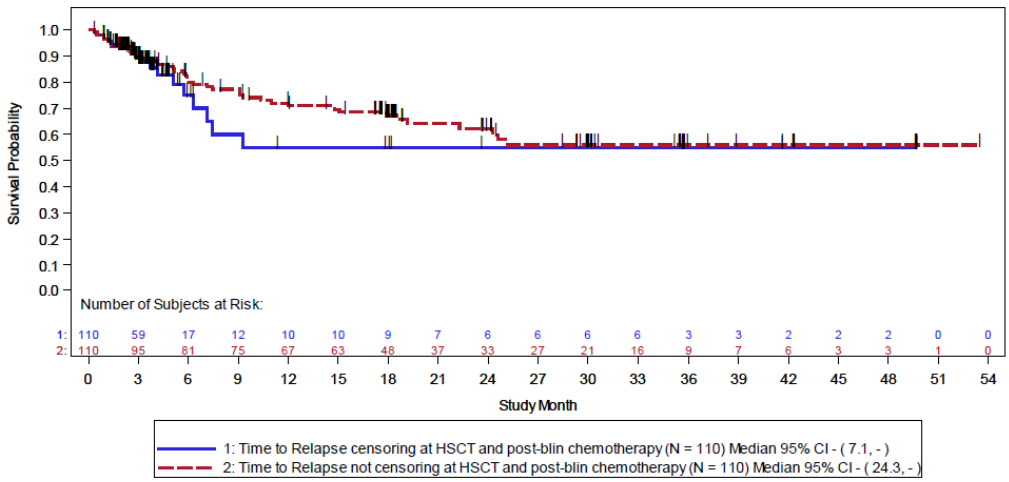
The 18-month KM estimate for TTHR in MRD non-responder was 30% versus 75% in complete MRD responder.

Table 14-4.4.2. Time to Relapse by MRD Response
Subjects both in Prim EP FAS & Key Sec EP FAS

	MRD complete responder at Cycle 1 (N=85)	MRD non-responder at Cycle 1 (N=13)	Measurable MRD at Cycle 1 (N=7)	MRD<LLOQ at Cycle 1 (N=6)
Number of events	23 (27.1)	8 (61.5)	3 (42.9)	5 (83.3)
Relapse	23 (27.1)	6 (46.2)	3 (42.9)	3 (50.0)
Secondary leukemia	0 (0.0)	1 (7.7)	0 (0.0)	1 (16.7)
Death due to Disease Progression	0 (0.0)	1 (7.7)	0 (0.0)	1 (16.7)
Number of censors	62 (72.9)	5 (38.5)	4 (57.1)	1 (16.7)
Time to Relapse from day 45				
Kaplan-Meier estimates (95% CI)				
3 months	0.94 (0.86, 0.97)	0.85 (0.51, 0.96)	1.00 (NE, NE)	0.67 (0.19, 0.90)
6 months	0.85 (0.75, 0.91)	0.59 (0.28, 0.81)	0.67 (0.19, 0.90)	0.50 (0.11, 0.80)
12 months	0.80 (0.69, 0.87)	0.51 (0.21, 0.74)	0.67 (0.19, 0.90)	0.33 (0.05, 0.68)
18 months	0.75 (0.63, 0.83)	0.30 (0.08, 0.57)	0.44 (0.07, 0.78)	0.17 (0.01, 0.52)
24 months	0.65 (0.50, 0.76)	0.30 (0.08, 0.57)	0.44 (0.07, 0.78)	0.17 (0.01, 0.52)
Median	NE (NE, NE)	13.6 (3.6, NE)	13.6 (3.7, NE)	7.1 (0.4, NE)
Q1	17.6 (7.6, NE)	3.7 (0.4, 10.5)	5.7 (3.7, NE)	1.6 (0.4, 10.5)
Q3	NE (NE, NE)	NE (10.5, NE)	NE (5.7, NE)	17.2 (1.6, NE)
Min, Max	0.9, 52.0	0.4, 34.0	3.2, 28.7	0.4, 34.0

N = Number of subjects in the analysis set. CI=Confidence Interval. NE=not estimable.
Note: only subjects alive without relapse at day 45 are included in this analysis.

Figure 14-4.4.1. Time to Relapse
Key Sec EP FAS



Duration of Complete MRD Response

The median duration of MRD response was analysed as the time from onset of MRD negativity until MRD or hematological relapse or date of last confirmation of negative MRD status. Only the subjects with MRD CR at cycle 1 were included in this analysis.

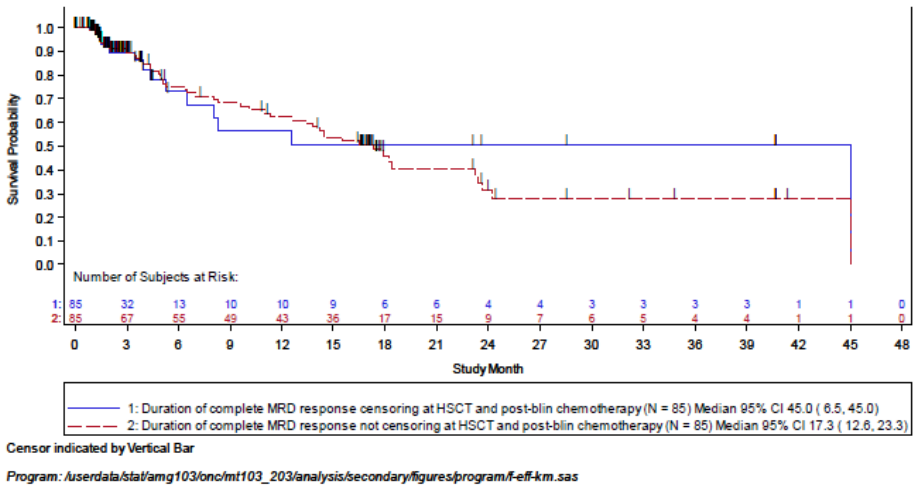
The results were analysed with and without censoring at the time of HSCT or post-Blincyto chemotherapy.

The median duration of MRD response for subjects who had complete MRD response at cycle 1 (N = 85) was 17.3 months (95% CI: 12.6 to 23.3 months) when uncensored and 45.0 months (95% CI: 6.5 to 45.0 months) when censored at the time of HSCT or post-Blincyto chemotherapy. The 18-month KM estimates were 46% (95% CI: 33% to 57%) and 51% (95% CI: 28% to 69%), respectively.

Table 23: Duration of MRD CR

	Key Sec EP FAS[1] (N=85)	Key Sec EP PPS[2] (N=72)	Key Sec EP FAS[1] Censored at HSCT and Post-blin Chemotherapy (N=85)	Key Sec EP PPS[2] Censored at HSCT and Post-blin Chemotherapy (N=72)
Number of events	45 (52.9)	38 (52.8)	16 (18.8)	14 (19.4)
Molecular relapse[a]	16 (18.8)	13 (18.1)	12 (14.1)	10 (13.9)
Hematologic relapse	13 (15.3)	11 (15.3)	3 (3.5)	3 (4.2)
Secondary leukemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	16 (18.8)	14 (19.4)	1 (1.2)	1 (1.4)
Number of censors	40 (47.1)	34 (47.2)	69 (81.2)	58 (80.6)
Kaplan-Meier estimates (95% CI)				
3 months	0.90 (0.80, 0.95)	0.91 (0.81, 0.96)	0.90 (0.79, 0.95)	0.89 (0.77, 0.95)
6 months	0.75 (0.63, 0.83)	0.78 (0.66, 0.86)	0.73 (0.53, 0.86)	0.75 (0.54, 0.87)
12 months	0.62 (0.50, 0.72)	0.63 (0.50, 0.74)	0.56 (0.33, 0.74)	0.56 (0.32, 0.75)
18 months	0.46 (0.33, 0.57)	0.47 (0.34, 0.60)	0.51 (0.28, 0.69)	0.50 (0.26, 0.70)
24 months	0.31 (0.19, 0.45)	0.32 (0.18, 0.46)	0.51 (0.28, 0.69)	0.50 (0.26, 0.70)
Median	17.3 (12.6, 23.3)	17.9 (12.6, 23.3)	45.0 (6.5, 45.0)	45.0 (6.5, 45.0)
Q1	5.3 (3.9, 10.1)	6.5 (4.4, 11.3)	5.3 (3.5, 8.4)	6.5 (3.5, 8.4)
Q3	45.0 (23.2, 45.0)	45.0 (23.2, 45.0)	45.0 (NE, NE)	45.0 (NE, NE)
Min, Max	0.0, 45.0	0.0, 45.0	0.3, 45.0	0.5, 45.0

Figure 13: Duration of complete MRD response by K-M
(Subjects in Both Key Sec EP FAS and Prim EP FAS with Complete MRD Response at Cycle 1)



Subject's Quality of Life During and After Therapy

The EORTC-QLQ-C30 including 5 functional scales was used to assess the quality of life of patients in this study.

Table 24: Change from baseline in EQ-5D scales (FAS)

EQ-5D Scale	Baseline Mean (SE)	Greatest Change from Baseline in Cycles 1 to 4 Mean (SE)/Cycle	Change from Baseline at End of Core Study Mean (SE)
Mobility	1.2 (0.0)	-0.2 (0.1)/C4	0 (0.1)
Self-Care	1.1 (0.0)	-0.1 (0.1)/C4	0 (0.0)
Usual Activity	1.5 (0.1)	-0.1 (0.1)/C3 + C4	-0.1 (0.1)
Pain/Discomfort	1.4 (0.0)	-0.2 (0.2)/C4	-0.1 (0.1)
Anxiety/Depression	1.4 (0.1)	-0.2 (0.1)/C2	-0.1 (0.1)

C = cycle; EQ-5D = EuroQol-5D; FAS = full analysis set; SE = standard error
Note: The evaluation took place at end of each cycle (day 29)

Subgroup analyses for efficacy

Effect of baseline covariates on primary endpoint

Table 25: MRD response at cycle 1 by covariate levels

	Prim EP FAS (N=113)	Prim EP Efficacy Set (N=103)	Prim EP PPS (N=98)
MRD[a] response at cycle 1 (%) (95% exact CI)			
Overall	88/113 (77.9) (69.1-85.1)	82/103 (79.6) (70.5-86.9)	77/98 (78.6) (69.1-86.2)
Age			
18 - 34	30/36 (83.3) (67.2-93.6)	29/32 (90.6) (75.0-98.0)	28/31 (90.3) (74.2-98.0)
35 - 54	28/38 (73.7) (56.9-86.6)	25/35 (71.4) (53.7-85.4)	24/34 (70.6) (52.5-84.9)
55 - 64	18/24 (75.0) (53.3-90.2)	17/23 (73.9) (51.6-89.8)	15/21 (71.4) (47.8-88.7)
≥65	12/15 (80.0) (51.9-95.7)	11/13 (84.6) (54.6-98.1)	10/12 (83.3) (51.6-97.9)
Gender			
Male	51/67 (76.1) (64.1-85.7)	47/60 (78.3) (65.8-87.9)	44/57 (77.2) (64.2-87.3)
Female	37/46 (80.4) (66.1-90.6)	35/43 (81.4) (66.6-91.6)	33/41 (80.5) (65.1-91.2)
Philadelphia status			
Philadelphia positive	3/5 (60.0) (14.7-94.7)	3/4 (75.0) (19.4-99.4)	2/3 (66.7) (9.4-99.2)
Philadelphia negative	85/108 (78.7) (69.8-86.0)	79/99 (79.8) (70.5-87.2)	75/95 (78.9) (69.4-86.6)
Patients by t(4;11) translocation and/or MLL-AF4+ ALL haematological remission			
Yes	2/5 (40.0) (5.3-85.3)	2/4 (50.0) (6.8-93.2)	1/3 (33.3) (0.8-90.6)
No	70/86 (81.4) (71.6-89.0)	65/78 (83.3) (73.2-90.8)	62/75 (82.7) (72.2-90.4)
Unknown	16/22 (72.7) (49.8-89.3)	15/21 (71.4) (47.8-88.7)	14/20 (70.0) (45.7-88.1)
Risk stratification			
Standard	48/59 (81.4) (69.1-90.3)	47/56 (83.9) (71.7-92.4)	46/55 (83.6) (71.2-92.2)
Low	2/2 (100.0) (15.8-100.0)	1/1 (100.0) (2.5-100.0)	1/1 (100.0) (2.5-100.0)

Intermediate	3/5 (60.0) (14.7-94.7)	3/5 (60.0) (14.7-94.7)	3/5 (60.0) (14.7-94.7)
High	28/35 (80.0) (63.1-91.6)	24/30 (80.0) (61.4-92.3)	21/27 (77.8) (57.7-91.4)
Very high	3/5 (60.0) (14.7-94.7)	3/4 (75.0) (19.4-99.4)	2/3 (66.7) (9.4-99.2)
Unknown	4/7 (57.1) (18.4-90.1)	4/7 (57.1) (18.4-90.1)	4/7 (57.1) (18.4-90.1)
Relapse history			
Patients in 1st CR	60/73 (82.2) (71.5-90.2)	55/66 (83.3) (72.1-91.4)	53/64 (82.8) (71.3-91.1)
Patients in 2nd CR	27/38 (71.1) (54.1-84.6)	26/35 (74.3) (56.7-87.5)	23/32 (71.9) (53.3-86.3)
Patients in 3rd CR	1/2 (50.0) (1.3-98.7)	1/2 (50.0) (1.3-98.7)	1/2 (50.0) (1.3-98.7)
MRD level at baseline by central lab			
≥10xE-1 and <10xE0	6/9 (66.7) (29.9-92.5)	6/9 (66.7) (29.9-92.5)	6/9 (66.7) (29.9-92.5)
≥10xE-2 and <10xE-1	36/44 (81.8) (67.3-91.8)	36/43 (83.7) (69.3-93.2)	36/43 (83.7) (69.3-93.2)
≥10xE-3 and <10xE-2	40/51 (78.4) (64.7-88.7)	40/51 (78.4) (64.7-88.7)	35/46 (76.1) (61.2-87.4)
<10xE-3	3/3 (100.0) (29.2-100.0)	0/0 (0.0) (NE-NE)	0/0 (0.0) (NE-NE)
Below LLOQ	3/5 (60.0) (14.7-94.7)	0/0 (0.0) (NE-NE)	0/0 (0.0) (NE-NE)
Unknown	0/1 (0.0) (NE-NE)	0/0 (0.0) (NE-NE)	0/0 (0.0) (NE-NE)
WBC at first diagnosis			
≤30,000/mm^3	59/76 (77.6) (66.6-86.4)	55/69 (79.7) (68.3-88.4)	53/67 (79.1) (67.4-88.1)
>30,000/mm^3	12/18 (66.7) (41.0-86.7)	11/16 (68.8) (41.3-89.0)	10/15 (66.7) (38.4-88.2)
Unknown	17/19 (89.5) (66.9-98.7)	16/18 (88.9) (65.3-98.6)	14/16 (87.5) (61.7-98.4)
Chemoresistance after the first week of chemotherapy			
Yes	6/8 (75.0) (34.9-96.8)	5/7 (71.4) (29.0-96.3)	3/5 (60.0) (14.7-94.7)
No	2/5 (40.0) (5.3-85.3)	2/4 (50.0) (6.8-93.2)	2/4 (50.0) (6.8-93.2)
Unknown	80/100 (80.0) (70.8-87.3)	75/92 (81.5) (72.1-88.9)	72/89 (80.9) (71.2-88.5)
Need of salvage therapy for CR			
Yes	27/38 (71.1) (54.1-84.6)	27/36 (75.0) (57.8-87.9)	25/34 (73.5) (55.6-87.1)
No	60/74 (81.1) (70.3-89.3)	54/66 (81.8) (70.4-90.2)	51/63 (81.0) (69.1-89.8)
Unknown	1/1 (100.0) (2.5-100.0)	1/1 (100.0) (2.5-100.0)	1/1 (100.0) (2.5-100.0)
Previous anti-tumor radiotherapies			
Yes	40/51 (78.4) (64.7-88.7)	39/49 (79.6) (65.7-89.8)	37/47 (78.7) (64.3-89.3)
Unknown	48/62 (77.4) (65.0-87.1)	43/54 (79.6) (66.5-89.4)	40/51 (78.4) (64.7-88.7)

Incidence of neurologic events during cycle 1			
Yes	41/52 (78.8) (65.3-88.9)	39/50 (78.0) (64.0-88.5)	34/45 (75.6) (60.5-87.1)
No	47/61 (77.0) (64.5-86.8)	43/53 (81.1) (68.0-90.6)	43/53 (81.1) (68.0-90.6)
Time from diagnosis to start of blinatumomab			
≤ 12 months	51/70 (72.9) (60.9-82.8)	46/61 (75.4) (62.7-85.5)	44/59 (74.6) (61.6-85.0)
> 12 months	37/43 (86.0) (72.1-94.7)	36/42 (85.7) (71.5-94.6)	33/39 (84.6) (69.5-94.1)
Time from last treatment to start of blinatumomab			
≤ 6 months	70/95 (73.7) (63.6-82.2)	64/85 (75.3) (64.7-84.0)	59/80 (73.8) (62.7-83.0)
> 6 months	18/18 (100.0) (81.5-100.0)	18/18 (100.0) (81.5-100.0)	18/18 (100.0) (81.5-100.0)
Clinical Trial Material			
CTM4 only	57/73 (78.1) (66.9-86.9)	53/66 (80.3) (68.7-89.1)	49/62 (79.0) (66.8-88.3)
CTM5 only	29/38 (76.3) (59.8-88.6)	27/35 (77.1) (59.9-89.6)	26/34 (76.5) (58.8-89.3)
CTM4 & CTM5	2/2 (100.0) (15.8-100.0)	2/2 (100.0) (15.8-100.0)	2/2 (100.0) (15.8-100.0)

N = Number of subjects in the analysis set
[a] MRD = Minimal residual disease

Effect of baseline covariates on Key secondary endpoint (RFS), OS and TTHR

Table 26: RFS by covariate level (univariate analysis) – key secondary EP FAS

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Age					0.36
18 - 34	16/33	24.6	0.64	Reference	
35 - 54	23/40	17.9	0.50	1.30 (0.68, 2.45)	
55 - 64	17/23	12.3	0.43	1.76 (0.89, 3.49)	
≥65	6/14	NE	0.57	0.95 (0.37, 2.42)	
Gender					0.45
Male	34/64	22.3	0.56	Reference	
Female	28/46	18.1	0.50	1.21 (0.74, 2.00)	
Patients by t(4;11) translocation and/or MLL-AF4+ ALL hematological remission					0.59
Yes	2/5	NE	0.60	Reference	
No	50/83	18.3	0.50	1.61 (0.39, 6.62)	
Unknown	10/22	24.6	0.64	1.20 (0.26, 5.48)	
Relapse history					0.0044
Patients in 1st CR	36/75	24.6	0.62	Reference	
Patients in 2nd CR and 3rd CR	26/35	11.0	0.34	2.09 (1.26, 3.48)	
MRD level at baseline					0.23
≥10xE-2 and <10xE0	32/51	18.9	0.51	1.37 (0.82, 2.27)	
<10xE-2	28/57	35.2	0.58	Reference	
WBC at first diagnosis					0.70
≤30,000/mm^3	41/74	18.9	0.54	Reference	
>30,000/mm^3	10/17	14.8	0.47	1.15 (0.57, 2.29)	
Need of salvage therapy for CR					0.99
Yes	20/37	18.7	0.54	Reference	
No	41/72	19.2	0.53	1.00 (0.58, 1.70)	

KM=Kaplan-Meier. CR=Complete remission. CI=Confidence Interval. NE=not estimable. a Events are relapses, secondary leukemia and deaths. b The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer relapse-free survival compared to the reference group.

Table 27: OS by covariate level (univariate analysis) –FAS

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Age					0.48
18 - 34	17/36	36.5	0.64	Reference	
35 - 54	19/41	40.4	0.63	0.96 (0.50, 1.85)	
55 - 64	13/24	19.2	0.58	1.21 (0.59, 2.50)	
≥65	4/15	NE	0.80	0.50 (0.17, 1.48)	
Gender					0.27
Male	28/68	NE	0.68	Reference	
Female	25/48	20.6	0.60	1.36 (0.79, 2.33)	
Philadelphia disease					0.017
Philadelphia positive	4/5	7.2	0.20	3.51 (1.26, 9.83)	
Philadelphia negative	49/111	36.5	0.67	Reference	

Table 28: time to relapse by covariate level (univariate analysis) – key secondary EP FAS

	Events[a]/Patients	Median (Months)	18 months KM estimate	Hazard Ratio[b] (95% CI)	P-value
Age					0.92
18 - 34	12/33	NE	0.72	Reference	
35 - 54	13/40	NE	0.70	0.96 (0.44, 2.12)	
55 - 64	9/23	22.3	0.58	1.28 (0.54, 3.05)	
≥65	5/14	NE	0.62	1.05 (0.37, 2.97)	
Gender					0.84
Male	24/64	NE	0.67	Reference	
Female	15/46	NE	0.68	0.94 (0.49, 1.79)	
Patients by t(4;11) translocation and/or MLL-AF4+ ALL hematological remission					0.62
Yes	1/5	NE	0.80	Reference	
No	32/83	NE	0.65	1.99 (0.27, 14.61)	
Unknown	6/22	NE	0.76	1.42 (0.17, 11.81)	
Relapse history					0.0031
Patients in 1st CR	20/75	NE	0.76	Reference	
Patients in 2nd CR and 3rd CR	19/35	15.0	0.48	2.60 (1.38, 4.89)	
MRD level at baseline					0.19
≥10xE-2 and <10xE0	21/51	24.6	0.65	1.54 (0.80, 2.96)	
<10xE-2	16/57	NE	0.72	Reference	
WBC at first diagnosis					0.18
≤30,000/mm^3	25/74	NE	0.68	Reference	
>30,000/mm^3	9/17	24.6	0.50	1.69 (0.79, 3.64)	

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29: Summary of Efficacy for trial MT103-203

Title: A confirmatory multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody Blincyto in adult patients with minimal residual disease (MRD) of B-precursor acute lymphoblastic leukemia			
Study identifier	MT103-203		
Design	Phase II ongoing open-label, confirmatory, multicenter, single-arm study		
	Duration of main phase:		39 months
Hypothesis	Statistical hypotheses for MRD response tested in this study: H0 π ≤ p0 (44%) vs H1 π ≥ p1 (61%) based on Fleming's standard single-stage procedure but using the exact binomial distribution with a one-sided type I error of 2.5% and a power of 90%.		
Treatment group	Blincyto		A cycle consisted a cIV infusion at 15µg/m2/day a constant flow rate over 28 days followed by an infusion free period of 14day. Subjects received at least 1 and up to 4 consecutive cycles of Blincyto N=116 (FAS), N=113 (Primary endpoint FAS)
Endpoints and definitions	Primary endpoint	MRD rate	Proportion of subjects who achieved a complete MRD response defined by the absence of MRD after 1 cycle of treatment with Blincyto
	Key Secondary endpoint	RFS rate	Hematological relapse-free survival rate at 18M following initiation of Blincyto, in Ph- subjects censored at HSCT or post-Blincyto chemotherapy. Hematological relapse defined as >5% leukemia cells in BM, presence of circulating leukemia blasts or extramedullary leukemia (whichever occurs first)
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	Mortality rate within 100d after alloHSCT	KM rate of subjects dying within 100d after HSCT
	Secondary endpoint	TTHR	Time to hematological relapse was measured from the start of Blincyto infusion until the subject experienced hematological or extramedullary relapse. Subjects who died or received HSCT or post-Blincyto chemotherapy after Blincyto were censored at their last hematological assessment prior to death or HSCT or post-Blincyto chemotherapy (whichever occurred first).

	Secondary endpoint	Duration of complete MRD response	Time from onset of MRD negativity until MRD or haematological relapse or date of last confirmation of negativity MRD status
	Secondary endpoint		Effect on MRD level
	Secondary endpoint		Overall incidence and severity of AEs
	Secondary endpoint		Subjects quality of life during and after therapy
Database lock	Primary efficacy 21/02/2014, Key secondary efficacy 05/08/2015		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	FAS: 116; Primary endpoint full analysis set: 113 Primary endpoint per protocol set: 98 Key secondary endpoint full analysis set: 110 Key secondary endpoint per protocol set: 96 HSCT full analysis set: 74 HSCT per protocol set: 66	
Descriptive statistics and estimate variability	Treatment group	Blincyto
	Number of subject	Primary endpoint full analysis set: 113 Key secondary endpoint full analysis set: 110
	Complete MRD response at C1	77.9% (95% CI: 69.1%, 85.1%)
	RFS (median)	NE (6.3, NE) censored at HSCT or post-Blincyto chemotherapy 18.9 months (12.3, 35.2) not censored at HSCT or post-Blincyto chemotherapy Landmark from 3M: HSCT 16.1M, No HSCT 22.1M Landmark from 6M: HSCT 29.2M, No HSCT n.e.
	RFS (18M KM estimate)	54% (33%, 70%) with censored at HSCT or post-Blincyto chemotherapy 53% (44%, 62%) not censored at HSCT or post-Blincyto chemotherapy with HSCT
	OS (median)	NE (NE, NE) with censored at HSCT or post-Blincyto chemotherapy 36.5 months (19.2, NE) not censored at HSCT or post-Blincyto chemotherapy Landmark from 3M: HSCT 21.2M, No HSCT 33.5M Landmark from 6M: HSCT 30.5M, No HSCT n.e.
	OS (18M KM estimate)	83% (55%, 94%) with censored at HSCT or post-Blincyto chemotherapy 65% (55%, 73%) not censored at HSCT or post-Blincyto chemotherapy
	TTHR (median)	NE (7.1, NE) with censored at HSCT or post-Blincyto chemotherapy NE (24.3, NE) not censored at HSCT or post-Blincyto chemotherapy
	Duration of complete MRD response (median)	45.0 months (95% CI: 6.5, 45.0) with censored at HSCT or post-Blincyto chemotherapy 17.3 months (95% CI: 12.6, 23.3) not censored at HSCT or post-Blincyto chemotherapy

Effect estimate per comparison	Endpoints	MT103-203	Historical analysis
	RFS (not censored at HSCT)	Median:18.9 M (95% CI: 12.3, 35.2)	9.9 M (95% CI: 6.8, 12.9)
		KM at 18M:	41% (95% CI: 34%, 49%)
	OS (not censored at HSCT)	Median: 36.5 M (95% CI: 19.2, NE)	27.6 M (95% CI: 17.3, 39.6)
		KM at 18M: 65% (95% CI: 55%, 73%)	56% (95% CI: 49%, 64%)
	Endpoints analysis adjusted by propensity score method	Blincyto	control
	RFS HSCT adjusted	HR (95% CI): 0.5 (0.32, 0.78)	
	OS HSCT adjusted	HR (95% CI): 0.76 (0.47, 1.24)	
Notes	RFS and TTHR were measured from the start of Blincyto infusion, not from CR documented for the first time, despite of big difference in the interval between documented CR and the start of Blincyto infusion.		

Analysis performed across trials (pooled analyses and meta-analysis)

Historical comparator study 20120148: "A retrospective analysis of Hematological RFS and OS in adult patients with Philadelphia-negative B-precursor ALL in complete hematological remission with MRD"

Historical data collection: between 02/10/2013 and 14/03/2014 from Czech Republic, France, Germany, UK, Italy, Poland, Spain and Russian study group data bases. The objective was to estimate the mortality rate (proportion) at 100 days following alloHSCT in patients who received an alloHSCT after MRD detection.

Research methods

Study design

Study 20120148 was a retrospective non-interventional cohort study of historical treatment and outcome data from MRD-positive subjects with Philadelphia chromosome-negative B-cell precursor ALL who had achieved complete haematological remission through receiving standard-of-care treatment according to national study protocols. The study population was assembled from patient databases of ALL study groups in Europe and Russia that included MRD testing in their protocols. All subjects who were treated at participating study group facilities, diagnosed with ALL in the year 2000 to 2013.

Study population

The direct comparison analysis set (DCAS) was a post-hoc additional analysis set defined as follows:

- adult subjects ≥18 years with Philadelphia chromosome-negative B-cell precursor ALL
- with MRD at a level of ≥ 1x 10-3 (molecular failure or molecular relapse) detected by PCR or by flow cytometry (i.e. regardless of detection method)
- time to relapse from the date of MRD detection greater than 14 days
- in CR1 (defined as less than 5% blasts in bone marrow after at least 3 intensive chemotherapy blocks, i.e. any standard or investigational regimen according to adult protocols)

- initial diagnosis of ALL occurred in the year 2000 or later
- Subjects were excluded from the analysis if they had extramedullary disease at the time point of MRD detection, were exposed to Blincyto within 18 months of MRD detection, or underwent allogeneic HSCT before MRD detection at required level.

Endpoints

Table 30: key efficacy endpoint definitions and statistical analysis methods

Efficacy Endpoint	Definition	Statistical Methods	Censoring
Primary Hematologic RFS	Calculated as the time from first MRD detection following CR1 (after at least 3 blocks of chemotherapy per inclusion criterion) to hematologic relapse or death. Based on DCAS (adult subjects 18 years or older with Philadelphia chromosome-negative B-cell precursor ALL in CR1 with MRD at a level of 1 x 10^{-3} or higher as detected by PCR or flow cytometry, with a time to relapse greater than 14 days from the date of MRD detection, and in first relapse) and the FAS (subjects 15 years or older with Philadelphia chromosome-negative B-cell precursor ALL in complete hematologic remission with MRD level of at least 1 x 10^{-4} regardless of detection method).	Median, range, Q1 and Q3 with 2-sided 95% CI by KM KM proportions at select time points Univariate Cox regressions to assess predictors of RFS Multivariate Cox regression with variables selection through forward selection, criterion for entry p-value < 0.10 Mantel-Byar analysis tested the null hypothesis that RFS is the same with or without allogeneic HSCT. It is an unbiased modification of the log-rank test where subjects may dynamically convert from the no-HSCT risk set to the HSCT risk set on the date of the procedure (Lee et al, 1982). Cox proportional hazard model defining allogeneic HSCT as a time-dependent covariate. Subjects who had transplants contributed to the estimation of RFS as subjects who had not received transplants from baseline to the date of allogeneic HSCT, then as subjects who received transplants from allogeneic HSCT to relapse/death or censor.	Censored at last disease assessment for subjects alive without relapse Censored and uncensored at HSCT
Secondary OS	Calculated as the time from MRD detection to death	Median, range, Q1 and Q3 with 2-sided 95% CI by KM Mantel-Byar analysis, as described for RFS Cox proportional hazard model, as described for RFS with death or censor as ending time	Censored at last disease assessment for subjects alive without relapse Censored and uncensored at HSCT

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CR1 = first complete remission; DCAS = direct comparison analysis set; FAS = full analysis set; HSCT = hematopoietic stem cell transplant; KM = Kaplan Meier; MRD = minimal residual disease; OS = overall survival; PCR = polymerase chain reaction; RFS = relapse-free survival

Objectives

This histological comparator study aimed to provide a frame of reference for single-arm pivotal and supportive studies in MRD+ adult ALL patients.

Primary objective:

- To estimate the RFS in patients with characteristics that correspond to the characteristics of subjects in the primary analysis of hematological RFS in study MT103-203: ≥18 years of age with MRD detected by PCR at a level of 1x10-3 or higher

Secondary objectives:

- To estimate the hematological RFS in patients with more general characteristics: ≥ 15 years with MRD-positive regardless of level or detection method

- To estimate OS in the 2 sets of patients described above
- To estimate the hematological RFS and OS in patients who did not receive allogeneic hematopoietic stem cell transplant (alloHSCT)
- To estimate the hematological RFS and OS in patients who received alloHSCT

Results

Disposition and demographics

182 subjects of a total population of 287 patients (FAS) constituted post-hoc DCAS. 32.4% of the subjects had their initial ALL diagnosis between 2000 and 2004, 58.8% were diagnosed between 2005 and 2010, with only 8.8% being diagnosed after 2010. German (n=70), Italy (n=47), France (n=25) and Poland (n=25) contributed to more than 90% of dataset.

A summary of demographic and baseline disease characteristics is presented in tables 3-6.

Table 31: Demographic characteristics

	Full Analysis Set (N = 287)	Direct Comparison Analysis Set (N=182)
Sex - n (%)		
Male	168 (59)	102 (56)
Female	119 (41)	80 (44)
Age at primary diagnosis (years)		
Mean	34.79	36.27
SD	13.39	13.65
Median	32.00	33.00
Q1, Q3	23.00, 44.00	24.00, 47.00
Min, Max	15.0, 65.0	18.0, 65.0
Age group at diagnosis – n (%)		
15 - 34	163 (56.79)	98 (53.85)
35 - 54	89 (31.01)	56 (30.77)
55 - 64	34 (11.85)	27 (14.84)
>= 65	1 (0.35)	1 (0.55)

Table 32: Baseline Disease characteristics

	Full Analysis Set (N = 287)	Direct Comparison Analysis Set (N=182)
Time from initial diagnosis to baseline MRD status[a] (months)		
n	285	182
Mean	6.0	6.1
SD	6.2	6.1
Median	4.2	4.3
Q1, Q3	3.5, 5.3	3.6, 5.5
Min, Max	1, 60	1, 60
Time from initial diagnosis to baseline MRD status group – n (%)		
<6 months	230 (80.1)	142 (78.0)
>=6 months	55 (19.2)	40 (22.0)
Unknown	2 (0.7)	0 (0.0)
Year of initial diagnosis – n (%)		
2000 to 2004	99 (34.5)	59 (32.4)
2005 to 2010	158 (55.1)	107 (58.8)
2010 or Later	30 (10.5)	16 (8.8)
Cytogenetic/molecular aberrations[b] – n (%)		
Philadelphia chromosome t(9;22)/bcr-abl	0 (0)	0 (0)
t(4;11)MLL-AF4	20 (7)	15 (8)
No	229 (80)	139 (76)
Other	37 (13)	27 (15)
Unknown	1 (0)	1 (1)
WBC at diagnosis – n (%)		
<30,000/µl	207 (72.1)	130 (71.4)
>=30,000/µl	77 (26.8)	51 (28.0)
Unknown	3 (1.0)	1 (0.5)
Group at study entry – n (%)		
Continuous first complete remission	284 (99)	182 (100)
Molecular failure[c]	223 (78)	138 (76)
Molecular relapse[d]	59 (21)	42 (23)
Molecular failure after relapse treatment	3 (1)	0 (0)
Number of MRD positive time points – n (%)		
1	251 (87.5)	158 (86.8)
2	18 (6.3)	12 (6.6)
3	18 (6.3)	12 (6.6)

Table 33 History of ALL treatment

	Full Analysis Set (N = 287)	Direct Comparison Analysis Set N=182)
Previous chemotherapy protocol – n (%)		
GMALL	117 (41)	76 (42)
GIMEMA	7 (2)	6 (3)
GRAALL	41 (14)	25 (14)
PETHEMA	10 (3)	8 (4)
UKALL	4 (1)	1 (1)
NILG	51 (18)	27 (15)
OTHER	57 (20)	39 (21)
Previous autologous HSCT – n (%)		
Yes	1 (0)	1 (1)
No	286 (100)	181 (99)
Prior Radiotherapy – n (%)		
Yes	168 (59)	105 (58)
Total body	0 (0)	0 (0)
Whole brain	167 (58)	104 (57)
Spinal cord	1 (0)	1 (1)
Mediastinum	0 (0)	0 (0)
Other	0 (0)	0 (0)
No	117 (41)	76 (42)
Unknown	2 (1)	1 (1)

Table 34: Baseline MRD status

	Full Analysis Set (N = 287)	Direct Comparison Analysis Set (N=182)
Baseline MRD status[a] – n (%)		
Persistent	223 (77.70)	138 (75.82)
Relapsed	59 (20.56)	42 (23.08)
Unknown	5 (1.74)	2 (1.10)
Methodology – n (%)		
PCR	230 (80.14)	130 (71.43)
Flow Cytometry	57 (19.86)	52 (28.57)
Sensitivity of assay – n (%)		
> 1x10^-4	51 (17.77)	46 (25.27)
1x10^-4 - 1x10^-5	234 (81.53)	134 (73.63)
< 1x10^-5	0 (0.00)	0 (0.00)
Missing	2 (0.70)	2 (1.10)

MRD level at baseline		
n	272	182
Mean	0.0322	0.0461
SD	0.1754	0.2129
Median	0.0027	0.0062
Q1, Q3	0.0007, 0.0100	0.0020, 0.0200
Min, Max	0.000, 2.400	0.001, 2.400
MRD level at baseline - n (%)		
>= 10^-0	2 (0.7)	2 (1.1)
>= 1x10^-1 to < 10^-0	13 (4.5)	11 (6.0)
>= 1x10^-2 to < 10^-1	71 (24.7)	65 (35.7)
>= 1x10^-3 to < 10^-2	109 (38.0)	104 (57.1)
>= 1x10^-4 to < 10^-3	77 (26.8)	0 (0.0)
Missing[b]	15 (5.2)	0 (0.0)

Table 35: Differences between DCAS of historical study and the FAS of Study MT103-203

	Pivotal Study MT103-203 N=116 (FAS)	Historical study 20120148 N=182 (DCAS)
Age (mean) 18-34 35-54 55-64 ≥65	44.6 years 31.0% 35.3% 20.7% 12.9%	36.3 years 53.9% 30.8% 14.9% 0.6%
Time from initial diagnosis (months) Mean (SD) Median (Q1, Q3)	to 1st dose of Blincyto: 20.4 (31.0) 8.1 (5.1, 22.9)	to baseline MRD status: 6.1 (6.1) 4.3 (3.6, 5.5)
WBC at diagnosis ≥ 30,000/µl	15.5%	28.0%
Previous radiotherapy	44%	58%
Relapse history CR1 CR2/CR3	64.7% 35.3%	100% 0%
HSCT post-baseline	77.6% (90/116)	36.8%
Diagnosis time	2011-2014	2000-2010 (one-third before 2004)
Time from last anti-leukemia chemotherapy to MRD detection	At least 2 weeks	Not provided
Time from CR1 documented for the first time to MRD detection	Not provided	Not provided
Time from MRD detection to	initiation of Blincyto: 14 days?	Initiation of 2nd line chemotherapy: not provided

Efficacy

RFS in the direct comparison analysis set (DCAS)

The median duration of hematologic RFS uncensored at HSCT, was 9.9 months (95% CI: 6.8, 12.9) from the baseline MRD assessment, with 41% (95% CI: 34%, 49%) of subjects alive without relapse at 18 M.

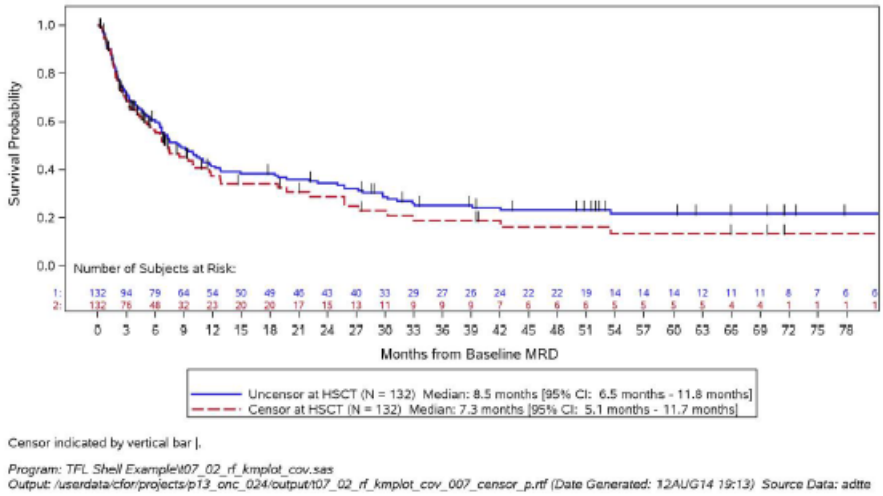
When analysis was censored at HSCT, the median duration of hematologic RFS was 8.5 months (95% CI: 5.6, 12.3) from the baseline MRD assessment, and at 18 months 37% (95% CI: 28, 46) of subjects alive without relapse.

Table 36: Haematological RFS analysis Study 20120148

		Uncensored at HSCT
	Full Analysis Set (N = 285)	Direct Comparison Analysis Set (N=182)
Subject Status		
Events - n(%)	190 (66.67)	131 (71.98)
Death in CR	26 (9.12)	14 (7.69)
Relapse	164 (57.5)	117 (64.3)
Censored - n(%)	95 (33.3)	51 (28.0)
Time to Event(months)		
KM Median (95% CI)	12.9 (10.6, 21.3)	9.9 (6.8, 12.9)
KM Q1, Q3	4.3, .	2.7, 47.9
Min, Max	0.2, 126.5	0.5, 126.5
KM proportion (95% CI)		
Month 3	0.79 (0.74, 0.83)	0.72 (0.65, 0.79)
Month 6	0.69 (0.64, 0.74)	0.61 (0.54, 0.69)
Month 9	0.61 (0.55, 0.66)	0.52 (0.44, 0.59)
Month 12	0.53 (0.47, 0.59)	0.45 (0.38, 0.53)
Month 18	0.47 (0.41, 0.53)	0.41 (0.34, 0.49)
Month 24	0.42 (0.36, 0.48)	0.37 (0.30, 0.44)
Month 30	0.38 (0.32, 0.44)	0.32 (0.25, 0.39)
Month 36	0.34 (0.29, 0.40)	0.28 (0.21, 0.34)

		Censored at HSCT
	Full Analysis Set (N = 285)	Direct Comparison Analysis Set (N=182)
Subject Status		
Events - n(%)	133 (46.67)	95 (52.20)
Death in CR	9 (3.16)	5 (2.75)
Relapse	124 (43.5)	90 (49.5)
Censored - n(%)	152 (53.3)	87 (47.8)
Time to Event(months)		
KM Median (95% CI)	12.7 (9.4, 21.2)	8.5 (5.6, 12.3)
KM Q1, Q3	3.9, 53.6	2.5, 30.3
Min, Max	0.1, 125.2	0.3, 125.2
KM proportion (95% CI)		
Month 3	0.77 (0.72, 0.82)	0.69 (0.62, 0.76)
Month 6	0.66 (0.60, 0.73)	0.57 (0.49, 0.65)
Month 9	0.60 (0.53, 0.66)	0.49 (0.40, 0.58)
Month 12	0.52 (0.45, 0.59)	0.42 (0.33, 0.51)
Month 18	0.45 (0.38, 0.53)	0.37 (0.28, 0.46)
Month 24	0.40 (0.32, 0.47)	0.31 (0.22, 0.41)
Month 30	0.36 (0.29, 0.44)	0.26 (0.17, 0.36)
Month 36	0.31 (0.24, 0.39)	0.21 (0.12, 0.30)

Figure 14: Kaplan- Meier plot of haematological RFS
Uncensored and censored at allogeneic HSCT (Primary analysis set)



OS

In the direct comparison analysis set (DCAS), the median OS duration uncensored at HSCT was 27.6 months (95% CI: 17.3, 39.6) from the baseline MRD assessment, and at 18 months 56% (95% CI: 49%, 64%) of subjects were alive.

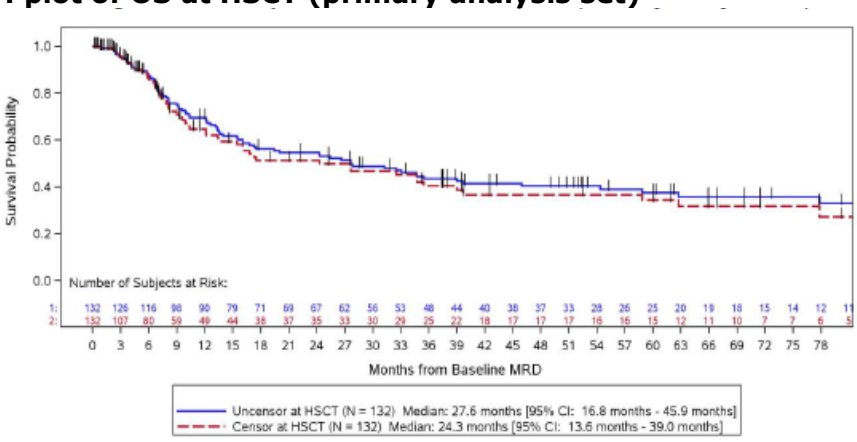
When analysis were censored at HSCT, the median OS (95% CI) duration in the DCAS was 18.0 months (95% CI: 13.6, 35.4) with 50% of subjects alive at 18 months (40, 59).

Table 37: OS analysis_ Study 20120148

	Full Analysis Set uncensored at HSCT* (N = 285)	Direct Comparison Analysis Set uncensored at HSCT* (N = 182)
Subject Status		
Events - n(%)	157 (55.09)	107 (58.79)
Censored - n(%)	128 (44.9)	75 (41.2)
Time to Event(months)		
KM Median (95% CI)	34.7 (24.3, 50.6)	27.6 (17.3, 39.6)
KM Q1, Q3	10.6, 123.9	8.1, 123.9
Min, Max	0.9, 137.8	0.9, 137.8
KM proportion (95% CI)		
Month 3	0.97 (0.95, 0.99)	0.95 (0.92, 0.98)
Month 6	0.88 (0.85, 0.92)	0.86 (0.81, 0.91)
Month 9	0.80 (0.75, 0.84)	0.74 (0.68, 0.81)
Month 12	0.73 (0.68, 0.79)	0.69 (0.62, 0.76)
Month 18	0.61 (0.56, 0.67)	0.56 (0.49, 0.64)
Month 24	0.57 (0.51, 0.63)	0.54 (0.46, 0.61)
Month 30	0.53 (0.47, 0.59)	0.49 (0.42, 0.57)
Month 36	0.48 (0.42, 0.55)	0.44 (0.36, 0.52)

	Full Analysis Set Censored at HSCT (N = 285)	Direct Comparison Analysis Set Censored at HSCT (N=182)
Subject Status		
Events - n(%)	102 (35.79)	73 (40.11)
Censored - n(%)	183 (64.2)	109 (59.9)
Time to Event(months)		
KM Median (95% CI)	32.5 (21.6, 43.6)	18.0 (13.6, 35.4)
KM Q1, Q3	9.9, 123.9	7.9, 84.4
Min, Max	0.1, 137.8	0.3, 137.8
KM proportion (95% CI)		
Month 3	0.97 (0.95, 0.99)	0.96 (0.92, 0.99)
Month 6	0.86 (0.82, 0.91)	0.84 (0.78, 0.90)
Month 9	0.78 (0.72, 0.84)	0.70 (0.62, 0.78)
Month 12	0.72 (0.66, 0.79)	0.63 (0.55, 0.72)
Month 18	0.60 (0.52, 0.67)	0.50 (0.40, 0.59)
Month 24	0.55 (0.47, 0.62)	0.48 (0.39, 0.58)
Month 30	0.51 (0.44, 0.59)	0.45 (0.35, 0.54)
Month 36	0.46 (0.38, 0.54)	0.39 (0.29, 0.49)

Figure 15: K-M plot of OS at HSCT (primary analysis set)



Censor indicated by vertical bar |.

Program: TFL Shell Example\t07_04_os_kmplot_cov.sas
Output: /userdata/cfor/projects/p13_onc_024/output/t07_04_os_kmplot_cov_007_censor_p.rtf (Date Generated: 12AUG14 19:13) Source Data: adtte

100-day mortality post-HSCT

Among the 70 subjects in the DCAS who had an allogeneic HSCT, mortality 100 days after receiving the transplant was 8.6% (95% CI: 2.0, 15.2)

Table 38: A summary of key results

Outcome	Primary Analysis Set Estimate	(95% CI)	Direct Comparison Analysis Set Estimate	(95% CI)
Hematological RFS				
Median, months	8.5	(6.5 - 11.8)	9.9	(6.8, 12.9)
At 18 Months, %	38%	(30% - 47%)	41%	(34%, 49%)
DoR				
Median, months	10.6	(7.4 - 19.7)	11.8	(8.6, 19.7)
At 18 Months, %	43%	(35% - 52%)	46%	(38%, 53%)
OS				
Median, months	27.6	(16.1 - 45.9)	27.6	(17.3, 39.6)
At 18 Months, %	56%	(48% - 65%)	56%	(49%, 64%)
Censoring at alloHSCT				
RFS at 18 Months, %	34%	(24% - 45%)	37%	(28%, 46%)
DoR at 18 Months, %	31%	(20% - 43%)	40%	(30%, 49%)
OS at 18 Months, %	51%	(41% - 62%)	50%	(40%, 59%)
Mortality after alloHSCT				
At 100 days, %	8.2%	(0.5% - 15.8%)	8.6%	(2.0%, 15.2%)

Propensity Score analysis

Objective:

A propensity score analysis was conducted to compare historical control Study 20120148 subjects with the clinical study MT103-203 subjects with respect to RFS and OS in the DCAS after making adjustments for each study patient's propensity score and controlling for HSCT.

To meet the RFS and OS comparison objectives, the first step was to achieve adequate balance between historical control population and the Blincyto study population using a propensity score approach. Once this balance was achieved, RFS and OS analyses were conducted by making adjustments for each patient's propensity score.

Endpoints:

The primary endpoint was RFS, defined as the time from the baseline date until the first event of hematological or extramedullary relapse, secondary leukemia, or death due to any cause, whichever occurs first (Cheson, 2003). The secondary endpoint was OS. Patients who did not have an event were censored on the date of their last hematological assessment.

OS was defined as the time from the baseline date until death from any cause. Patients who did not die were censored on the last date the patient was known to be alive.

The baseline date for both relapse-free and overall survival was defined as 14 days after the MRD baseline date for historical control patients and the date of the first Blincyto treatment for Blincyto patients.

Study Design/Type:

This was a retrospective, post-hoc propensity score analysis of adult patients with MRD of B-precursor acute lymphoblastic leukemia. The propensity score in this context was the propensity to be treated with Blincyto.

Methods:

The databases from the MT103-203 study and historical control study were merged programmatically and used for analysis. Data from the historical control study 20120148 were filtered to match the key inclusion criteria from the MT103-203 study so that key study endpoints could be summarized to provide a historical context to the Blincyto efficacy results from the MT103-203 study. Because the historical data mostly included patients in first remission, only that patient subgroup was analyzed for the primary analysis. In addition to the primary analysis which included patients in their first remission with MRD>1 x 10-3 detected at baseline by PCR or flow cytometry, two additional analysis sets were defined: (1) restricting the data to only those with baseline MRD detected by PCR, and (2) including subjects in 2nd and 3rd remission. Separate propensity score analyses were performed for each analysis set.

Propensity scores were derived for each patient via a variable selection algorithm for logistic regression models that included age at primary diagnosis, sex, country, presence of t(4;11)MLL-AF4, time from primary diagnosis to MRD baseline, baseline MRD level, white blood cells at diagnosis, and the GMALL regimen as prior chemotherapy. The dependent variable for these models was whether or not the subject was treated with Blincyto (i.e. came from the MT103-203 study). The propensity score-based weight formula chosen was that for average treatment effects (ATE), which estimates the average treatment effect from moving the entire population from untreated to treated (Imbens, 2004). This approach mirrors the objective of a randomized study. For an exploratory sensitivity analysis, average treatment effect of the treated weights were also considered (ATT).

Inverse probability of treatment weights (IPTW) were derived from the scores for each subject according to their treatment status, and the balance between the two groups with respect to the baseline covariates, after weighting, was assessed primarily by evaluating standardized differences. To reduce the influence of extreme IPTW values, stabilized IPTW (sIPTW) were applied for the primary analysis. RFS and OS were then analysed using weighted Cox proportional hazard models with the treatment indicator as a baseline covariate and including a time-varying covariate for HSCT. A hazard ratio (HR) and 95% confidence interval (CI) were calculated to measure the risk of RFS or death among Blincyto-treated subjects relative to historical controls. Sensitivity analyses excluding the HSCT time-varying covariate were conducted in order to ascertain robustness. RFS and OS estimates at specific time-points could only be calculated from the models that did not adjust for HSCT.

Results

Covariate balance was assessed before and after weighting, calculating standardized differences between treatment groups, and using univariate models for each covariate with treatment as the predictor. Covariate balance before and after adjustment according to sIPTW for the primary analysis set is shown in Table 15.

Table 15. Covariate Balance Before and After Propensity Score Adjustments With Stabilized IPTW: Propensity Score Analysis

Characteristic	Unweighted				Stabilized IPTW			
	Control	Blinatumomab	Standard	P-value[a]	Control	Blinatumomab	Standard	P-value
Mean (SD)/n (%)	(N=182)	(N=73)	Difference		(N=174.3)	(N=78.5)	Difference	
Age at primary diagnosis (years)	36.3 (13.6)	44.8 (16.6)	-0.56	<0.001	37.8 (13.8)	36.5 (16.4)	0.09	0.573
Gender (Female)	80 (44.0)	32 (43.8)	0.00	0.986	76.6 (43.9)	27.0 (34.4)	0.20	0.226
Country (Not Germany)	112 (61.5)	35 (47.9)	0.28	0.048	143.6 (58.8)	151.6 (55.3)	0.07	0.674
MRD at Baseline (recoded)	-1.5 (0.6)	-1.7 (0.7)	0.16	0.249	-1.6 (0.60)	-1.5 (0.8)	-0.08	0.688
Time from diagnosis to baseline (months)	6.6 (6.1)	12.8 (14.3)	-0.56	<.001	7.3 (7.2)	8.1 (9.7)	-0.09	0.463
WBC at diagnosis (>30 000/mm^3)	51 (28.0)	15 (20.5)	0.17	0.220	45.2 (26.0)	19.1 (24.3)	0.04	0.822
WBC at diagnosis (continuous, log10)	4.15 (0.62)	0.533	0.26	0.072	4.13 (0.60)	4.07 (0.60)	0.10	0.542
t(4;11)MLL-AF4 mutation (Yes)	15 (8.2)	5 (6.8)	0.05	0.709	14.1 (8.1)	5.6 (7.2)	0.03	0.820
Prior chemotherapy (GMALL)	76 (41.8)	42 (57.5)	-0.32	0.023	78.0 (44.7)	39.2 (50.0)	-0.10	0.533

GMALL = German Multicenter study Group for Adult Acute Lymphoblastic Leukemia; IPTW = inverse probability of treatment weight; MRD = minimal residual disease; WBC = white blood cell count
Note: Before and after adjustment with stabilized IPTW from propensity score model fitted values. An absolute standard difference of < 0.2 is considered well balanced.
p-value is not related to standard difference, but based on a univariate regression model with covariate as outcome and treatment as predictor.
Source: Table 11-2 of Propensity Score Analysis Report

For this analysis, stabilized IPTW provided the best overall balance of baseline covariates. All but 1 stabilized IPTW adjusted covariate achieved standardized differences less than 0.2 (the standard acceptance cutoff), with only 1 borderline at 0.2. The overlap in the propensity scores between the 2 treatment groups was considered adequate with the criterion that was pre-specified in the statistical analysis plan.

Table 11-3. Summary of Endpoints Analysis Adjusted by Propensity Score Method (Primary Analysis Set)

Endpoint	Control	Blinatumomab	Ratio (95% CI)
Relapse-Free Survival, HSCT adjusted			0.50 (0.32, 0.78)
Overall Survival, HSCT adjusted			0.76 (0.47, 1.24)
Relapse-Free Survival[a]			0.47 (0.30, 0.73)
at 12-month	0.42	0.70	
95% CI	(0.35, 0.50)	(0.61, 0.80)	
at 18-month	0.39	0.67	
95% CI	(0.33, 0.48)	(0.58, 0.78)	
at 24-month	0.35	0.63	
95% CI	(0.28, 0.43)	(0.53, 0.76)	
at 30-month	0.29	0.52	
95% CI	(0.23, 0.37)	(0.41, 0.65)	
Overall Survival[a]			0.68 (0.42, 1.09)
at 12-month	0.67	0.80	
95% CI	(0.60, 0.75)	(0.72, 0.88)	
at 18-month	0.55	0.71	
95% CI	(0.48, 0.63)	(0.62, 0.81)	
at 24-month	0.52	0.67	
95% CI	(0.44, 0.60)	(0.57, 0.79)	
at 30-month	0.48	0.62	
95% CI	(0.41, 0.56)	(0.52, 0.74)	

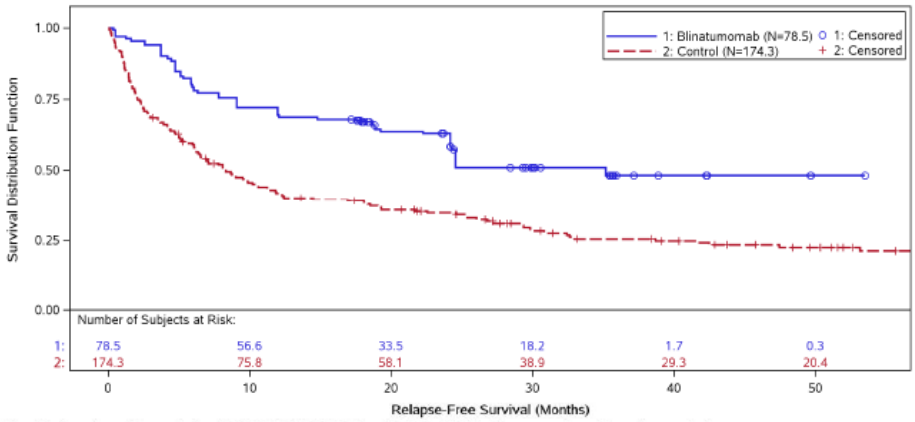
Note: Analysis utilizes the stabilized IPT weights.
[a]Ratio and related time point estimates do not include adjustment for time-varying covariate HSCT
Study snapshot data (MT103_203:18SEPT2015; 20120148:28MAY2015)

Primary endpoint: RFS

The RFS hazard ratio and 95% CI based on the Cox Proportional Hazard model with sIPTW and adjusting for HSCT was estimated at 0.50 (0.32, 0.78), suggesting a statistically significant 50% reduction in the risk of relapse or death associated with Blincyto compared to historical controls.

The 18-month RFS (unadjusted for HCST) was estimated at 0.39 (95% CI = 0.33 to 0.48) for control and 0.67 (95% CI= 0.58 to 0.78) for Blincyto, representing a 1.7 fold increase in 18-month RFS. Kaplan-Meier based median RFS (95% CI), unadjusted for HSCT, was estimated at 8.3 months (6.2, 11.8) for control and 35.2 months (24.2, NE) for Blincyto representing a 26.9 month improvement in median RFS.

Figure 10-14. Kaplan Meier Curve of Relapse-Free Survival (Primary Analysis Set With Stabilized IPTW)

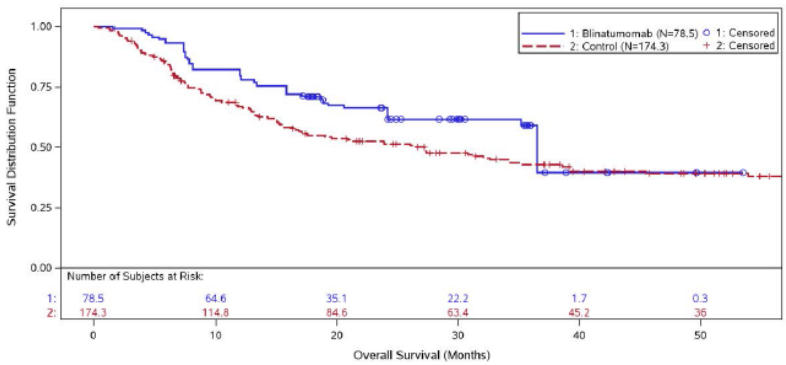


Note: Median relapse-free survival and 95% CI is 35.2 (24.2, -) and 8.3 (6.2, 11.8) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)

Secondary endpoint: OS

The OS hazard ratio and 95% CI based on the Cox proportional hazard model with sIPTW and adjusting for HSCT was estimated at 0.76 (0.47, 1.24), suggesting a directional, but not significant, improvement associated with Blincyto compared to historical controls. The 18-month OS (unadjusted for HCST) was estimated at 0.55 (95% CI = 0.48 to 0.63) for control and 0.71 (95% CI= 0.62 to 0.81) for Blincyto, representing a 1.3 fold increase in 18-month OS. Kaplan-Meier based median OS (95% CI), unadjusted for HSCT, was estimated at 27.2 months (16.4, 38.6) for control and 36.5 months (24.2, NE) for Blincyto, representing a 9.3 month improvement in median OS.

Figure 10-18. Kaplan Meier Curve of Overall Survival (Primary Analysis Set With Stabilized IPTW)



Note: Median overall survival and 95% CI is 36.5 (24.2, -) and 27.2 (16.4, 38.6) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)

Program: /userdata/stat/amg103/meta/propen/analysis/mrd/figures/program/f-ps-km.sas
Output: f-08-001-003-ps-km-os-siptw-pas.rtf (Date Generated: 09FEB16 05:51) Source Data: adam.propsc

The use of propensity score adjustments was successful in creating a balanced population of Blincyto-treated and control subjects with respect to numerous important baseline covariates. This balance allowed for more valid statistical comparisons between the 2 treatment groups that demonstrated a statistically significant improvement in RFS associated with the use of Blincyto (hazard ratio = 0.50, 95% CI: 0.32, 0.78), as well as a directional improvement in OS (hazard ratio = 0.76, 95% CI: 0.47, 1.24), though not statistically significant. Results of the endpoint analyses were largely consistent across analysis sets and sensitivity analyses. Exploratory analyses with alternative propensity score weightings (average treated effect of the treated weights; ATT) suggest a more pronounced treatment effect for OS in favor of Blincyto.

Exploration of HSCT effect:

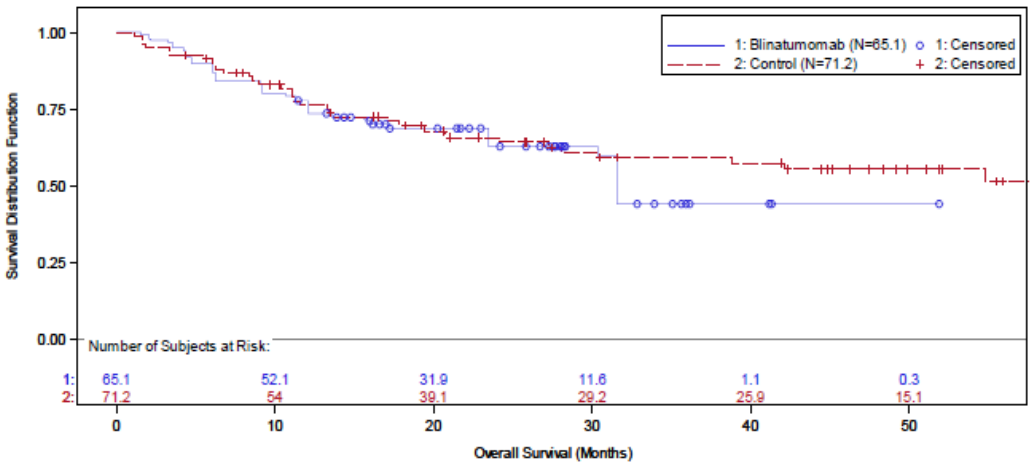
Table 11-4. Evaluation of Treatment by HSCT Interaction for Overall Survival With Propensity Score Adjustment (Primary Analysis Set)

Comparison	At	Hazard Ratio*	(95% CI)
Blinatumomab vs. Control	No HSCT	0.405	(0.165, 0.995)
	After HSCT	1.033	(0.611, 1.748)
HSCT vs. No HSCT	Control	0.617	(0.400, 0.952)
	Blinatumomab	1.574	(0.594, 4.167)

* Estimates are from a Cox proportional hazards model with terms for the treatment group, a time dependent covariate for HSCT, and treatment-by-HSCT interaction using sIPT weights to adjust for the propensity score.
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)
Program: /userdata/stat/amg103/meta/propen/analysis/mrd/tables/program/t-ps-hsct.sas
Output: t-05-001-ps-hsct.rtf (Date generated: 24JUN2016:06:54) Source data: adam.propsc

In order to further evaluate the potential impact of HSCT on the OS treatment effect, additional Cox models were generated with the addition of an interaction term for the treatment group and the time-dependent HSCT covariate and through the use of sIPT weights. With the addition of this term, there was evidence of an interaction effect (p=0.0795). Blincyto was associated with a meaningful improvement in OS prior to or in the absence of HSCT (HR = 0.405, 95% CI = 0.165 to 0.995) but there was no difference in OS following HSCT (HR = 1.03, 95% CI = 0.611 to 1.748). Similarly, undergoing an HSCT was associated with an improvement in OS for the historical control group (HR = 0.617, 95% CI = 0.400 to 0.952) but there was no improvement in OS among the Blincyto group (HR = 1.57, 95% CI = 0.594 to 4.167).

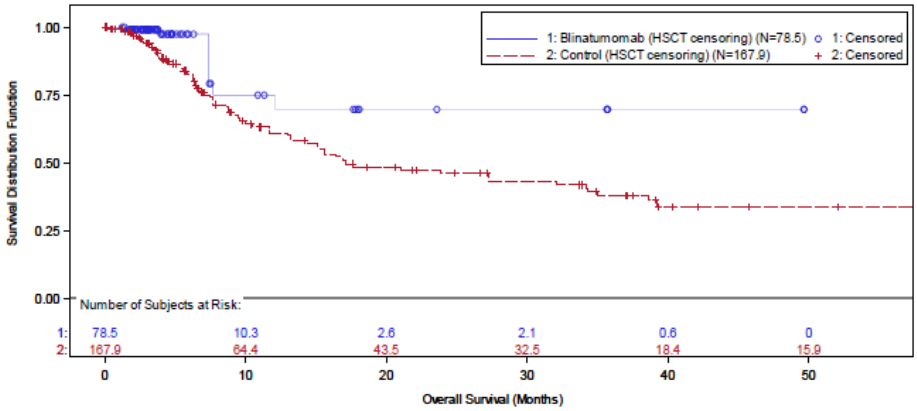
Figure 10-19. Overall Survival After HSCT Propensity-Score Adjusted Kaplan-Meier Estimates (Primary Analysis Set Patients Who Underwent an HSCT)



Note: Median overall survival and 95% CI is 31.6 (23.5, -) and 77.1 (27.2, -) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)

Program: /userdata/stat/amg103/meta/propen/analysis/mrd/figures/program/f-ps-km-hsct.sas
Output: f-08-004-001-ps-km-os-siptw-pas-hsct.rtf (Date Generated: 27JUN16 08:16) Source Data: adam.propsc

Figure 10-20. Overall Survival Censoring for HSCT Propensity-Score Adjusted Kaplan-Meier Estimates (Primary Analysis Set)



Note: Median overall survival and 95% CI is - (7.7, -) and 17.1 (13.2, 34.3) for Blinatumomab and Control respectively
Study snapshot data(MT103_203:18SEPT2015; 20120148:28MAY2015)

Program: /userdata/stat/amg103/mela/propen/analysis/mrd/figures/program/f-ps-km-hsct.sas
Output: f-08-004-002-ps-km-os-siptw-hsct-pas.rtf (Date Generated: 27JUN16 08:16) Source Data: adam.propsc

Supportive study

2.4.1. Study MT103-202

An exploratory open-label, multicenter phase 2 study to investigate the efficacy, safety, and tolerability of the Bi-specific T-cell Engager (BiTE®) MT103 in patients with MRD of positive B-precursor ALL

Study objectives:

Primary objective: to assess the efficacy of Blincyto as defined by the effect on MRD.

Secondary Objectives: to assess the effect of Blincyto on duration of complete haematological remission, level of MRD, duration of MRD negativity, to evaluate the safety, tolerability PK and PD of blinatumomab

Methodology:

Study MT103-202 was an exploratory, open-label, multicenter, single-arm, phase 2 study in adult subjects with MRD-positive B-cell precursor ALL. Subjects were ≥ 18 years of age and were in complete hematologic remission with molecular failure or molecular relapse starting any time after consolidation I of front-line therapy (after at least 3 intense chemotherapy blocks) with GMALL standards or any time outside GMALL standards. Subjects had MRD at a level of ≥ 1x 10-4 in any assay with a minimum sensitivity of 1 x 10-4. The study was conducted at 6 centers in Germany. The study was planned with a Simon's 2-stage design. Under the original study design, a minimum of 7 subjects were planned to be treated if the study was stopped at stage 1 and a minimum of 14 and a maximum of 21 subjects if the study continued to stage 2 (n= 7 each in stage 1 and stage 2). The first 4 subjects were enrolled in stage 1 and received cIV infusion of blinatumomab at 15 µg/m2/day over 4 weeks followed by a treatment-free period of 2 weeks (1 cycle = 6 weeks). After 1 cycle of blinatumomab treatment, a data review committee reviewed the data from these subjects as prespecified by the protocol.

In 3 of 4 subjects, responses were observed by the data review committee. Thus, the protocol was amended twice on 27 October 2008 and 24 March 2009 which permitted dose escalation of blinatumomab to 30 µg/m2/day after cycle 1 for subjects without a positive response. Responders were defined as subjects with MRD negativity and subjects who did not respond (nonresponders) were defined as subjects

with an MRD level not reduced by ≥ 1 log within 4 treatment cycles or within 2 years of treatment completion. Subjects who were positive for bcr/abl and received concomitant treatment with a TKI during cycle 1 of blinatumomab treatment and who did not respond received 15 µg/m2/day of blinatumomab in cycle 2 without a TKI. If the subject did not respond after 2 cycles at 15 µg/m2/day of blinatumomab, the dose was increased to 30 µg/m2/day of blinatumomab.

Study participants:

Key inclusion criteria:

1. B-precursor ALL adult patients in complete hematological remission with molecular failure or molecular relapse starting at any time after consolidation I of frontline therapy within GMALL standards or at any time outside GMALL standards 2.

2. Patients with molecular marker for evaluation of MRD, which is either: bcr/abl and/or t(4;11) translocation at any detection level measured by RT-PCR, or individual rearrangements of immunoglobulin or TCR-genes measured by an assay with a sensitivity of minimum 10-4: at least 1 individual marker at a quantitative level ≥ 10-4.

3. ECOG Performance Status ≤ 1

Key exclusion criteria

Current extra-medullary involvement; history of or current relevant CNS pathology; current infiltration of cerebrospinal fluid by ALL; any prior alloHSCT or HSCT within 6 weeks prior to study entry; recent cancer immune-chemotherapy or radiotherapy prior to study treatment; abnormal bone marrow function (defined as WBC < 3.000/µL, Platelets < 50.000/µL), renal or hepatic function; active severe infection.

Treatment duration:

Subjects who showed neither MRD progression nor response received up to 7 cycles of treatment.

In subjects who had achieved MRD response, 3 additional cycles of treatment were administered, starting from the time of the first record of MRD negativity (up to a maximum of 10 cycles were possible).

Study endpoints:

The primary endpoint of this study was MRD response rate, which was measured by the incidence of subjects with MRD negativity/response (bcr/abl and/or t[4;11] below detection limit and/or individual rearrangements of immunoglobulin or TCR genes below 10-4) within 4 cycles of treatment with blinatumomab

Secondary Endpoints:

- MRD response rate defined by the incidence of MRD negativity after any treatment cycle

- Time to hematological relapse

- Change in MRD level. MRD progression is defined as the increase in the number of MRD positive cells by one log level as compared to the baseline level, which is equal to a 10-fold increase in the number of MRD positive cells. Progression has to be confirmed within six weeks. The time point of progression is the date of the first measurement.

- Time to molecular relapse as defined by the period from the first detection of MRD negativity until the first detection of relapse. Molecular relapse is defined by the detection of bcr/abl, and/or t(4-1 1 1) translocation at any level, and/or by the detection of individual rearrangements of immunoglobulin or

TCR-genes in ≥10-4 cells measured by an assay with a sensitivity of minimum 10-4. Molecular relapse has to be confirmed within six weeks.

- Overall incidence and severity of adverse events

- Quantification and characterization of peripheral blood lymphocytes

- Cytokine serum concentrations

- Pharmacokinetic parameters: serum half-life, maximum concentration, area under the curve, volume of distribution and clearance of MT103

Statistical methods:

The following hypotheses were tested in this study: H0: π ≤ p0 = 5% vs. H1: π ≥ p1 = 30%.

P0, the MRD response probability, which, if true, means that the agent was not worth studying further, was estimated to be not higher than 5%. The future use of blinatumomab would be of considerable interest if the true MRD response probability (π) was 30% or higher (p1).

General considerations were based on Simon's 2-Stage MinMax design with the following specifications:

p0 = 0.05, p1 = 0.3, alpha = 0.05, power = 0.8.

A total sample size planned: 21

Summary of Results:

First subject enrolled: 08 January 2008

Data cut-off date for primary analysis: 14 January 2010

Date of long-term follow-up analysis: 03 November 2014

Subject Disposition:

A total of 32 subjects were screened in this study and 20 subjects were included in the FAS (all subjects from the safety analysis set [SAS; n = 21] who completed at least treatment cycle 1 and for whom at least 1 MRD response assessment was available). One subject in the SAF completed < 1 cycle of blinatumomab treatment and, thus, was not included in the FAS.

Table 9-2. Disposition of Subjects (Full Analysis Set)

	Blinatumomab Cohorts					
	Constant Dose [15 µg/m²/d] (N=17)		Dose Increase [15/30 µg/m²/d] (N=3)		Total (N=20)	
	n	%	n	%	n	%
Patient Completed the Study	8	(47.1%)	2	(66.7%)	10	(50.0%)
Reason for Study Termination						
End of Study	7	(41.2%)	1	(33.3%)	8	(40.0%)
Other: Patient received a bone marrow transplant after 4 cycles of treatment	1	(5.9%)	1	(33.3%)	2	(10.0%)
Patient Terminated the Study Prematurely	9	(52.9%)	1	(33.3%)	10	(50.0%)
Reason for Study Termination						
Adverse Event	1	(5.9%)	0	(0.0%)	1	(5.0%)
Patient was not Compliant	1	(5.9%)	0	(0.0%)	1	(5.0%)
Hematological Relapse	1	(5.9%)	0	(0.0%)	1	(5.0%)
MRD Relapse	1	(5.9%)	0	(0.0%)	1	(5.0%)
Other: Patient received a bone marrow transplant after at least 1 or maximal 3 cycles of treatment	5	(29.4%)	1	(33.3%)	6	(30.0%)

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Note: Subject 111-005 documented as reason for study termination "End of study" and was transplanted afterwards. Therefore, this subject was evaluated as "Other: Patient received a bone marrow transplant after 4 cycles of treatment".
MRD: minimal residual disease
Source: Table 14-1.2

Demographics

The Demographics and Baseline characteristics comparison (FAS) between pivotal (MT103-203) and supportive (MT103-202) studies are presented in Table 17:

Table 17. Demographics and Baseline Characteristics: Study MT103-202 and MT103-203 (Full Analysis Set)

	Study MT103-202 N = 20	Study MT103-203 N = 116	Total N = 136
Age (years) – n (%)			
N	21[a]	116	137[a]
Mean ± SD	Not available	44.6 ± 16.4	45.2 ± 16.8
Median	Not available	45.0	45.0
Quartile 1, Quartile 3	Not available	29.5, 60.5	30.0, 61.0
Minimum, Maximum	Not available	18, 76	18, 77
Age Group – n (%)[a]			
≥ 18 to < 35	7 (33.3)	36 (31.0)	43 (31.6)
≥ 35 to < 55	4 (19.0)	41 (35.3)	45 (33.1)
≥ 55 to < 65	4 (19.0)	24 (20.7)	28 (20.6)
≥ 65	6 (28.6)	15 (12.9)	21 (15.4)
Sex			
Male	9 (42.9)	68 (58.6)	77 (56.6)
Female	12 (57.1)	48 (41.1)	60 (44.1)
Race			
White	20 (100.0)	102 (87.9)	122 (89.7)
Asian	0	1 (0.9)	1 (0.7)
Other	0	1 (0.9)	1 (0.7)
Unknown[b]	0	12 (10.3)	12 (8.8)
Regions			
Europe	20 (100)	116 (100)	136 (100)
White Blood Cell Count			
≤ 30,000/mm^3	Not Collected	78 (67.2)	78 (57.4)
> 30,000/mm^3	Not Collected	18 (15.5)	18 (13.2)
Not Reported	20	20 (17.2)	40 (29.4)
Philadelphia chromosome status[c]			
Positive	5 (23.8)	5 (4.3)	10 (7.4)
Negative	15 (75.0)	111 (95.7)	126 (92.6)
Relapse history			
Subjects in CR1	19 (95.0)	75 (64.7)	94 (69.1)
Subjects in CR2	1 (5.0)	39 (33.6)	40 (29.4)
Subjects in CR3	0	2 (1.7)	2 (1.5)

CR1 = complete remission 1 (no prior relapse); CR2 = complete remission 2 (after first relapse); CR3 = complete remission 3 (after second relapse)
[a] The safety analysis set where N = 21 was used for the MT103-202 study
[b] Race was not collected in France per regulations.
[c] Chromosome status was determined by metaphase cytogenetics, fluorescence in site hybridization, or polymerase chain reaction.
Source: Table 14-2.1 and Table 14-2.2 of Study MT103-203 Primary Analysis CSR, Table 9-3 of Study MT103-202 Primary Analysis CSR, SCE Table 14-3.1, SCE Table 4.10.4.1, SCE Table 4.10.7.1, SCE Table 4.10.8.1, Table iss-02.1, and Table iss-02.1.1

Efficacy Results

Primary Efficacy Endpoint: MRD Response Rate within First 4 Cycles

Table 8. Summary of MRD Response Within 4 Cycles by Dose Cohort, Baseline Genetic Alteration, Relapsed/Refractory MRD status, and by MRD Level at Screening: Study MT103-202 (Full Analysis Set)

Analysis Group or Subgroup	% Subjects with MRD Response in the First 4 Cycles
Full Analysis Set	• 80% (16/20); All MRD responses were observed within the first treatment cycle
Dose cohort	• 88% (15/17) of subjects in the constant dose cohort • 33% (1/3) of subjects in the dose increase cohort
Baseline genetic alteration	• 92% (12/13) of subjects with only rearrangements • 57% (4/7) of subjects with rearrangements and translocations (ie, rearrangements with or without translocations)
Refractory and relapsed MRD	• 80% (12/15) of subjects with molecular refractory disease 80% (4/5) of subjects with molecular relapse
MRD level at screening	• 90% (9/10) of subjects with MRD level ≥ 10^{-2} • 83% (5/6) of subjects with MRD level < 10^{-2} to ≥ 10^{-3} • 50% (2/4) of subjects with MRD level < 10^{-3} to ≥ 10^{-4}

MRD = minimal residual disease

Source: Table 10-1, Table 10-2, Table 10-3, and Table 10-4 of Study MT103-202 Primary Analysis CSR (Module 5.3.5.4, Initial Adult Relapsed/Refractory ALL Filing)

Table 18. MRD Response Rates in Cycle 1: Study MT103-202 Study MT103-203 (Prim EP FAS & Target Disease Population

MRD Response Rate	Study MT103-202	Study MT103-203
Primary Endpoint Full Analysis Set	N = 20	N = 113
MRD response[a] - n (%) (Confidence interval)[b]	16 (80.0) (56.3 to 94.3)	98 (86.7) (79.1 to 92.4)
Complete response- n (%)[c] (Confidence interval)[b]	NA	88 (77.9) (69.1 to 85.1)
MRD < LLoQ – n (%) (Confidence interval)[b]	NA	10 (8.8) (4.3 to 15.7)
No MRD response – n (%) (Confidence interval)[b]	4 (20.0) (5.7 to 43.7)	15 (13.3) (7.6 to 20.9)
Target Disease Population Set	N = 15	N = 110
MRD response[a] - n (%) (Confidence interval)[b]	13 (86.7) (59.5 to 98.3)	95 (86.4) (78.5 to 92.2)
Complete response- n (%)[c] (Confidence interval)[b]	NA	85 (77.3) (68.3 to 84.7)
MRD < LLoQ – n (%) (Confidence interval)[b]	NA	10 (9.1) (4.4 to 16.1)
No MRD response – n (%) (Confidence interval)[b]	2 (13.3) (1.7 to 40.5)	15 (13.6) (7.8 to 21.5)

MRD response was achieved within the first 4 cycles in 80% (16/20) of subjects in the FAS, with all MRD responses from positive to negative were achieved within cycle 1 including 15 complete MRD responders receiving 15µg/m2/d and 1 subject achieved MRD complete response with escalated dose at 15/30µg/m2/d.

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.

MRD progression

Seven of 20 subjects overall had MRD progression, the overall median time to MRD progression was 7.2 months (95% CI: 3.3, n.e.). MRD progression was reported in 6 of 17 subjects who received

blinatumomab 15 µg/m2/day and occurred at days 84, 99, 101, 170, 221, and 438 respectively; 1 subject of the 3 with escalated dose at 15/30 µg/m2/d had an MRD progression at day 206.

Duration of MRD Response

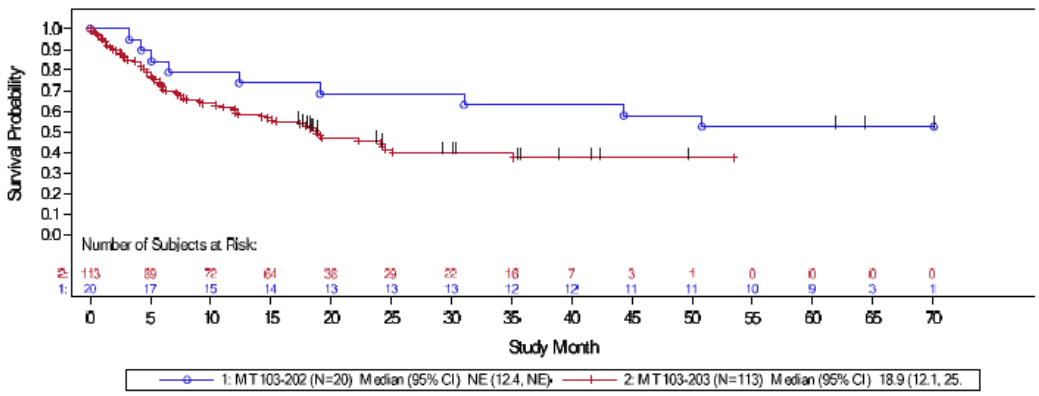
The median duration of MRD response for the 16 subjects who had an MRD response in the FAS overall was 13.0 months (95% CI: 2.8, n.e.). 5 subjects had MRD relapse. All 5 subjects received blinatumomab at 15 µg/m2/day. The follow-up duration for the 11 subjects who did not experience MRD relapse (censored) raged from 15 to 1955 days.

Relapse-free Survival

As in pivotal study, hematologic RFS was assessed during the long-term follow-up analysis and was calculated from the time of start of the first infusion until hematologic relapse or death. Subjects without an event were censored on their last available date of bone marrow biopsy.

After a median follow-up time of 1550 days (> 4 years) the median RFS was not reached (95% CI: 12.4 months, not estimable). Of the 20 subjects in the FAS, 11 subjects completed the study in hematologic remission and 9 subjects had an RFS event (8 hematologic relapses on days 99, 129, 155, 198, 582, 947, 1352, and 1550; and 1 death). Three of the 8 subjects who had hematological relapse had HSCT prior to haematological relapse. When subjects were censored at the date of HSCT, the median RFS was also not reached (95% CI: 5.1 months, not estimable): 6 out of 20 subjects (30%) completed the study in remission (censored), 9/20 subjects (45%) were censored at HSCT, and 5/20 subjects (25%) had a relapse event.

Figure 16: K-M curves of RFS in MT103-202 and MT103-203 (primary endpoint FAS)



Censor indicated by vertical bar |.
PEFAS: subjects received at least one infusion of blinatumomab, excluding subjects who had no MRD assessment during study follow-up (MT103-202) subjects received at least one infusion of blinatumomab, and had a PCR MRD assay with minimum sensitivity of 1x10E-4 at baseline (MT103-203).

Program: Figures\program\f-eff-rfs.sas
Output: fisc-06-001-001-km-rfs-all-pdfasfl.rtf (Date Generated: 30JUN16 23:30) Source Data: adam.adsl, adam.adttceff

RFS was measured from the start of the first infusion of blinatumomab.

Table 39: Summary of RFS: MT103-202, MT103-203 (primary EP FAS / target disease population sets)

Number of subjects	Study MT103-202	Study MT103-203	Total
Primary Endpoint Full Analysis Set N	20	113	133
Events – n (%)	9 (45.0)	64 (56.6)	73 (54.9)
Relapse – n (%)	8 (40.0)	39 (34.5)	47 (35.3)
Death – n (%)	1 (5.0)	24 (21.1)	25 (18.8)
Secondary leukemia – n (%)	0	1 (0.9)	1 (0.8)
Censored – n (%)	11 (55.0)	49 (43.4)	60 (45.1)
Subjects in remission at completion	11 (55.0)	49 (43.4)	60 (45.1)
Kaplan-Meier time-to-event (months)			
Median (95% CI)	NE (12.4, NE)	18.9 (12.1, 25.1)	22.3 (15.0, 44.3)
Kaplan-Meier estimates (95% CI)			
At 3 months	1.00 (NE, NE)	0.86 (0.78, 0.91)	0.88 (0.81, 0.92)
At 6 months	0.84 (0.59, 0.95)	0.72 (0.62, 0.79)	0.74 (0.65, 0.80)
At 12 months	0.79 (0.53, 0.92)	0.60 (0.51, 0.69)	0.63 (0.54, 0.71)
At 24 months	0.68 (0.43, 0.84)	0.46 (0.36, 0.55)	0.49 (0.40, 0.58)
At 36 months	0.63 (0.38, 0.80)	0.38 (0.27, 0.48)	0.42 (0.32, 0.51)
At 48 months	0.58 (0.33, 0.76)	0.38 (0.27, 0.48)	0.39 (0.29, 0.49)
Target Disease Population Set N	15	110	125
Events – n (%)	8 (53.3)	62 (56.4)	70 (56.0)
Relapse – n (%)	7 (46.7)	38 (34.5)	45 (36.0)
Death – n (%)	1 (6.7)	23 (20.9)	24 (19.2)
Secondary leukemia – n (%)	0	1 (0.9)	1 (0.8)
Censored – n (%)	7 (46.7)	48 (43.6)	55 (44.0)
Subjects in remission at completion	7 (46.7)	48 (43.6)	55 (44.0)
Kaplan-Meier time-to-event (months)			
Median (95% CI)	4.7 (6.5, NE)	18.9 (12.1, 35.2)	19.2 (14.3, 35.2)
Kaplan-Meier estimates (95% CI)			
At 3 months	1.00 (NE, NE)	0.85 (0.77, 0.91)	0.87 (0.80, 0.92)
At 6 months	0.86 (0.54, 0.96)	0.72 (0.62, 0.79)	0.73 (0.65, 0.80)
At 12 months	0.79 (0.47, 0.93)	0.60 (0.50, 0.68)	0.62 (0.53, 0.70)
At 24 months	0.64 (0.34, 0.83)	0.46 (0.36, 0.55)	0.48 (0.39, 0.57)
At 36 months	0.57 (0.28, 0.78)	0.38 (0.27, 0.48)	0.40 (0.30, 0.49)
At 48 months	0.50 (0.23, 0.72)	0.38 (0.27, 0.48)	0.36 (0.25, 0.47)

MRD = minimal residual disease; Prim EP FAS = primary endpoint full analysis set
Note: Subjects in the primary endpoint full analysis set received at least 1 infusion of blinatumomab and excluded subjects in Study MT103-202 who lacked an MRD assessment in the follow-up period. Subjects were included in Study MT103-203 who had 1 infusion of blinatumomab with an MRD assay via polymerase chain reaction techniques with a minimum sensitivity 1×10^{-4}. Subjects in the target disease population set excluded subjects in the primary endpoint full analysis set who had blast counts > 5% at baseline, or baseline polymerase chain reaction MRD assay with sensitivity > 1×10^{-4} or MRD level < 1×10^{-3} as per central laboratory testing at screening.
RFS was measured from the start of the first infusion of blinatumomab.

2.4.2. Discussion on clinical efficacy

To support this variation, a single pivotal study (MT103-203) was submitted together with a supportive study (MT103-202) and a retrospective historical study (study 20120148). Indirect comparisons with historical studies by propensity score analysis were also submitted.

Design and conduct of clinical studies

Pivotal study MT103-203 is a multicentre, open-label, single-arm, uncontrolled phase 2 study enrolling 116 adult subjects with MRD-positive B-cell precursor ALL in complete hematological remission with the presence of MRD at a level of ≥10-3 in an local assay with a minimum sensitivity of 10-4 documented after an interval of at least 2 weeks from last systemic chemotherapy. Philadelphia chromosome-positive (Ph+) patients should have documented treatment failure of or intolerance/contraindication to at least 2 TKIs. Patients should not receive prior allogeneic HSCT.

Blincyto was used as monotherapy at a dose of 15µg/m2/day at a constant flow rate over 28 days per treatment cycle followed by an infusion-free period of 14 days. Patients could receive up to 4 cycles regardless of whether or not achieved MRD response at the end of C1. The dose of 15µg/m2/day for this pivotal study was based on 2 clinical trials: phase 1 study in patients with R/R NHL (Study MT103-104) and supportive phase 2 study in MRD-positive B-precursor ALL (Study MT103-202). This dose was given for 1 to 7 cycles in Study MT103-202 and shown to be efficacious at achieving a MRD response with an acceptable safety profile. BSA-based dosing was used in pivotal and supportive studies in MRD, while a fixed dosing was proposed in SmPC. The switch from BSA-based dosing to fixed dosing had been justified by population PK analysis based on an integrated dataset of 8 studies, and considered acceptable for patients at least 45 kg in weight. Indeed, similar exposure levels had been observed with either 15 µg/m2/day BSA-based dosing or the 28µg/day fixed dosing across clinical studies and supported by a PK simulation regardless of indications, as assessed in initial MAA.

The primary efficacy endpoint of the study was the proportion of subjects who achieved a complete MRD response defined by the absence of MRD after 1 cycle of treatment with Blincyto evaluated by the central MRD laboratory. As yet, MRD has not been used as a surrogate endpoint in ALL studies; the appropriateness of MRD response as a validated surrogate endpoint of direct clinical benefit should be established by robust evidence based on a documented and measurable correlation between MRD status and validated endpoints such as OS or EFS. However, although available data have shown that MRD negativity at the end of induction therapy is a strong and independent prognostic indicator for relapse risk, no randomized and controlled studies have established a treatment effect on MRD could quantitatively explain a treatment effect in terms of validated endpoints such as EFS or OS.

Furthermore, the application consisted of only one single-arm pivotal study with a small sample size that used a non-validated biological outcome, which makes it extremely difficult to draw any firm conclusions on the efficacy. In this context, additional efficacy data from better-designed trials are necessary to confirm that the magnitude of the MRD response in Study MT103-203 can be translated into clinically measurable benefit and that the efficacy is not outweighed by the risk of the treatment in a population at a relatively subclinical stage.

The diagnosis of MRD status at inclusion was based on local lab analyses either by PCR or by MFC per protocol. The primary efficacy endpoint, the complete MRD response rate after 1 cycle of Blincyto infusion, was based on central lab MRD assessment.

The key secondary endpoint was defined as the hematological RFS rate at 18 months following initiation of Blinctyo, evaluated in Ph-negative ALL subjects censored at HSCT or post-Blincyto chemotherapy, by a central laboratory. Other secondary efficacy endpoints included OS, mortality rate within 100 days after allogeneic HSCT, time to hematological relapse (TTHR), duration of complete MRD response, effect on MRD level, subject's quality of life during and after therapy. Per guideline, RFS, OS and TTHR were calculated from the time of the bone marrow aspiration when CR or CRh* was detected for the first time, until the date of documented hematological relapse, progressive disease, extramedullary relapse, or death due to any cause, whichever occurred earlier. However, in this study, they were calculated from initiation of Blincyto instead of detection of CR for the first time. The time of CR detection varied from 1 month to several years before the first dose of Blincyto in participating subjects. These heterogeneous intervals between the time of CR detection and 1st dose of Blincyto could bias RFS/OS calculation at inclusion.

Efficacy data and additional analyses

The pivotal study enrolled 116 adult subjects with MRD-positive B-cell precursor ALL in complete hematological remission with the presence of MRD at a level of ≥10-3, without prior HSCT. The majority of studied population was Ph-negative (111/116) and in first CR (CR1 64.7%).

Among 116 subjects in FAS, 83 subjects (71.6%; 83/116) completed the core study defined as completing the D29 visit of 4 cycles for non-transplanted patients and a least the D29 visit of 1 cycle for transplanted subjects. Majority of subjects completed core study (83/116). The median duration of the core study was 2.7 months. Two major reasons for not completing the core study included adverse events (17.2%; 20/116) and disease relapse (8.6%; 10/116). 46.6% (54/116) of subjects who had at least 1 major protocol violation. 19 of 116 subjects were not included in primary endpoint PPS, and 20 subjects were not included in key secondary endpoint PPS.

RFS was calculated from initiation of Blincyto in this study, but not calculated by the consensus from detection of CR for the first time. However there was a wide variation in time from last anti-ALL treatment to first dose of Blincyto (Min, Max: 0, 55M) as well as in time from diagnosis to 1st dose of Blincyto (Min, Max 3, 208M).

A complete MRD response rate was observed within the first cycle in 77.9% (88/113; 95% CI: 69.1, 85.1) of subjects. 2 additional subjects had a complete MRD response at day 66 and day 77 respectively. The overall complete response rate for the Prim EP FAS was 79.6% (90/113; 95% CI: 71.0, 86.6), with a median time to complete MRD response of 29 days (range: 5 to 71 days). The MRD complete response achieved at cycle 1 was sustainable, with a median duration of 17.3 months.

These results suggest a strong, rapid and sustained activity of Blincyto in MRD-negativity in subjects in CR with MRD+ ALL.

RFS was calculated from initiation of Blincyto in this study in Ph-negative subjects at 18 months. The 18-month KM estimate for haematological RFS, censored at HSCT or post-Blincyto chemotherapy, was 54% (95% CI: 33% to 70%) with not estimable median RFS (95% CI: 6.3 months to not estimable [n.e.]). The RFS was 17.9 months longer in MRD complete responders than in MRD non-responders (23.6M vs 5.7M) according to a landmark analysis from day 45. RFS (not censored at HSCT or post-Blincyto chemotherapy) was 13.6 months longer in patients in CR1 than in CR2 or CR3 (24.6M vs 11.0M). Relapse history before Blincyto treatment seemed to represent a potential predictive factor on RFS outcome, although a high level of MRD-negativity was obtained in both CR1 (82.2%) and CR2 (71.1%) subgroups.

After at least 18M follow-up, the median of OS, calculated from initiation of Blincyto, was not estimable. Nearly twice as many subjects who had an MRD complete response than MRD non-responders were alive as of the data cut-off date (62.5% vs 33.3%). The median OS was 28.4m longer for complete MRD responder at C1 compared with MRD non-responder. The 18-months OS uncensored at HSCT or post Blinatumomab chemotherapy is 65%.

MRD non-responder at C1 had a median TTHR clearly shorter than in MRD complete responder (13.6m vs NE).

In the supportive study (MT103-202) conducted in 21 adult subjects with MRD-positive (≥ 1x 10-4) B-cell precursor ALL, a high MRD response rate of 80% was observed which was similar to that in the pivotal study. All MRD responses were observed within the first cycle of Blincyto, with a median duration of MRD response of 13.0M. The median of KM estimate of hematologic RFS was not estimable after a median follow-up time more than 4 years. Due to small size, uncontrolled design and differences in Blincyto posology and permitted TKIs, this trial has only an informative value: it only brings some support to the activity of Blincyto in MRD-negativity.

Per guideline, RFS, OS and TTHR should be calculated from the time of the bone marrow aspiration when CR or CRh* was detected for the first time, until the date of documented hematological relapse, progressive disease, extramedullary relapse, or death due to any cause, whichever occurred earlier. However, in this study, these clinical endpoints were not well-defined. They were calculated from initiation of Blincyto instead of detection of CR for the first time, while the time of CR detection varied from 1 month to several years before the first dose of Blincyto in patients. These heterogeneous intervals

between the time of CR detection and the first dose of Blincyto could bias RFS/OS calculation at inclusion. True RFS/OS calculated from the time of the bone marrow aspiration when CR or CRh* was unknown.

The study population represents adult non-transplanted patients having Ph-negative ALL in CR/CRi without associated poor prognosis. The activity of Blincyto in Ph-positive patients was unknown.

Of 53 deaths, 23 occurred while the subjects were in CR after HSCT (23 out of a total of 90 subjects who received HSCT after starting Blincyto, 25.6%), and only 3 deaths occurred in subjects achieved a CR without undergoing HSCT (3 out of a total of 26 subjects who did not receive HSCT, 11.5%). Some transplanted patients died even 30 months after their HSCT. Uncertainties exist in reasons of all fatal outcomes and their causality relative to Blincyto, to HSCT or to disease progression.

Landmark analysis by HSCT status showed that median RFS and OS were shorter in transplanted subjects than in non-transplanted subjects after Blincyto. It is still questionable how Blincyto could hide the benefit of HSCT, and the increased mortality in subjects who received HSCT after treatment with blinatumomab is not understood. Possible deleterious effects of HSCT in subjects after achieving MRD-negativity by Blincyto cannot be clearly excluded.

Furthermore, the exploration of HSCT effect in propensity score analysis clearly demonstrated a paradoxical phenomenon: In the absence of HSCT, Blincyto group reduced 60% of death as compared to historical control, while this clinically meaningful improvement was not observed in subjects with HSCT. Paradoxically, in historical control arm, the risk of mortality was reduced by 38% in subject with HSCT than without HSCT. While, in Blincyto arm, this risk of mortality was increased by 57% in subject with HSCT than without HSCT.

Some indirect comparisons with limited reliability by nature were performed between pivotal study and post-hoc collected historical data. No clear conclusion can be drawn from this external comparison.

To conclude, as the application consisted of only one confirmatory uncontrolled small size pivotal study which used a questionable biological outcome, the positive benefit of Blincyto in the claimed population is extremely difficult to assess. In this context, it is necessary to have additional efficacy data to confirm that the magnitude of the MRD response in Study MT103-203 can be translated to clinically measurable benefit and that the efficacy is not outweighed by the risk of the treatment in a population at a relatively subclinical stage.

The studied population in Study MT103-203 represented an adult non-transplanted patients having Ph-negative ALL without associated poor prognosis, in CR1/CR2 after induction and consolidation therapies of chemotherapy with MRD ≥10-3. The MAH provided additional data by separating 14 subjects who had undergone HSCT after relapse post-blinatumomab from non-HSCT group. 10 of 14 subjects had died as of August 2015 cut-off, the outcome was worse in these subjects than in subjects without HSCT or in subjects with HSCT in CR (death rate was 71.4%, 57.7% and 52.6% respectively).

The submitted data of this single-arm small size uncontrolled Study MT103-203 indicate that outcome (RFS, OS) of subjects in CR who underwent the HSCT was not better than those without HSCT after blinatumomab treatment. Considering the totality of the information, no clear conclusions can be drawn.

Three randomized, controlled, phase 3 studies are currently ongoing:

- Study E1910, a phase 3, randomized, controlled study to assess the effect of blinatumomab in combination with induction chemotherapy compared with induction chemotherapy alone for adult patients (30 through 70 years of age) with newly diagnosed Ph-negative B cell ALL. HSCT is not mandated in this study.

- Study AALL1331, a phase 3, randomized, controlled study to assess efficacy and safety of blinatumomab compared with standard combination chemotherapy in treating patients (≥ 1 to < 31

years) with B cell ALL that has returned after a period of improvement (relapsed). HSCT is mandated in this study.

- Study 20120215, a randomized, open-label, controlled, phase 3 study to investigate the efficacy and safety of blinatumomab as consolidation therapy versus conventional consolidation therapy in pediatric subjects (> 28 days to < 18 years of age) with high risk (HR) first relapse B-cell precursor ALL. HSCT is mandated in this study.

All three phase 3 studies have robust designs, validated and well-defined clinical endpoints as well as post-HSCT follow-up, and have the potential to provide high quality and long-term data in patients with B-ALL. Despite the fact that patient populations in these phase 3 studies are different to the one covered by the proposed claimed MRD indication, these phase 3 randomised studies together with two observational studies to collect data are considered important in resolving uncertainties in the context of a rare and serious disease where unmet medical is high.

At this stage, data are still immature to conclude on positive efficacy of Blinatumomab in MRD positive patients.

Additional expert consultation

The SAG-O was consulted on the following questions:

1. **Do the experts consider ALL with MRD-positivity for patients already in complete haematological remission (e.g. CR1) as unmet medical need?**

Persistent MRD-positivity in adult patients after induction therapy and/or consolidation therapy in complete haematological remission (e.g. CR1) is considered an unmet medical need. The main goal in these patients is inducing MRD-negativity of sufficient duration to allow for stem-cell transplantation, the only potentially curative option in this setting with otherwise very poor prognosis.

In a recent meta-analysis, MRD-negativity was shown to be correlated with event-free survival (EFS) and OS at patient-level.[1] Although data on blinatumumab were not included and the correlation may differ across mechanisms of action, the strength of the correlation was remarkable (HR for EFS and OS <0.3) and homogeneous across a number of different (chemotherapy) agents. *A priory*, there are no reasons to suspect that the correlation would be significantly different for blinatumomab.

Furthermore, the risk of relapse has been shown to be directly proportional to the MRD level.[2] Although protocols vary in this respect (e.g., paediatric protocols), persistence of MRD-positivity is also seen as important, with e.g., week 16 persistence being chosen as the threshold for the poorest prognosis (German Multicenter ALL Study Group).

However, MRD-negativity has not been validated as a surrogate endpoint for importanty clinical outcomes for blinatumumab or indeed any other agents. All these considerations make MRD a reasonably likely surrogate endopint for clinical benefit but cannot be considered as a validated surrogate endpoint.

In conclusion, MRD-negativity is a useful endpoint for benefit-risk decisions to accelerate regulatory approval in areas of high unmet need such as the indication applied for. However, confirmation should be provided prospectively in terms of important clinical endpoints.

There was a concern about the finding that blinatumomab followed by allogeneic hematopoietic cell transplantation may be associated with slightly higher mortality although this effect was not well understood and based on small numbers (study MT103-203). Further analyses of this apparent effect should explore main characteristics of the allogeneic hematopoietic stem cell transplantation procedures, including conditioning regimen (reduced intensity conditioning, RIC; myeloablative conditioning, MAC) and donor (HLA-matched sibling; well-matched unrelated adult, MUD; or HLA-haploidentical relative).

The collection of safety and efficacy data in a registry for patients treated with blinatumomab and HSCT should be requested as post-marketing study to monitor long-term efficacy and safety

Longer follow-up on OS should be collected and presented post-approval to address some of the uncertainty about long term outcome for the randomized trial in patients with relapsed/refractory ALL (TOWER). Data from the ongoing ECOG-ACRIN Cancer Research Group (Combination Chemotherapy With or Without Blinatumomab in Treating Patients With Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia, NCT02003222) should also be presented post-approval.

2. **As yet, no randomized and controlled data have demonstrated that a MRD response to a treatment could quantitatively explain a treatment effect in terms of clinical benefit (e.g. OS, EFS). Please discuss whether MRD can be used as a surrogate primary endpoint for measuring the direct clinical benefit.**

See answer to question No. 1.

3. **If MRD positivity is accepted as a component for a therapeutic indication, would the experts recommend that a specific validated method is prospectively developed any treatment is approved, or would local diagnostic procedures available so far be acceptable? If local procedures are possible, what are the specific technical recommendations needed in the product information?**

Real-time quantitative PCR (RQ-PCR) is the current gold standard for the analysis of MRD. This method is generally considered more robust than multicolour flow cytometry particularly in the setting of Ab treatments or next-generation sequencing. The method is available in the EU and many centers are accredited according to the guidelines of the EuroMRD Consortium, a standard that has been widely recognised. Regardless of the specific guidelines, it is important that local procedures follow established technical guidelines for the interpretation of RQ-PCR MRD data based on knowledge of Ig/TCR gene rearrangements, experience in Ig/TCR gene analysis and RQ-PCR for MRD detection, and number of ALL patients per year.

4. **Complete MRD response was defined as no detection of PCR amplification of individual rearrangement of Ig- or TCR-. Please discuss if such MRD response induced by Blincyto is considered equivalent to MRD-negativity "spontaneously" achieved by front-line chemotherapy on both of prognostic and biologic aspect.**

See answer to question No. 1 about the need for confirmation of long-term effects (EFS, OS) with blinatumumab, and some added uncertainty in extrapolating results for chemotherapy to blinatumomab.

5. **MRD-positivity is defined as ≥ 10^{-3} at inclusion. Please discuss under what circumstances in case of MRD_positivity a treatment is justified, and if the magnitude of Blincyto effect on MRD can be translated to real clinically benefit.**

The risk of relapse has been shown to be directly proportional to the MRD level (see answer to question No. 1). Although no optimum cut-off has been established, 10^{-3} is not considered stringent enough as it probably selects patients just prior to morphological relapse. A more stringent cut-off of 10^{-4} is likely to be preferred for patient selection, given the expected prognostic implications.

2.4.3. Conclusions on the clinical efficacy

At present, there are still uncertainties associated with the design of the uncontrolled, small size pivotal study, definition of the endpoint, translation of the observed efficacy in terms of Minimal Residual Disease (MRD) to survival, and uncertainties on the impact of the treatment on potential HSCT after

blinatumomab and on long-term outcomes. Furthermore, MRD-negativity has also not been validated as a surrogate endpoint for important clinical outcomes for blinatumumab. Therefore efficacy has not been conclusively demonstrated on the basis of the data provided.

2.5. Clinical safety

Introduction

Blincyto is currently indicated for the treatment of Philadelphia chromosome-negative R/R B-cell precursor ALL. The safety profile in SmPC was mainly based on one pivotal Phase II Study MT103-211 where 189 adult patients with R/R ALL received Blincyto, administered as a continuous intravenous infusion (CIVI). The initial dose of blinatumomab is 9 µg/day for the first 7 days of treatment (to mitigate for potential CRS and neurologic events associated with introduction to blinatumomab) which then will be escalated (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4) of the cycle 1 and for up to 5 cycles.

In the approved indication (R/R ALL), the most serious adverse reactions that may occur during blinatumomab treatment include: infections (31.7%), neurologic events (16.4%), neutropenia/febrile neutropenia (15.3%), cytokine release syndrome (0.5%), and tumour lysis syndrome (0.5%). The most common adverse reactions include: infusion-related reactions (67.2%), infections (63.0%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral oedema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), cough (18.5%), diarrhoea (18.0%), tremor (17.5%), neutropenia (17.5%), abdominal pain (16.9%), insomnia (15.3%), fatigue (15.3%) and chills (15.3%). Events of special interest (EOI) for blinatumomab included central neuropsychiatric events due to direct neurotoxicities (neurologic events), infections, CRS, TLS, elevated liver enzymes, infusion reactions, acute pancreatitis, embolic and thrombotic events, medication errors and product use issues, cytopenias (including febrile neutropenia and neutropenia), lymphopenias, capillary leak syndrome (CLS), decreased immunoglobulins, and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

A total of 843 subjects from 8 clinical studies received blinatumomab, including 706 subjects with relapsed/refractory ALL from 6 clinical studies and 137 subjects in the adult MRD-positive ALL population from 2 clinical studies. In support of the present variation in MRD, the safety of blinatumomab is based on data from pivotal Study MT103-203, a pivotal, phase 2, open-label, single-arm study in adult subjects with MRD-positive B-cell precursor ALL (N = 116) and supportive study MT103-202, a phase 2, open-label, single-arm study in adult subjects with MRD-positive B-cell precursor ALL (N = 21).

Patient exposure

In Study MT103-203 Blincyto was used as monotherapy at a dose of 15µg/m2/day at a constant flow rate over 28 days per treatment cycle followed by an infusion-free period of 14 days. Patients could receive up to 4 cycles regardless of whether or not achieved MRD response at the end of C1.

The core study was defined as follows: completing the day 29 visit of 4 cycles for subjects not proceeding to HSCT and completing of at least day 29 of cycle 1 for subjects proceeding to HSCT.

Safety analyses were performed on the FAS that included all subjects who received ≥ 1 dose of Blincyto and who had at least 1 available MRD response assessment.

The data cut-off date for the primary analysis of Study MT103-203 was 21 February 2014 (with all subjects completing the core study period); the data cut-off date for the secondary analysis (18-month follow-up was 05 August 2015). Study MT103-203 is ongoing for collection of OS data; no additional

safety data will be collected. Study MT103-202 is complete; CSRs for the primary analysis and final analysis are included in this submission.

In the FAS, 116 subjects received blinatumomab and 84 (72%; 84/116) subjects completed 1 cycle of treatment. In the core study, the median treatment exposure was 55 days (range: 1 to 113 days).

Per the protocol, subjects were considered to have discontinued treatment in cycle 1 if they planned to receive HSCT, prior to cycle 4 if they had not planned to receive HSCT after blinatumomab therapy, or due to adverse events. Overall, 28% (33/116) of subjects discontinued treatment. Of those 33 subjects, 20 (17%; 20/116) subjects discontinued treatment as a result of an adverse event.

The subject incidence of treatment-emergent adverse events that led to treatment interruption was 31% (36/116).

Table 14-5.1. Summary of Blinatumomab Exposure

	Full Analysis Set (N = 116)
Core study	
Treatment exposure (days)	
n	116
Mean (SD)	53 (32)
Min, Max	1, 113
Q1, Q3	28, 74
Median	55
Total exposure in patient years	16.68
Number of started cycles	
1	116 (100)
2	75 (65)
3	33 (28)
4	20 (17)
Number of completed cycles	
1	84 (72)
2	56 (48)
3	24 (21)
4	12 (10)
Number of subjects with study drug discontinuation	33 (28)
Number of subjects with study drug discontinuation due to AE – n(%)	20 (17)
Number of subjects with prior interruption due to AE – n(%)	16(14)
Number of interrupted cycles	
1	51 (44)
2	20 (17)
3	11 (9)
4	2 (2)
Number of subjects with study drug interruption due to AE – n(%)	36 (31)
Re-treatment Period	
n	3
Mean (SD)	35 (12)
Min, Max	28, 49
Q1, Q3	28, 49
Median	29
Total exposure in patient years	0.29

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N=Number of subjects in the analysis set.
Note: Patients with prior interruption due to AE is a subcategory of subjects with study drug discontinuation.
Note: Treatment exposure duration is the time on blinatumomab excluding period between cycles.

Table 12-2. Summary of Blinatumomab Exposure by Cycle

Cycle	Started Cycle n (%)	Completed Cycle n (%)	Interrupted Cycle n (%)	Resumed Cycle after Interruption n (%)
1	116 (100)	84 (72)	51 (44)	29 (25)
2	75 (65)	56 (48)	20 (17)	12 (10)
3	33 (28)	24 (21)	11 (9)	5 (4)
4	20 (17)	12 (10)	2 (2)	1 (1)

Note: Treatment exposure duration is the time on blinatumomab excluding period between cycles.
Source: Table 14-5.1 and Table 14-5.2

Adverse events

A summary of the subject incidence of treatment-emergent adverse events (TEAE) is presented. The subject incidence of AE was 100.0%; 62.9% of subjects experienced SAE. The subject incidence of TEAE was 96.6%; 51.7% of subjects experienced treatment-related SAE. AEs leading to interruption and permanent discontinuation of blinatumomab were reported for 31.0% and 17.2% of subjects, respectively. Grade 3 or higher AEs were reported for 61.2% of subjects; 51.7% of subjects experienced a treatment-related Grade 3 or higher AE. Two subjects (1.7%) experienced fatal AE; 1 was considered treatment-related.

Table 14-6.1.1. Summary of Subject Incidence of Treatment-Emergent Adverse Events

	Full Analysis Set (N = 116)
All treatment-emergent adverse events - n (%)	116 (100.0)
Serious adverse events	73 (62.9)
Grade ≥ 3	71 (61.2)
Grade ≥ 4	33 (28.4)
Fatal adverse events	2 (1.7)
Leading to permanent discontinuation of blinatumomab	20 (17.2)
Serious adverse events	15 (12.9)
Grade 4 adverse events	4 (3.4)
Fatal adverse events	2 (1.7)
Neurologic events	11 (9.5)
Leading to interruption of blinatumomab	36 (31.0)
Serious adverse events	28 (24.1)
Fatal adverse events	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	112 (96.6)
Serious adverse events	60 (51.7)
Grade ≥ 3	60 (51.7)
Grade ≥ 4	26 (22.4)
Fatal adverse events	1 (0.9)

A summary of the subject incidence of TEAE by disease history, by baseline MRD level are presented in following tables.

Table 14-6.1.2. Summary of Subject Incidence of Treatment-Emergent Adverse Events by Disease History

	Full Analysis Set Patients in 1st CR (N = 75)	Full Analysis Set Patients in 2nd CR (N = 39)	Full Analysis Set Patients in 3rd CR (N = 2)
All treatment-emergent adverse events - n (%)	75 (100.0)	39 (100.0)	2 (100.0)
Serious adverse events	46 (61.3)	25 (64.1)	2 (100.0)
Grade ≥ 3	45 (60.0)	25 (64.1)	1 (50.0)
Grade ≥ 4	21 (28.0)	12 (30.8)	0 (0.0)
Fatal adverse events	1 (1.3)	1 (2.6)	0 (0.0)
Leading to permanent discontinuation of blinatumomab	12 (16.0)	8 (20.5)	0 (0.0)
Serious adverse events	10 (13.3)	5 (12.8)	0 (0.0)
Grade 4 adverse events	2 (2.7)	2 (5.1)	0 (0.0)
Fatal adverse events	1 (1.3)	1 (2.6)	0 (0.0)
Neurologic events	7 (9.3)	4 (10.3)	0 (0.0)
Leading to interruption of blinatumomab	23 (30.7)	12 (30.8)	1 (50.0)
Serious adverse events	17 (22.7)	10 (25.6)	1 (50.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	72 (96.0)	38 (97.4)	2 (100.0)
Serious adverse events	35 (46.7)	23 (59.0)	2 (100.0)
Grade ≥ 3	38 (50.7)	22 (56.4)	0 (0.0)
Grade ≥ 4	16 (21.3)	10 (25.6)	0 (0.0)
Fatal adverse events	0 (0.0)	1 (2.6)	0 (0.0)

Table 14-6.1.3. Summary of Subject Incidence of Treatment-Emergent Adverse Events by Baseline MRD Level Full Analysis Set

	Patients with baseline MRD 10^{-2} or higher (N = 54)	Patients with baseline MRD 10^{-3} until $<10^{-2}$ (N = 52)	Patients with baseline MRD less than 10^{-3} (N = 8)
All treatment-emergent adverse events - n (%)	54 (100.0)	52 (100.0)	8 (100.0)
Serious adverse events	35 (64.8)	33 (63.5)	3 (37.5)
Grade ≥ 3	36 (66.7)	31 (59.6)	3 (37.5)
Grade ≥ 4	16 (29.6)	13 (25.0)	3 (37.5)
Fatal adverse events	1 (1.9)	1 (1.9)	0 (0.0)
Leading to permanent discontinuation of blinatumomab	11 (20.4)	8 (15.4)	1 (12.5)
Serious adverse events	7 (13.0)	7 (13.5)	1 (12.5)
Grade 4 adverse events	3 (5.6)	0 (0.0)	1 (12.5)
Fatal adverse events	1 (1.9)	1 (1.9)	0 (0.0)
Neurologic events	7 (13.0)	3 (5.8)	1 (12.5)
Leading to interruption of blinatumomab	15 (27.8)	17 (32.7)	3 (37.5)
Serious adverse events	13 (24.1)	12 (23.1)	2 (25.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	53 (98.1)	49 (94.2)	8 (100.0)
Serious adverse events	32 (59.3)	23 (44.2)	3 (37.5)
Grade ≥ 3	30 (55.6)	26 (50.0)	3 (37.5)
Grade ≥ 4	13 (24.1)	10 (19.2)	2 (25.0)
Fatal adverse events	0 (0.0)	1 (1.9)	0 (0.0)

N=Number of subjects in the analysis set.
The two subjects with missing MRD level at baseline are excluded from this table.

Treatment-emergent Adverse Events

All 116 subjects (100%) in the FAS experienced at least 1 TEAE. Of the 116 subjects, 74 subjects received CTM4, 40 subjects received CTM5, and 2 subjects received both CTM4 and CTM5. There was no difference in the incidence of treatment-emergent adverse events between subjects treated with CTM4 and CTM5. The highest incidences (≥ 50%) of TEAE by system organ class (SOC) were General Disorders and Administration Site Conditions (94.8%; 110/116), Nervous System Disorders (68.1%; 79/116), and Gastrointestinal Disorders (53.4%; 62/116). The most frequently reported TEAEs (preferred terms in >

20% of subjects) were pyrexia (88.8%; 103/116), headache (37.9%; 44/116), tremor (30.2%; 35/116), chills (25.9%; 30/116), fatigue (24.1%; 28/116), nausea (23.3%; 27/116), and vomiting (22.4%; 26/116).

Table 15. Treatment-emergent Adverse Events by Preferred Term Reported for ≥ 10% of Subjects in Descending Order of Frequency - Study MT103-203 (Full Analysis Set)

Preferred Term	Full Analysis Set (N = 116) n (%)
Number of subjects reporting treatment-emergent adverse events	116 (100.0)
Pyrexia	103 (88.8)
Headache	44 (37.9)
Tremor	35 (30.2)
Chills	30 (25.9)
Fatigue	28 (24.1)
Nausea	27 (23.3)
Vomiting	26 (22.4)
Diarrhoea	23 (19.8)
Hypokalaemia	18 (15.5)
Neutropenia	18 (15.5)
Insomnia	17 (14.7)
Aphasia	15 (12.9)
Arthralgia	15 (12.9)
Cough	15 (12.9)
Hypotension	14 (12.1)
Constipation	13 (11.2)

N=Number of subjects in the analysis set.
Coded using Medical Dictionary for Regulatory Activities version 18.0
Source: Table 14-6.2 of Study MT103-203 Secondary Analysis CSR

Of the most frequently reported events described above, all occurred at a higher incidence in cycle 1 versus cycles 2, 3, or 4. Pyrexia (88.8%), headache (37.9%), tremor, chills, and diarrhea were reported at a higher incidence for subjects who relapsed once compared to subjects who had not relapsed. TEAEs of grade ≥ 3, grade ≥ 4, and fatal (grade 5) were 61.2% (71/116), 28.4% (33/116), and 1.7% (2/116), respectively. Grade 5 events (preferred terms) included atypical pneumonia and subdural haemorrhage. (Sepsis after allogeneic HSCT [considered unrelated to study treatment by the investigator] was reported as a grade 5 treatment-emergent event in the primary analysis report, but was no longer classified as an adverse event because it was reported after the End-of-Study visit).

Treatment-emergent grade ≥ 3 adverse events (preferred term in ≥ 5% of subjects) included neutropenia (15.5%; 18/116), pyrexia (7.8%; 9/116), leukopenia (6%; 7/116), and alanine aminotransferase (ALT) increased and tremor (5.2%; 6/116 for each). Among the most frequently reported treatment emergent grade ≥ 3 adverse events, there was no trend toward increased subject incidence of events of pyrexia, neutropenia, or leukopenia across treatment cycles; grade ≥ 3 ALT increased and tremor were only reported in cycle 1 at an incidence of 5.2% (6/116 for each). The subject incidences of grade ≥ 3, grade ≥ 4, and fatal events were similar between subjects in first remission compared to subjects in second remission.

Treatment-related treatment-emergent Adverse Events

TEAEs considered related to blinatumomab by the investigator were reported for 96.6% (112/116) of subjects. Treatment-related TEAE (preferred terms in > 10% of subjects) were pyrexia (83.6%; 97/116), tremor (27.6%; 32/116), headache (25%; 29/116), chills (23.3%; 27/116), fatigue (18.1%, 21/116), nausea (16.4%, 19/116), neutropenia (13.8% 16/116), aphasia (12.1%, 14/116), vomiting (11.2%, 13/116) and hypotension (10.3%, 12/116), with similar incidence for subjects who were treated in C1, C2 or C3. Treatment-related TEAEs of grade ≥ 3, grade ≥ 4, and grade 5 were 51.7% (60/116), 22.4%

(26/116), and 0.9% (1/116), respectively. One subject experienced treatment-related treatment-emergent grade 5 atypical pneumonia.

Table 14-6.5. Treatment-Related Adverse Events by Preferred Term

Preferred Term	Full Analysis Set (N = 116) n (%)
Number of subjects reporting treatment-related adverse events	112 (96.6)
Pyrexia	97 (83.6)
Tremor	32 (27.6)
Headache	29 (25.0)
Chills	27 (23.3)
Fatigue	21 (18.1)
Nausea	19 (16.4)
Neutropenia	16 (13.8)
Aphasia	14 (12.1)
Vomiting	13 (11.2)
Hypotension	12 (10.3)

Treatment Interruptions Due to Adverse Events

The subject incidence of TEAE that led to interruption of treatment was 31.0% (36/116). Of these 36 subjects, events were considered serious for 28 subjects (24.1%; 28/116). By SOC, general disorders and administration site conditions (11.2%), nervous system disorders (10.3%), Injury, poisoning and procedural complications (6.0%) and investigations (5.2%) led frequently (>5%) to treatment interruption. TEAEs (preferred terms in ≥ 2% of subjects) that led to treatment interruption were pyrexia (7.8%; 9/116), aphasia, encephalopathy, overdose, and tremor (3.4%; 4/116 for each), and ALT increased, aspartate aminotransferase (AST) increased, and chills (2.6%; 3/116 for each). No TEAE that led to interruption of treatment were fatal.

Table 14-6.6. Treatment-Emergent Adverse Events Leading to Treatment Interruption by Preferred Term

Preferred Term	Full Analysis Set (N = 116) n (%)
Number of subjects reporting treatment-emergent adverse events leading to treatment interruption	36 (31.0)
Pyrexia	9 (7.8)
Aphasia	4 (3.4)
Encephalopathy	4 (3.4)
Overdose	4 (3.4)
Tremor	4 (3.4)
Alanine aminotransferase increased	3 (2.6)
Aspartate aminotransferase increased	3 (2.6)
Chills	3 (2.6)
Confusional state	2 (1.7)
Hypersensitivity	2 (1.7)
Hypotension	2 (1.7)
Infusion related reaction	2 (1.7)
Sinus tachycardia	2 (1.7)

Discontinuation due to adverse events

The subject incidence of TEAE that led to permanent discontinuation of blinatumomab was 17.2% (20/116). Of these 20 subjects, 15 subjects (12.9%; 15/116) experienced SAEs that led to permanent discontinuation treatment. Eleven subjects (9.5%; 11/116) had neurologic TEAE that led to permanent

discontinuation of blinatumomab. Nervous system disorders was the SOC leading to the most treatment discontinuation. TEAEs (preferred terms in ≥ 2% of subjects) that led to permanent treatment discontinuation were tremor (4.3%; 5/116), and aphasia, encephalopathy, and seizure (2.6%; 3/116 for each).

Table 14-6.7. Treatment-Emergent Adverse Events Leading to Permanent Treatment Discontinuation by Preferred Term

Preferred Term	Full Analysis Set (N = 116) n (%)
Number of subjects reporting treatment-emergent adverse events leading to permanent treatment discontinuation	20 (17.2)
Tremor	5 (4.3)
Aphasia	3 (2.6)
Encephalopathy	3 (2.6)
Seizure	3 (2.6)
Memory impairment	2 (1.7)
Acute myeloid leukaemia	1 (0.9)
Agitation	1 (0.9)
Atypical pneumonia	1 (0.9)
Blood pressure increased	1 (0.9)
Catheter site erosion	1 (0.9)
Catheter site infection	1 (0.9)
Depressed level of consciousness	1 (0.9)
Dizziness	1 (0.9)
Dysarthria	1 (0.9)
General physical health deterioration	1 (0.9)
Generalised tonic-clonic seizure	1 (0.9)
Hepatic enzyme increased	1 (0.9)
Incision site haemorrhage	1 (0.9)
Leukoencephalopathy	1 (0.9)
Puncture site pain	1 (0.9)
Pyrexia	1 (0.9)
Sinus bradycardia	1 (0.9)
Sinus tachycardia	1 (0.9)
Subdural haemorrhage	1 (0.9)
Thrombosis	1 (0.9)
Vena cava thrombosis	1 (0.9)

Table iss-06.3.6. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term in Descending Frequency (Safety Analysis Set)

System Organ Class Preferred Term	Adult R/R Ph- ALL MT103-211 MT103-206 00103311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL MT103-205 20130320 (N = 133) n (%)	Adult R/R Ph+ ALL 20120216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL MT103-202 MT103-203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
Nervous system disorders	21 (4.0)	3 (2.3)	0 (0.0)	24 (3.4)	13 (9.5)	37 (4.4)
Encephalopathy	7 (1.3)	0 (0.0)	0 (0.0)	7 (1.0)	3 (2.2)	10 (1.2)
Tremor	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.4)	5 (3.6)	8 (0.9)
Seizure	1 (0.2)	2 (1.5)	0 (0.0)	3 (0.4)	4 (2.9)	7 (0.8)
Aphasia	2 (0.4)	1 (0.8)	0 (0.0)	3 (0.4)	3 (2.2)	6 (0.7)
Depressed level of consciousness	1 (0.2)	2 (1.5)	0 (0.0)	3 (0.4)	1 (0.7)	4 (0.5)
Memory impairment	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	2 (1.5)	3 (0.4)
Dizziness	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.7)	2 (0.2)
Epilepsy	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.7)	2 (0.2)
Leukoencephalopathy	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.7)	2 (0.2)
Somnolence	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.7)	2 (0.2)
Cognitive disorder	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Headache	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Neurotoxicity	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.1)
Generalised tonic-clonic seizure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.1)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.1)

Serious adverse events

In the FAS, the subject incidence of treatment-emergent SAEs was 62.9% (73/116). Treatment-emergent serious adverse events (preferred terms in ≥ 5% of subjects) were pyrexia (14.7%; 17/116), tremor (6.9%; 8/116), aphasia and encephalopathy (5.2%; 6/116 for each). The subject incidence of treatment-emergent serious adverse events was similar regardless of remission status.

Table 14-6.3. Treatment-Emergent Serious Adverse Events by Preferred Term

Preferred Term	Full Analysis Set (N = 116) n (%)
Number of subjects reporting treatment-emergent serious adverse events	73 (62.9)
Pyrexia	17 (14.7)
Tremor	8 (6.9)
Aphasia	6 (5.2)
Encephalopathy	6 (5.2)
Neutropenia	5 (4.3)
Overdose	5 (4.3)
C-reactive protein increased	4 (3.4)
Device related infection	3 (2.6)
Seizure	3 (2.6)
Staphylococcal infection	3 (2.6)
Alanine aminotransferase increased	2 (1.7)
Aspartate aminotransferase increased	2 (1.7)
Ataxia	2 (1.7)
Cytokine release syndrome	2 (1.7)

The subject incidence of treatment-emergent serious adverse events considered related to blinatumomab by the investigator was 51.7% (60/116). It was slightly higher for subjects in second remission (59.0%; 23/39) compared to subjects in first remission (46.7%; 35/75).

In the adult MRD-positive ALL population (n=137), SAEs were reported for 60.6% of subjects, which was consistent with the adult R/R Ph-negative ALL population (63.4%). For the adult MRD-positive ALL population, the most frequently reported SAE was pyrexia, reported for 12.4% of subjects compared with 6.4% for the adult R/R Ph- ALL population. Serious tremor, also reported for ≥ 5% of the adult MRD-

positive ALL population (5.8%), was reported for 1.7% of the adult relapsed/refractory Philadelphia chromosome-negative ALL. Serious febrile neutropenia was reported less frequently in the adult MRD-positive ALL population than in the adult R/R Ph- (1.5% vs 8.5%).

Deaths

Table 40: Deaths and cause of death

	Full Analysis Set (N = 116)
Total number of deaths	53 (45.7)
Death in CR without HSCT - n (%)	3 (2.6)
Death in CR after HSCT - n (%)	23 (19.8)
Death after relapse without HSCT - n (%)	9 (7.8)
Death after relapse pre-HSCT - n (%)	9 (7.8)
Death after relapse post-HSCT - n (%)	9 (7.8)

A total of 1.7% (2/116) of subjects died as a result of an adverse event that occurred within 30 days of their last treatment of blinatumomab. Fatal TEAEs were atypical pneumonia and subdural hemorrhage, occurring in 1 subject each. The event of atypical pneumonia was considered related to blinatumomab. Of the 2 subjects who died, 1 subject was in first remission and 1 subject was in his second remission.

Adverse events of special interest

Events of interest (EOI) for the blinatumomab program include neurologic events, infections, CRS, drug related hepatic disorders, infusion reactions, tumor lysis syndrome (TLS), thromboembolic events, medication errors, cytopenias, decreased immunoglobulins, capillary leak syndrome (CLS), pancreatitis and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

Medication errors - n (%)[a]	6 (5.2)	4 (3.4)
Serious adverse events	6 (5.2)	4 (3.4)
Grade ≥ 3	0 (0.0)	0 (0.0)
Grade ≥ 4	0 (0.0)	0 (0.0)
Cytopenias - n (%)[a]	32 (27.6)	25 (21.6)
Serious adverse events	8 (6.9)	5 (4.3)
Grade ≥ 3	29 (25.0)	23 (19.8)
Grade ≥ 4	20 (17.2)	16 (13.8)
Decreased immunoglobulins - n (%)[a]	8 (6.9)	8 (6.9)
Serious adverse events	0 (0.0)	0 (0.0)
Grade ≥ 3	2 (1.7)	2 (1.7)
Grade ≥ 4	0 (0.0)	0 (0.0)
Capillary leak syndrome - n (%)[a]	19 (16.4)	14 (12.1)
Serious adverse events	1 (0.9)	1 (0.9)
Grade ≥ 3	2 (1.7)	1 (0.9)
Grade ≥ 4	1 (0.9)	1 (0.9)

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EOI = event of interest; N = number of subjects in the analysis set.
[a] No fatal events were identified in this category
Events were coded using Medical Dictionary for Regulatory Activities version 18
Source: modified from Table 14-6.11 and Table 14-6.12

Overall, treatment-emergent EOIs were identified for 95.7% (111/116) of subjects. Serious treatment-emergent EOIs were identified for 45.7% (53/116) of subjects. The subject incidences of grade ≥ 3 (severe), grade ≥ 4 (life-threatening), and grade 5 (fatal) treatment-emergent EOIs were 52.6% (61/116), 27.6% (32/116), and 0.9% (1/116), respectively.

Treatment-related treatment-emergent EOIs were identified for 91.4% (106/116) of subjects. Serious treatment-related treatment-emergent EOIs were identified for 39.7% (46/116) of subjects. The subject incidences of grade ≥ 3, grade ≥ 4, and fatal treatment-related treatment-emergent EOIs were 45.7% (53/116), 21.6% (25/116), and 0.9% (1/116), respectively (Table 12-5).

Neurologic Events

52.6% (61/116) of subjects were identified as having neurologic events. The most frequently identified neurologic events (preferred terms in ≥ 5% of subjects) were tremor (30.2%; 35/116), aphasia (12.9%; 15/116), dizziness (7.8%; 9/116), ataxia and paraesthesia (6%; 7/116 for each), and encephalopathy (5.2%; 6/116). Serious treatment-emergent neurologic events were identified for 21.6% (25/116) of subjects, including (preferred terms in > 2 subjects) tremor (6.9%; 8/116), aphasia and encephalopathy (5.2%; 6/116 for each), and seizure (2.6%; 3/116). Neurologic events (preferred terms in > 2 subjects) that led to permanent discontinuation of treatment included tremor (4.3%; 5/116), and aphasia, encephalopathy, and seizure (2.6%; 3/116 for each). Neurologic events (preferred terms in > 2 subjects) that led to treatment interruption included aphasia, encephalopathy, and tremor (3.4%; 4/116 for each). The subject incidences of grade ≥ 3 and grade 4 neurologic events were 12.1% (14/116) and 2.6% (3/116), respectively. No fatal neurologic events were identified.

Of the 61 subjects identified as having a neurologic event, 55 subjects (47.4%; 55/116) were identified as having events considered related to blinatumomab by the investigator. Serious related neurologic events were identified for 21.6% (25/116) of subjects. The subject incidences of treatment-related grade ≥ 3 and grade 4 neurologic events were 12.1% (14/116) and 2.6% (3/116), respectively.

Table 36. Treatment-emergent Events of Interest by System Organ Class and Preferred Term (≥ 5 Subjects in the Total Population) in Descending Frequency - Neurologic Events Pooled ALL Population (Safety Analysis Set)

System Organ Class Preferred Term	Adult R/R Ph- ALL MT103-211 MT103-206 00103311 (Blin arm) (N = 528) n (%)	Pediatric R/R ALL MT103-205 20130320 (N = 133) n (%)	Adult R/R Ph+ ALL 20120216 (N = 45) n (%)	R/R ALL Total (N = 706) n (%)	Adult MRD+ ALL MT103-202 MT103-203 (N = 137) n (%)	Total All Studies (N = 843) n (%)
No. of subjects reporting neurologic events (All Terms)	353 (66.9)	69 (51.9)	28 (62.2)	450 (63.7)	98 (71.5)	548 (65.0)
Grade ≥ 3	73 (13.8)	11 (8.3)	6 (13.3)	90 (12.7)	22 (16.1)	112 (13.3)
Grade ≥ 4	8 (1.5)	1 (0.8)	0 (0.0)	9 (1.3)	3 (2.2)	12 (1.4)
Serious	70 (13.3)	9 (6.8)	6 (13.3)	85 (12.0)	31 (22.6)	116 (13.8)
Fatal	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Ear and labyrinth disorders	13 (2.5)	0 (0.0)	0 (0.0)	13 (1.8)	6 (4.4)	19 (2.3)
Vertigo	8 (1.5)	0 (0.0)	0 (0.0)	8 (1.1)	6 (4.4)	14 (1.7)
Tinnitus	6 (1.1)	0 (0.0)	0 (0.0)	6 (0.8)	0 (0.0)	6 (0.7)
Gastrointestinal disorders	10 (1.9)	0 (0.0)	0 (0.0)	10 (1.4)	1 (0.7)	11 (1.3)
Hypoaesthesia oral	5 (0.9)	0 (0.0)	0 (0.0)	5 (0.7)	0 (0.0)	5 (0.6)
General disorders and administration site conditions	11 (2.1)	0 (0.0)	2 (4.4)	13 (1.8)	2 (1.5)	15 (1.8)
Gait disturbance	11 (2.1)	0 (0.0)	1 (2.2)	12 (1.7)	1 (0.7)	13 (1.5)
Injury, poisoning and procedural complications	10 (1.9)	1 (0.8)	0 (0.0)	11 (1.6)	3 (2.2)	14 (1.7)
Post lumbar puncture syndrome	8 (1.5)	1 (0.8)	0 (0.0)	9 (1.3)	2 (1.5)	11 (1.3)
Nervous system disorders	303 (57.4)	58 (43.6)	25 (55.6)	386 (54.7)	91 (66.4)	477 (56.6)
Headache	172 (32.6)	37 (27.8)	14 (31.1)	223 (31.6)	54 (39.4)	277 (32.9)
Tremor	75 (14.2)	9 (6.8)	4 (8.9)	88 (12.5)	40 (29.2)	128 (15.2)
Dizziness	52 (9.8)	6 (4.5)	4 (8.9)	62 (8.8)	14 (10.2)	76 (9.0)
Paraesthesia	28 (5.3)	3 (2.3)	6 (13.3)	37 (5.2)	7 (5.1)	44 (5.2)
Aphasia	17 (3.2)	2 (1.5)	2 (4.4)	21 (3.0)	16 (11.7)	37 (4.4)
Somnolence	25 (4.7)	3 (2.3)	0 (0.0)	28 (4.0)	2 (1.5)	30 (3.6)
Encephalopathy	18 (3.4)	2 (1.5)	1 (2.2)	21 (3.0)	6 (4.4)	27 (3.2)
Seizure	14 (2.7)	5 (3.8)	0 (0.0)	19 (2.7)	4 (2.9)	23 (2.7)
Hypoaesthesia	15 (2.8)	2 (1.5)	1 (2.2)	18 (2.5)	2 (1.5)	20 (2.4)
Ataxia	9 (1.7)	2 (1.5)	1 (2.2)	12 (1.7)	7 (5.1)	19 (2.3)
Memory impairment	11 (2.1)	0 (0.0)	2 (4.4)	13 (1.8)	3 (2.2)	16 (1.9)
Dysarthria	10 (1.9)	0 (0.0)	0 (0.0)	10 (1.4)	3 (2.2)	13 (1.5)
Lethargy	10 (1.9)	1 (0.8)	0 (0.0)	11 (1.6)	1 (0.7)	12 (1.4)
Cognitive disorder	7 (1.3)	2 (1.5)	0 (0.0)	9 (1.3)	2 (1.5)	11 (1.3)
Dysgraphia	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.6)	6 (4.4)	10 (1.2)
Depr. level of consciousness	4 (0.8)	3 (2.3)	1 (2.2)	8 (1.1)	1 (0.7)	9 (1.1)
Neurotoxicity	9 (1.7)	0 (0.0)	0 (0.0)	9 (1.3)	0 (0.0)	9 (1.1)
Nervous system disorder	5 (0.9)	0 (0.0)	2 (4.4)	7 (1.0)	1 (0.7)	8 (0.9)
Intention tremor	3 (0.6)	0 (0.0)	0 (0.0)	3 (0.4)	4 (2.9)	7 (0.8)
Neuralgia	4 (0.8)	2 (1.5)	1 (2.2)	7 (1.0)	0 (0.0)	7 (0.8)
Hyperaesthesia	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.6)	2 (1.5)	6 (0.7)
Speech disorder	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	3 (2.2)	5 (0.6)
Disturbance in attention	4 (0.8)	0 (0.0)	0 (0.0)	4 (0.6)	1 (0.7)	5 (0.6)
Dysaesthesia	4 (0.8)	1 (0.8)	0 (0.0)	5 (0.7)	0 (0.0)	5 (0.6)
Psychiatric disorders	154 (29.2)	18 (13.5)	10 (22.2)	182 (25.8)	35 (25.5)	217 (25.7)
Insomnia	61 (11.6)	4 (3.0)	3 (6.7)	68 (9.6)	22 (16.1)	90 (10.7)
Anxiety	33 (6.3)	7 (5.3)	1 (2.2)	41 (5.8)	4 (2.9)	45 (5.3)
Confusional state	27 (5.1)	3 (2.3)	5 (11.1)	35 (5.0)	7 (5.1)	42 (5.0)
Disorientation	14 (2.7)	0 (0.0)	1 (2.2)	15 (2.1)	4 (2.9)	19 (2.3)
Depression	14 (2.7)	2 (1.5)	1 (2.2)	17 (2.4)	1 (0.7)	18 (2.1)
Agitation	6 (1.1)	5 (3.8)	1 (2.2)	12 (1.7)	1 (0.7)	13 (1.5)
Sleep disorder	8 (1.5)	1 (0.8)	1 (2.2)	10 (1.4)	1 (0.7)	11 (1.3)
Mental status changes	9 (1.7)	0 (0.0)	0 (0.0)	9 (1.3)	0 (0.0)	9 (1.1)
Restlessness	6 (1.1)	1 (0.8)	0 (0.0)	7 (1.0)	1 (0.7)	8 (0.9)
Hallucination	5 (0.9)	0 (0.0)	0 (0.0)	5 (0.7)	0 (0.0)	5 (0.6)
Irritability	1 (0.2)	4 (3.0)	0 (0.0)	5 (0.7)	0 (0.0)	5 (0.6)
Respiratory, thoracic and mediastinal disorders	5 (0.9)	0 (0.0)	1 (2.2)	6 (0.8)	3 (2.2)	9 (1.1)
Dysphonia	2 (0.4)	0 (0.0)	1 (2.2)	3 (0.4)	3 (2.2)	6 (0.7)

ALL = acute lymphoblastic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; depr. = depressed; MRD = minimum residual disease; Ph = Philadelphia chromosome; R/R = relapsed/refractory
Safety analysis set: All subjects who received at least 1 infusion of blinatumomab.
Severity graded using CTCAE version 4.03
Adverse events coded using Medical Dictionary for Regulatory Activities version 18.1
Source: Table iss-06.6.1, Table iss-06.7.1

As compared the adult MRD-positive ALL population (n=137) to the adult R/R ALL population, neurologic events (preferred terms) were generally more frequently reported in the adult MRD-positive ALL population (≥ 10% of subjects) than in the adult R/R Ph- ALL population: headache (39.4% vs 32.6%), tremor (29.2% vs 14.2%), insomnia (16.1% vs 11.6%), aphasia (11.7% vs 3.2%), and dizziness (10.2% vs 9.8%). Permanent discontinuation by nervous system disorders (SOC 9.5% vs 3.4%) was more frequently reported in MRD+ population than in R/R ALL population: tremor (3.6%), seizure (2.9%), encephalopathy (2.2%) and aphasia (2.2%) in the adult MRD-positive ALL population versus ≤ 1.3% for each in the adult R/R Ph- ALL populations.

In the adult MRD-positive ALL population (n=137), the median time to first onset of neurologic events was shorter for the R/R Ph- ALL populations (2.0 days vs 6.0 days), as well as the median time to first grade ≥ 3 neurologic event (4.0 days vs 17.0 days). The median duration of neurologic events (KM) was shorter (10.0 days; 95% CI: 6.0, 15.0) than in the adult R/R Ph- ALL population (19.0 days; 95% CI: 13.0, 29.0). The subject incidence of neurologic events that persisted for > 14 days was similar across the 2 ALL populations (41.7%, 47.9%).

Leukoencephalopathy

Grade 2 leukoencephalopathy was identified for 1 subject (Subject 1002-003; 0.9%; 1/116). This subject was in the first remission. The event occurred during cycle 1, and was considered serious and related to blinatumomab. Treatment was permanently discontinued. The time to onset of the leukoencephalopathy event was 17.0 days for the 1 subject in adult MRD-positive ALL population. The median time to onset of the first event was 24.0 days (range: 13 to 401 days) for the 4 subjects in the adult relapsed or refractory Philadelphia chromosome-negative ALL population, and 23.0 days (range: 9 to 401 days) for the 7 subjects in the total relapsed or refractory ALL population with leukoencephalopathy events

Infections

In the FAS, 41.4% (48/116) of subjects were identified as having an infection. The most frequently identified infection events (preferred terms in ≥ 5% of subjects) were device related infection and nasopharyngitis (6.9%; 8/116 for each), and upper respiratory tract infection (5.2%; 6/116). Serious infection events were identified for 12.9% (15/116) of subjects. Serious infections (preferred terms in > 2 subjects) included device-related infection and staphylococcal infection (2.6%; 3/116 each). Infection events (preferred terms) that led to permanent discontinuation of treatment included atypical pneumonia and catheter site infection (0.9%; 1/116 for each). Infection events (preferred terms) that led to interruption of treatment included bacterial infection and device related infection (0.9%, 1/116 for each). Subject incidences of grade ≥ 3 and grade ≥ 4 infection events were 10.3% (12/116) and 3.4% (4/116) respectively. One subject (0.9%; 1/116) experienced a fatal infection (preferred term: atypical pneumonia).

Of the 48 subjects who were identified as having infection events, 9 subjects (7.8%; 9/116) experienced events that were considered related to blinatumomab by the investigator. Serious treatment-related infection events were identified for 4.3% (5/116) of subjects. The subject incidence of related grade ≥ 3 infection events was 2.6% (3/116). One subject (0.9%; 1/116) experienced a fatal infection (preferred term: atypical pneumonia) event that was considered related to treatment by the investigator.

Cytokine Release Syndrome

The subject incidence of events coded as CRS was 3.4% (4/116). All events occurred in treatment cycle 1. All events were coded as CRS; no event was coded as cytokine storm. Two subjects (1.7%, 2/116) experienced a serious CRS event. The subject incidence of grade 3 CRS was 1.7% (2/116). No grade ? 4 CRS events were identified. All serious and grade 3 treatment-related CRS were considered related to blinatumomab treatment. One subject (0.9%, 1/116) experienced a CRS event leading to treatment interruption; no adverse events led to treatment discontinuations.

Using the broad search strategy, events suggestive of CRS were identified for 87.1% (101/116) of subjects. The most frequently identified events suggestive of CRS (preferred terms in ≥ 5% of subjects) were pyrexia (68.1%; 79/116), chills (20.7%; 24/116), headache (15.5%; 18/116), vomiting (12.9%; 15/116), nausea and hypotension (8.6%; 10/116 for each).

Drug Related Hepatic Disorders

The subject incidence of events that may be suggestive of drug related hepatic disorders was 14.7% (17/116). The most frequently identified drug related hepatic disorders (preferred terms in ≥ 2% of subjects) were ALT increased (6%; 7/116), AST increased (4.3%; 5/116), and prothrombin time prolonged (2.6%; 3/116). Serious drug related hepatic disorders were identified for 6% (7/116) of subjects and included hepatotoxicity, prothrombin time prolonged, blood bilirubin increased, hepatic enzyme increased, liver function test abnormal (0.9%, 1/116 for each); and ALT increased and AST increased (1.7%, 2/116 for each). Drug related hepatic disorder events (preferred terms) that led to permanent discontinuation of treatment included hepatic enzymes increased (0.9%; 1/116). Events (preferred terms in > 2 subjects) that led to treatment interruption included ALT increased and AST increased (2.6%; 3/116 for each). The subject incidences of grade ? 3 (severe) and grade 4 (life-threatening) drug related hepatic disorders were 8.6% (10/116) and 6% (7/116), respectively. Grade 4 events included ALT increased (4.3%, 4/116), AST increased (2.6%, 3/116), hepatic enzyme increased (1.7%, 2/116), and hepatotoxicity (0.9%, 1/116). No fatal drug related hepatic disorders were identified.

Of the 17 subjects who were identified as having drug related hepatic disorders, 13 subjects (11.2%; 13/116) were identified as having events that were considered related to blinatumomab. The subject incidence of serious treatment-related drug related hepatic disorders was 5.2% (6/116). All grade ≥ 3 events were considered related to blinatumomab.

Infusion Reactions

Signs and symptoms suggestive of infusion reactions were identified in 86.2% (100/116) of subjects. The most frequently reported events (preferred terms in ≥ 5% of subjects) that may be associated with infusion reactions were pyrexia (68.1%; 79/116), chills (20.7%; 24/116), headache (15.5%; 18/116), vomiting (12.9%; 15/116), and hypotension and nausea (8.6%; 10/116 for each). Serious infusion reaction events were identified for 5.2% (6/116). The subject incidences of grade ≥ 3 and grade 4 infusion reaction events were 8.6% (10/116) and 1.7% (2/116), respectively. No fatal infusion reaction events were identified. Of the 100 subjects who were identified as having infusion reaction events, 92 subjects (79.3%; 92/116) were identified as having events were considered related to blinatumomab. All serious and grade ≥3 and grade 4 infusion reaction events were considered related to blinatumomab treatment.

As compared the adult MRD-positive ALL population (n=137) to the adult R/R ALL population, infusion reaction events were reported for 90.5% of subjects including 13.9% serious infusion events, which were both higher than in the adult R/R Ph- ALL population (50.8% and 2.5% serious). Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 10.2% and 0.7% in the adult MRD-positive ALL population, which was generally consistent with other populations. No fatal infusion reaction events were reported. In the adult MRD-positive ALL population, two most frequently reported infusion reaction events was pyrexia (85.4%) and hypotension (12.4%), both of these were higher than in the adult R/R Ph- ALL population(pyrexia 40.0%, hypotension <5%).

The median time to onset of the first infusion reaction event was 1.0 days (range: 1 to 87 days) for the adult MRD-positive ALL population and 2.0 days (range: 1 to 190 days) for the adult R/R ALL populations.

Tumor Lysis Syndrome

Tumor lysis syndrome describes a combination of metabolic abnormalities that occur due to the release of nuclear and cytoplasmic degradation products of malignant cells. Characteristic findings of TLS include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. High tumor burden is an important risk factor for TLS, and therefore these events are unlikely in subjects in hematologic remission.

There were no subjects that experienced an adverse event coded as the preferred term of TLS. The subject incidence of adverse events with coded preferred terms retrieved from the TLS broad search strategy was 6.9% (8/116), and included adverse events of cytokine release syndrome (3.4%, 4/116), hypocalcemia (1.7%, 2/116), and hyperkalemia and oliguria (0.9%, 1/116 for each). Of these events, 2 were considered serious (both with preferred term cytokine release syndrome) and 2 events were grade 3 in severity; no fatal TLS events were identified.

Thromboembolic Events

In the FAS, 4.3% (5/116) of subjects experienced signs and symptoms suggestive of thromboembolic events, including (preferred terms): thrombosis in device (1.7%; 2/116) and device occlusion, thrombosis, and vena cava thrombosis (0.9%; 1/116 for each). No events of disseminated intravascular coagulation (DIC) were identified. Serious thromboembolic events were identified for 2.6% (3/116) of subjects including thrombosis, thrombosis in device, and vena cava thrombosis (0.9%; 1/116 for each). Thromboembolic events (preferred terms) that led to permanent discontinuation of treatment included thrombosis and vena cava thrombosis (0.9%; 1/116 for each) (Table 14-6.7); no thromboembolic events led to treatment interruption. The subject incidences of ≥ grade 3 and grade 4 thromboembolic events were 3.4% (4/116) and 1.7% (2/116), respectively; grade 4 events included thrombosis and thrombosis in device (0.9%, 1/116 for each). No fatal thromboembolic events were identified. No thromboembolic events were considered related to blinatumomab.

Medication Errors

Variations in dosing that fell within < 10% of the intended dose were not considered overdoses and were excluded. Overdoses were to be reported as serious events for this study, including overdose with or without associated adverse events. An overdose was always reported as serious adverse regardless of outcome.

Medication error events were identified for 5.2% (6/116) of subjects. Events in 5 subjects (4.3%, 5/116) were coded as overdose, and in 1 subject (0.9%) as accidental overdose (preferred term), and therefore, considered serious. No medication error events were grade ≥ 3. Of the 6 subjects who were identified as having medication error events, 4 subjects (3.4%; 4/116) were identified as having events that were considered related to blinatumomab (2.6% [3/116] as overdose and 0.9% [1/116, 1/116]) as accidental overdose). Medication errors led to treatment interruption for 5 subjects (4.3%; 5/116). No subjects permanently discontinued treatment as a result of a medication error.

Cytopenias (including febrile neutropenia and neutropenia)

In the FAS, 27.6% (32/116) of subjects were identified cytopenias by laboratory testing. The most frequently identified cytopenia events (preferred terms ≥ 5% of subjects) were neutropenia (15.5%; 18/116) including, leukopenia (6.9%; 8/116), anemia (6.0%, 7/116), and thrombocytopenia (5.2%; 6/116). Serious cytopenia events were identified for 6.9% (8/116) of subjects. Serious cytopenia events (preferred terms in > 2 subjects) included neutropenia (4.3%; 5/116). No subjects permanently discontinued treatment as a result of cytopenias. Cytopenias leading to treatment interruption included leukopenia and thrombocytopenia (0.9%, 1/116 for each). The subject incidences of grade ≥ 3 and grade 4 cytopenia events were 25% (29/116) and 17.2% (20/116), respectively. No fatal cytopenia events were identified. Of the 32 subjects who were identified as having cytopenia events, 25 subjects (21.6%; 25/116) were identified as having events were considered related to blinatumomab. Serious treatment-

related events were identified for 4.3% (5/116) of subjects. The subject incidences of grade ≥ 3 and grade 4 treatment-related events were 19.8% (23/116) and 13.8% (16/116), respectively.

Febrile neutropenia was reported in 3 subjects (2.6%), 2 (1.7%) of them were serious.

Decreased Immunoglobulins

Decreased immunoglobulin levels were identified for 6.9% (8/116) of subjects. The following events (preferred terms) were identified: blood immunoglobulin G (IgG) decreased (5.2%; 6/116), and hypogammaglobulinemia and immunoglobulins decreased (0.9%; 1/116 for each). No serious treatment-emergent events or adverse events that led to treatment discontinuation or interruption were identified. The subject incidence of grade 3 events was 1.7% (2/116). No grade 4 or fatal decreased immunoglobulin levels were identified. All events were considered related to blinatumomab.

Capillary Leak Syndrome

Capillary leak syndrome comprises a set of signs and symptoms such as edema, hypoalbuminemia, and hypotension, which can occur at any time while on treatment in patients with hematologic malignancies and may be a manifestation of CRS. The subject incidence of events suggestive of CLS was 16.4% (19/116). The following events (preferred terms) that were suggestive of CLS were identified: hypotension (12.1%; 14/116), edema peripheral (2.6%; 3/116), blood albumin decreased, hypoalbuminaemia, and CLS (0.9%; 1/116 for each). One subject (0.9%; 1/116) was identified as having a serious CLS event (preferred term: hypotension). No subjects permanently discontinued treatment as a result of CLS events. Subjects with events suggestive of CLS who had an interruption of treatment included hypotension (1.7%, 2/116). The subject incidences of grade ≥ 3 and grade 4 CLS events were 1.7% (2/116) and 0.9% (1/116), respectively. No fatal CLS events were identified. Of the 19 subjects who were identified as having experienced events suggestive of CLS, 14 subjects (12.1%; 14/116) were identified as having events were considered related to blinatumomab. One subject each (0.9%; 1/116 for each) experienced a treatment-related event that was serious and grade 4 in severity.

Pancreatitis

For the adult MRD-positive ALL population (n=137), pancreatitis (preferred term) was reported for 1 (0.7%) subject (non-serious), which was consistent with all other ALL populations (< 0.5%; ≤ 0.2% serious). Grade ≥ 3 events were reported for 2 (0.4%) subjects in the adult relapsed or refractory Philadelphia chromosome-negative ALL population. No grade ≥ 4 or fatal events of pancreatitis were reported.

Laboratory findings

For the adult MRD-positive ALL population (n=137), few changes from baseline of ≥ 3 toxicity grades were reported; most were hematologic laboratory parameters. Changes from baseline of ≥ 3 toxicity grades reported for > 2.0% of subjects in the adult MRD-positive ALL population were absolute lymphocytes decreased (8.0%), WBC count decreased (5.1%), absolute neutrophils granulocytes decreased (4.4%), ALT increased, absolute neutrophils decreased (3.6% each), platelet count decreased (2.9%), and AST increased (2.2%). The percentage of subjects with changes from baseline of ≥ 3 toxicity grades in the adult MRD-positive ALL population was consistent with the adult relapsed/refractory Philadelphia chromosome-negative ALL and the total relapsed/refractory ALL population.

Hemoglobin

Grade 3 hemoglobin values are defined as 65 to < 80 g/L, and grade 4 hemoglobin values are not defined (considered life-threatening). In the FAS, the baseline median hemoglobin concentration was 113.0 g/L (range: 86 to 161 g/L). There was a trend toward increasing median hemoglobin concentrations starting at day 8 of cycle 1 and continued to be above the median baseline value throughout the core study. The

following maximum shifts from grade < 3 to grade ≥ 3 occurred during the core study: 2 subjects (1.7%; 2/116) had a shift from grade 1 to grade 3; and 4 subjects (3.4%; 4/116) had a shift from grade 2 to grade 3. During the core study, no subjects had hemoglobin decreased and 6.0% (7/116) had anemia (preferred terms).

Platelet Count

Grade 3 platelet values are defined as 25 to < 50 x 109/L, and grade 4 platelet values are defined as < 25 x 109/L. In the FAS, the baseline median platelet counts were 170.0 x 109/L (range: 18.0 to 436.0 x 109/L). An initial decrease in platelet counts was observed during cycle 1 from days 2 and 3; however, median platelet concentrations returned toward the baseline concentration on day 8 of cycle 1 and did not change appreciably to the end of the core study. During the core study, 1.7% (2/116) of subjects had platelet counts decreased and 5.2% (6/116) of subjects had thrombocytopenia (preferred terms).

White Blood Cell Count

Grade 3 WBC counts (leukocytes) are defined as 1.0 to < 2.0 x 109/L, and grade 4 WBC values are defined as < 1.0 x 109/L. In the FAS, the baseline median WBC counts were 4.3 x 109/L (range: 1.2 to 15.7 x 109/L). Increases in median WBC counts were observed on day 2 of each treatment cycle, consistent with corticosteroid premedication; however, median WBC counts returned toward baseline by the end of each cycle during the core study. During the core study, 2.6% (3/116) of subjects had WBC decreased, 1.7% (2/116) had lymphopenia, 6.9% (8/116) had leukopenia, and 15.5% (18/116) had neutropenia (preferred term).

Electrocardiograms

Standard 12-lead ECGs were performed at screening and at the end of core study. A subset of subjects (N = 27) at selected sites in Germany had additional ECG assessment. These additional ECGs were performed in triplicate and analyzed by a central vendor. The mean (SD) baseline QTcF was 406.37 (22.04) msec and the maximum post baseline mean (SD) QTcF interval was 416.44 (16.42) msec. The mean (SD) maximum increase in the QTcF was 14.64 (8.99) msec. Two subjects (1.7%; 2/116; Subject 1002-005 and Subject 1018-003) had maximum increases from baseline > 30 to 60 msecs. For both of these subjects, QT prolongation was detected within 2 days of starting treatment. Neither of these subjects had a history of cardiac disorders, nor did they have an adverse event temporally associated with QT prolongation. No increase > 60 msecs or maximum values > 500 msec were reported. Seven subjects (6%; 7/116) had maximum increases from baseline > 30 to 60 msecs. No increase > 60 msecs or maximum values > 500 msec were reported.

Hospitalizations

In the FAS, the median total duration of hospitalization was 14.0 days (range: 3 to 63 days). The median duration of hospitalization was 6 days for cycle 1, 4 days for cycles 2 and 3, and 3 days for cycle 4. In the FAS, 70.7% (82/116) of subjects had prolonged hospitalizations. Of these 82 subjects, 51 subjects (44%; 51/116) had prolonged hospitalization as a result of adverse events and 39 subjects (33.6%; 39/116) had prolonged hospitalizations as a result of other reasons. The subject incidence of prolonged hospitalizations decreased with increasing number of cycles.

Immunogenicity Data

Anti-blinatumomab binding antibody was evaluated with a validated blinatumomab anti-drug antibody assay with the electrochemiluminescence detection technology. For samples considered to be "potentially positive" were further re-analyzed. A total of 106 subjects dosed in the study had paired blood serum samples (predose and postdose) and were evaluated for anti-blinatumomab antibodies. All enrolled patients who received blinatumomab treatment were classified as negative for the presence of anti blinatumomab antibodies at end of study. Thus, the immunogenicity rate for this clinical study was 0%.

Safety in special populations

Adverse events were not analysed by subgroups for the pivotal Study MT103-203 or the supportive Study MT103-202.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with blinatumomab.

Post marketing experience
From the International Birth Date of 03 December 2014 to 02 December 2016 (data lock point for Periodic Benefit-risk Evaluation Report/Periodic Safety Update Report [PBRER/PSUR] #2), an estimated 2236 patients had been exposed to blinatumomab in the marketed setting.

As of 02 December 2016, Amgen received, cumulatively, a total of 1786 serious adverse drug reactions (ADRs) in the post-marketing setting, from spontaneous and solicited sources. In addition, 808 non serious ADRs were reported spontaneously.

Overall, among the 1786 total serious ADRs reported from spontaneous and solicited sources, the most frequently reported adverse reactions (≥ 10%) were from the system organ classes of Nervous System Disorders (17.1%), General Disorders and Administrative Site Conditions (17.0%), and Investigations (11.0%). Serious adverse reactions with an event incidence ≥ 1% were pyrexia (5.5%); cytokine release syndrome (5.0%); neurotoxicity (4.5%); death (3.9%); ALL recurrent and neutropenia (2.4% each); blast cell count increased (1.9%); hospitalization (1.7%); seizure and febrile neutropenia (1.5% each); ALL (1.4%); confusional state (1.3%); sepsis, disease progression, hypotension, and platelet count decreased (1.2% each); and headache (1.0%). These events are consistent with the known safety profile of blinatumomab or representative of the underlying malignancy.

Overall, the safety information received in the post marketing setting was consistent with the established safety profile and cumulative experience of blinatumomab. The overall benefit-risk profile of blinatumomab remains favorable in the approved indication.

2.5.1. Discussion on clinical safety

A total of 843 subjects from 8 clinical studies received blinatumomab, including 706 subjects with relapsed/refractory ALL from 6 clinical studies and 137 subjects in the adult MRD-positive ALL population from 2 clinical studies. In support of the present variation in MRD, the safety of blinatumomab is based on data a pivotal, phase 2, open-label, single-arm study (MT103-203) in adult subjects with MRD-positive B-cell precursor ALL (N = 116) and a supportive study phase 2, open-label, single-arm study (MT103-202) in adult subjects with MRD-positive B-cell precursor ALL (N = 21).

The specific safety profile of blinatumomab (causality) is difficult to assess in a clinical relevant way because on the one hand there is a high risk of investigator's bias in the judgment of treatment-related TEAE due to open-label design, and on the other hand the majority of toxicities (eg general disorders, haematological and gastrointestinal toxicities, infections and infestations, etc) are commonly related to underlying malignancy, disease burden or prior anti-tumor therapy.

Considering that notable differences exist between pivotal and supportive MRD studies (concomitant use of TKI and different posology in supportive study) and that the supportive study (n=21) is too small, the assessment of the safety profile of Blincyto in MRD-positive ALL is primarily focused on data from the pivotal study MT103-203. BSA-based dosing (15µg/m2/day) was used in pivotal and supportive studies in MRD, while a fixed dosing (28µg/day) was proposed in SmPC. The switch from BSA-based dosing to fixed

dosing had been justified by population PK analysis based on an integrated dataset of 8 studies, and is considered acceptable for patients with a weight of at least 45 kg.

The key difference between the adult MRD-positive ALL population and the other populations examined was the requirement for subjects in MRD studies to be in hematologic remission at baseline. This difference was reflected in baseline laboratory values where platelet count, neutrophil count, and WBC count were generally more favorable for the adult MRD-positive ALL population than for other populations. Furthermore, none of the subjects in the adult MRD-positive ALL population had bone marrow blasts based on central and local laboratory assessments at baseline. Across all other populations and in the pooled ALL population, at least 54% of subjects had ≥ 50% bone marrow blasts based on central and local laboratory assessments at baseline. The overall subject incidences of adverse events were similar across the adult MRD-positive and R/R ALL populations examined (> 99%).

Blincyto was used as monotherapy at a dose of 15µg/m2/day at a constant flow rate over 28 days per treatment cycle followed by an infusion-free period of 14 days. Patients could receive up to 4 cycles regardless of whether or not MRD response was achieved at the end of C1. Per protocol, subjects were considered to have discontinued treatment in cycle 1 if they planned to receive HSCT, prior to cycle 4 if they had not planned to receive HSCT after blinatumomab therapy, or due to adverse events. Overall, 28% (33/116) of subjects discontinued treatment. Of those 33 subjects, 20 (17%; 20/116) subjects discontinued treatment as a result of an adverse event.

The subject incidence of AE was 100.0%; 62.9% of subjects experienced SAE. The subject incidence of TEAE was 96.6%; 51.7% of subjects experienced treatment-related SAE. AEs leading to interruption and permanent discontinuation of blinatumomab were reported for 31.0% and 17.2% of subjects, respectively. Grade 3 or higher AEs were reported for 61.2% of subjects; 51.7% of subjects experienced a treatment-related Grade 3 or higher AE. Two subjects (1.7%) experienced fatal AE; 1 was considered treatment-related.

The safety profile of Blincyto in subjects in CR1 was not notably different from that of subjects in CR2/CR3. The analyses of TEAE by baseline MRD level suggest a better tolerance of Blincyto in subjects with baseline MRD <10-3 as compared to >10-3 (SAE 37.5% vs 64.8%, TEAE leading to discontinuation: 12.5% vs 20.4%). However, due to too small subgroup size and the absence of comparator group, no clear conclusion can be drawn in this small single-arm study.

For Study MT103-203, the highest incidences (≥ 50%) of TEAE by system organ class (SOC) were General Disorders and Administration Site Conditions (94.8%; 110/116), Nervous System Disorders (68.1%; 79/116), and Gastrointestinal Disorders (53.4%; 62/116). The most frequently reported TEAEs (preferred terms in > 20% of subjects) were pyrexia (88.8%; 103/116), headache (37.9%; 44/116), tremor (30.2%; 35/116), chills (25.9%; 30/116), fatigue (24.1%; 28/116), nausea (23.3%; 27/116), and vomiting (22.4%; 26/116).

Treatment-emergent grade ≥ 3 adverse events (preferred term in ≥ 5% of subjects) included neutropenia (15.5%; 18/116), pyrexia (7.8%; 9/116), leukopenia (6%; 7/116), and alanine aminotransferase (ALT) increased and tremor (5.2%; 6/116 for each).

The subject incidence of TEAE that led to interruption of treatment was 31.0% (36/116). Of these 36 subjects, events were considered serious for 28 subjects (24.1%; 28/116). Nervous system disorders (10.3%) such as encephalopathy, tremor, aphasia leading to interruption of blinatumomab were more frequently reported for the MRD-positive ALL population than for R/R Ph- ALL population (<2%). The subject incidence of TEAE that led to permanent discontinuation of blinatumomab was 17.2% (20/116). Of these 20 subjects, 15 subjects (12.9%; 15/116) experienced SAEs that led to permanent discontinuation treatment. Eleven subjects (9.5%; 11/116) had neurologic TEAE that led to permanent

discontinuation of blinatumomab. Nervous system disorders leading to permanent discontinuation was more frequently reported in MRD+ population than in R/R ALL population (9.5% vs 3.4%).

The most frequently reported adverse events leading to permanent discontinuation of study drug (17.2%) in the adult MRD-positive ALL population were tremor (3.6%); seizure (2.9%); and encephalopathy and aphasia (2.2%), which were each reported for ≤ 1.3% of subjects in the adult R/R Ph- ALL populations.

In the FAS, the subject incidence of treatment-emergent SAEs was 62.9% (73/116). Treatment-emergent serious adverse events (preferred terms in ≥ 5% of subjects) were pyrexia (14.7%; 17/116), tremor (6.9%; 8/116), aphasia and encephalopathy (5.2%; 6/116 for each). Serious pyrexia and tremor were more frequently reported in the adult MRD-positive ALL population than for adult R/R Ph- ALL (1.7%).

A total of 53 deaths (45.7%, 53/116) were reported in the study. Of these, 23 deaths (19.8%, 23/116) occurred while the subjects were in CR after HSCT (out of a total of 90 subjects who received HSCT after starting blinatumomab , 3 deaths (2.6%, 3/116) occurred while subjects were in CR without receiving HSCT (out of a total of 26 subjects who did not receive HSCT, and deaths after relapse without HSCT, pre-HSCT, and post-HSCT were reported in 9 subjects each (7.8%, 9/116 each). A total of 1.7% (2/116) of subjects died as a result of an adverse event that occurred within 30 days of their last treatment of blinatumomab. Fatal TEAEs were atypical pneumonia and subdural hemorrhage, occurring in 1 subject each. The event of atypical pneumonia was considered related to blinatumomab. Consistent with the nature and severity of the background diseases, the subject incidence of fatal adverse events in the adult MRD-positive ALL population (1.5%) was lower than in all other ALL populations (> 10% of subjects).

Events of interest (EOI) for the blinatumomab program include neurologic events, infections, CRS, drug related hepatic disorders, infusion reactions, tumor lysis syndrome (TLS), thromboembolic events, medication errors, cytopenias, decreased immunoglobulins, capillary leak syndrome (CLS), pancreatitis and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]). All these events are already included in the current SmPC in the sections covering posology, warning and precautions for use, effects on ability to drive and use machine, and ADR. These EOI are also included in the RMP. Pancreatitis, one of recently added EOI, was also reported in MRD+ trials.

52.6% (61/116) of subjects were identified as having neurologic events. The most frequently identified neurologic events were tremor (30.2%), aphasia (12.9%), dizziness (7.8%), ataxia and paraesthesia (6% for each), and encephalopathy (5.2%). Serious treatment-emergent neurologic events were identified for 21.6% of subjects, including tremor (6.9%), aphasia and encephalopathy (5.2% for each), and seizure (2.6%). Neurologic events that led to permanent discontinuation of treatment included tremor (4.3%), and aphasia, encephalopathy, and seizure (2.6% for each). The subject incidences of grade ≥ 3 and grade 4 neurologic events were 12.1% and 2.6%, respectively. No fatal neurologic events were identified. Of the 61 subjects identified as having a neurologic event, 55 subjects (47.4%) were identified as having events considered related to blinatumomab by the investigator.

As compared the adult MRD-positive ALL population (n=137) to the adult R/R ALL population, neurologic events were generally more frequently reported in the adult MRD-positive ALL population than in the adult R/R Ph- ALL population: headache (39.4% vs 32.6%), tremor (29.2% vs 14.2%), insomnia (16.1% vs 11.6%), aphasia (11.7% vs 3.2%), and dizziness (10.2% vs 9.8%). Permanent discontinuation by nervous system disorders (SOC 9.5% vs 3.4%) was more frequently reported in MRD+ population than in R/R ALL population: tremor (3.6%), seizure (2.9%), encephalopathy (2.2%) and aphasia (2.2%) in the adult MRD-positive ALL population versus ≤ 1.3% for each in the adult R/R Ph- ALL populations.

The incidences of serious neurologic events, grade ≥ 3 neurologic events, neurological events leading to treatment discontinuation and interruption were all much higher in MRD than in R/R ALL population. The onset of neurological events after 1st dose of Blincyto was more quickly in MRD than in R/R ALL

population (median 2.0 days vs 6.0 days). The median time to first onset of grade ≥ 3 neurologic event was also much shorter in MRD population than in R/R ALL population (4.0 days vs 17.0 days).

Signs and symptoms suggestive of infusion reactions were identified in 86.2% (100/116) of subjects. The most frequently reported events (preferred terms in ≥ 5% of subjects) that may be associated with infusion reactions were pyrexia (68.1%; 79/116), chills (20.7%; 24/116), headache (15.5%; 18/116), vomiting (12.9%; 15/116), and hypotension and nausea (8.6%; 10/116 for each). Serious infusion reaction events were identified for 5.2% (6/116). The subject incidences of grade ≥ 3 and grade 4 infusion reaction events were 8.6% (10/116) and 1.7% (2/116), respectively. No fatal infusion reaction events were identified.

As compared the adult MRD-positive ALL population (n=137) to the adult R/R ALL population, infusion reaction events were reported for 90.5% of subjects including 13.9% serious infusion events, which were both higher than in the adult R/R Ph- ALL population (50.8% and 2.5% serious). Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 10.2% and 0.7% in the adult MRD-positive ALL population, which was generally consistent with other populations. No fatal infusion reaction events were reported. In the adult MRD-positive ALL population, two most frequently reported infusion reaction events was pyrexia (85.4%) and hypotension (12.4%), both of these were higher than in the adult R/R Ph- ALL population(pyrexia 40.0%, hypotension <5%). The median time to onset of the first infusion reaction event was 1.0 days (range: 1 to 87 days) for the adult MRD-positive ALL population and 2.0 days (range: 1 to 190 days) for the adult R/R ALL populations.

2.5.2. Conclusions on clinical safety

The safety profile of Blincyto treatment in ALL subjects with MRD was generally consistent with the known safety information of Blincyto monotherapy in R/R ALL indication.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.7. Update of the Product information

Not applicable

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This type II variation seeks to broaden the existing Blincyto indication for ALL to include all adult patients with minimal residual disease (MRD) positive B-precursor ALL.

3.1.2. Available therapies and unmet medical need

As per the EMEA/CHMP/SAWP/788794/2009 the proposed indication did not constitute an unmet medical need.

3.1.3. Main clinical studies

The MAH submitted a single pivotal open-label non-comparative (Study MT103-203, n=116)) which was supported by a supportive study (MT103-202, n=20) and a retrospective historical study (study 20120148). Indirect comparisons with historical studies by propensity score analysis were also submitted. The primary efficacy endpoint was the proportion of subjects who achieved a complete MRD response. RFS, OS, duration of MRD response, TTHR, mortality within 100-day after alloHSCT were analysed as secondary endpoints. The pivotal study enrolled 116 adult subjects with MRD-positive B-cell precursor ALL in complete hematological remission with the presence of MRD at a level of ≥10-3, without prior HSCT. The majority of studied population was Ph-negative (111/116) and in first CR (CR1 64.7%).

3.2. Favourable effects

A complete MRD response rate was observed within the first cycle in 77.9% (88/113; 95% CI: 69.1, 85.1) of subjects. 2 additional subjects had a complete MRD response at day 66 and day 77 respectively. The overall complete response rate for the Prim EP FAS was 79.6% (90/113; 95% CI: 71.0, 86.6), with a median time to complete MRD response of 29.0 days (range: 5 to 71 days). The MRD complete response achieved at cycle 1 was sustainable, with a median duration of 17.3 months.

These results suggest a strong, rapid and sustained activity of Blincyto in MRD-negativity in subjects in CR with MRD+ ALL.

RFS was calculated from initiation of Blincyto in this study in Ph-negative subjects at 18 months. The 18-month KM estimate for haematological RFS, censored at HSCT or post-Blincyto chemotherapy, was 54% (95% CI: 33% to 70%) with not estimable median RFS (95% CI: 6.3 months to not estimable [n.e.]). The RFS was 17.9 months longer in MRD complete responders than in MRD non-responders (23.6M vs 5.7M) according to a landmark analysis from day 45. RFS (not censored at HSCT or post-Blincyto chemotherapy) was 13.6 months longer in patients in CR1 than in CR2 or CR3 (24.6M vs 11.0M). Relapse history before Blincyto treatment seem representing a potential predictive factor on RFS outcome, although a high level of MRD-negativity was obtained in both CR1 (82.2%) and CR2 (71.1%) subgroups.

After at least 18M follow-up, the median of OS, calculated from initiation of Blincyto, was not estimable. Nearly twice as many subjects who had an MRD complete response than MRD non-responders were alive as of the data cut-off date (62.5% vs 33.3%). The median OS was 28.4m longer for complete MRD responder at C1 compared with MRD non-responder. The 18-months OS uncensored at HSCT or post Blinatumomab chemotherapy is 65%. MRD non-responder at C1 had a median TTHR clearly shorter than in MRD complete responder (13.6m vs NE).

3.3. Uncertainties and limitations about favourable effects

The appropriateness of MRD response as a validated surrogate endpoint of direct clinical benefit is not established by robust evidence based on a documented and measurable correlation between MRD status and validated endpoints such as OS or EFS. Although available data have shown that MRD negativity at the end of induction therapy is a strong and independent prognostic indicator for relapse risk, no randomized and controlled studies have established a treatment effect on MRD that could quantitatively explain a treatment effect in terms of validated endpoints such as EFS or OS.

Although no optimum cut-off has been established, 10^{-3} is not considered stringent enough as it probably selects patients just prior to morphological relapse. A more stringent cut-off of 10^{-4} would have been preferred for patient selection.

Per guideline, RFS, OS and TTHR should be calculated from the time of the bone marrow aspiration when CR or CRh* was detected for the first time, until the date of documented hematological relapse, progressive disease, extramedullary relapse, or death due to any cause, whichever occurred earlier. However, in this study, these clinical endpoints were not well-defined. They were calculated from initiation of Blincyto instead of detection of CR for the first time, while the time of CR detection varied from 1 month to several years before the first dose of Blincyto in patients. These heterogeneous intervals between the time of CR detection and the first dose of Blincyto could bias RFS/OS calculation at inclusion. True RFS/OS calculated from the time of the bone marrow aspiration when CR or CRh* was unknown.

The study population represents adult non-transplanted patients having Ph-negative ALL in CR/CRi without associated poor prognosis. The activity of Blincyto in Ph-positive patients was unknown.

Median RFS and OS were shorter in transplanted subjects than in non-transplanted subjects after Blincyto. It is still questionable how Blincyto could hide the benefit of HSCT, and the increased mortality in subjects who received HSCT after treatment with blinatumomab is not understood. Possible deleterious effects of HSCT in subjects after achieving MRD-negativity by Blincyto cannot be clearly excluded.

Furthermore, the exploration of HSCT effect in propensity score analysis clearly demonstrated a paradoxical phenomenon: In the absence of HSCT, Blincyto group reduced 60% of death as compared to historical control, while this clinically meaningful improvement was not observed in subjects with HSCT. Paradoxically, in historical control arm, the risk of mortality was reduced by 38% in subject with HSCT than without HSCT. While, in Blincyto arm, this risk of mortality was increased by 57% in subject with HSCT than without HSCT.

3.4. Unfavourable effects

A total of 843 subjects from 8 clinical studies received blinatumomab. Of these 843 subjects, 706 subjects with relapsed/refractory ALL are included in the total relapsed/refractory ALL population from 6 of the 8 clinical studies and 137 subjects are included in the adult MRD-positive ALL population from pivotal study MT103-203 (N = 116) or supportive study MT103-202 (N = 21).

The highest incidences (≥ 50%) of TEAE by system organ class (SOC) were General Disorders and Administration Site Conditions (94.8%; 110/116), Nervous System Disorders (68.1%; 79/116), and Gastrointestinal Disorders (53.4%; 62/116). The most frequently reported TEAEs (preferred terms in > 20% of subjects) were pyrexia (88.8%; 103/116), headache (37.9%; 44/116), tremor (30.2%; 35/116), chills (25.9%; 30/116), fatigue (24.1%; 28/116), nausea (23.3%; 27/116), and vomiting (22.4%; 26/116).

Treatment-emergent grade ≥ 3 adverse events (preferred term in ≥ 5% of subjects) included neutropenia (15.5%; 18/116), pyrexia (7.8%; 9/116), leukopenia (6%; 7/116), and alanine aminotransferase (ALT) increased and tremor (5.2%; 6/116 for each).

Events of interest (EOI) for the blinatumomab program include neurologic events, infections, CRS, drug related hepatic disorders, infusion reactions, tumor lysis syndrome (TLS), thromboembolic events, medication errors, cytopenias, decreased immunoglobulins, capillary leak syndrome (CLS), pancreatitis and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

The incidences of neurologic events and infusion reaction in MRD+ studies were unusually high with quick onset.

3.5. Uncertainties and limitations about unfavourable effects

Although data are limited due to the small size of the trial and hampered by the open-label design, safety was generally in line with the known safety profile of Blincyto.
There were no uncertainties in the knowledge of the unfavourable effects.

3.6. Effects Table

Table 41 Effects Table for Blincyto in the treatment of adults with MRD positive B-cell precursor ALL – Pivotal study MT103-203 (data cut-off: 05 August 2015)

Effect	Short Description	Unit	Blincyto N=116	Uncertainties/ Strength of evidence
Favourable Effects				
MRD	proportion of subjects who achieved a complete MRD response defined by the absence of MRD after 1 cycle of Blincyto	Percentage (95% CI)	77.9% (69.1%, 85.1%)	Similar high MRD response rate was also observed in supportive study. The MRD response was sustainable 45.0 months (95% CI: 6.5, 45.0) with censored at HSCT or post-Blincyto chemotherapy 17.3 months (95% CI: 12.6, 23.3) not censored at HSCT or post-Blincyto chemotherapy. These differences in this single arm uncontrolled study should not be interpreted as direct effects of achieving a complete MRD response since there could be underlying baseline characteristics that influence both the ability to achieve a complete MRD response and improvements in RFS.
RFS	hematological RFS rate at 18 months following initiation of Blincyto, evaluated in Ph-negative ALL subjects censored at HSCT or post-Blincyto chemotherapy	Months (KM median; 95% CI) RFS (KM rate; 95% CI)	Median RFS not estimable (6.3, NE) Landmark from 3M: HSCT 16.1M, No HSCT 22.1M Landmark from 6M: HSCT 29.2M, No HSCT n.e. 54% (33%, 70%) with censored at HSCT or post-Blincyto chemotherapy 53% (44%, 62%) not censored at HSCT or post-Blincyto chemotherapy with HSCT	In absence of comparison, no conclusive conclusion can be drawn. RFS was calculated from start of Blincyto when patients were still CR since 1month in some patients and several years in others
OS	Time from treatment start with Blincyto until	Months (KM median; 95% CI)	NE (NE, NE) with censored at HSCT or post-Blincyto chemotherapy 36.5 months (19.2,	In absence of comparison, no conclusive conclusion can be drawn. RFS was calculated from start of Blincyto when patients were still CR since 1month in some patients and

Effect	Short Description	Unit	Blincyto N=116	Uncertainties/ Strength of evidence
	death	OS (KM rate; 95% CI)	NE) not censored at HSCT or post-Blincyto chemotherapy Landmark from 3M: HSCT 21.2M, No HSCT 33.5M Landmark from 6M: HSCT 30.5M, No HSCT n.e. 83% (55%, 94%) with censored at HSCT or post-Blincyto chemotherapy 65% (55%, 73%) not censored at HSCT or post-Blincyto chemotherapy	several years in others
Unfavourable Effects				
AEs	Incidence as percentage of patients involved	Percentage	All grades 100% ≥grade 3 AE: 61.2% (primarily: pyrexia, headache, tremor, chills, fatigue, nausea, vomiting)	Open-label single arm trials make difficult to assess causality of AE with Blincyto in MRD
SAEs	Incidence as percentage of patients involved	Percentage	62.9% (primarily: pyrexia, tremor, aphasia and encephalopathy)	Neurological events and infusion reaction were unusually high.
Discontinuation	Incidence as percentage of patients involved	Percentage	Discontinuation 17.2% *(*primarily: tremor, seizure, aphasia and encephalopathy*)*	More discontinuation due to neurological events and infusion reactions in MRD than in R/R ALL. Dose modification or delay was not provided.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A strong, rapid and sustained activity of Blincyto in MRD-negativity subjects with MRD positive B-cell precursor ALL has been demonstrated in the pivotal and supportive trials and deemed relevant in itself. However, as yet, it is uncertain that MRD-negativity in ALL subject obtained by Blincyto is equivalent to "spontaneous" MRD-negative. There is no robust indisputable evidence to prove its plausibility by establishing a measurable correlation between MRD negativity and a direct clinical benefit. Clinical endpoints such as RFS and OS were not appropriately and therefore cannot be considered as evidence of benefit. Median RFS and OS were shorter in transplanted subjects than in non-transplanted subjects after Blincyto. Of a total of 53 deaths, 23 occurred while the subjects were in CR after HSCT (23 out of a total of 90 subjects who received HSCT after starting Blincyto, 25.6%), and only 3 deaths occurred in subjects achieving a CR without undergoing HSCT (3 out of a total of 26 subjects who did not receive HSCT, 11.5%). Some transplanted patients died even 30 months after their HSCT. The causes of these fatal

outcomes are unknown. Their causality relative to Blincyto, to HSCT or to disease progression has to be analysed.

Safety data were collected from uncontrolled and open-label studies, however there were no specific concerns as the type of adverse events with Blincyto treatment of ALL subjects with MRD was consistent with known safety information from Blincyto monotherapy in R/R ALL indication.

3.7.2. Balance of benefits and risks

Therapeutic efficacy of Blincyto in the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO has not been established. Specifically, whilst an effect on MRD response has been quantified, a clinical benefit of MRD response is not established and surrogacy of MRD response to increased survival has not been established. In the absence of demonstrated efficacy, the benefit – risk of Blincyto in this setting is considered negative.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Blincyto is negative.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend, by a majority of 23 out of 28 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO;
as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology, and to update the safety information. The Package Leaflet is updated in accordance. RMP version 4.0 is included in this submission.

The Norwegian CHMP member agrees with the above-mentioned recommendation of the CHMP on variation to the terms of the marketing authorisation.

Grounds for refusal:

Whereas,

- Therapeutic efficacy of Blincyto in the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO has not been established. Specifically, whilst an effect on MRD response has been quantified, a

clinical benefit of MRD response is not established and surrogacy of MRD response to increased survival has not been established.

- In the absence of demonstrated efficacy, the benefit – risk of Blincyto in this setting is considered negative.

The CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

5. Re-examination of the CHMP opinion of 15 November 2018

Following the CHMP conclusion that the extension of indication applied for Blincyto was not approvable, the MAH submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

The applicant presented its grounds for re-examination in writing. A summary of the MAH's grounds for re-examination is presented below.

Clinical Ground No. 1 (Therapeutic efficacy of Blincyto in the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO has not been established).

The MAH considered that blinatumomab's ability to induce a high complete MRD response did lead to a durable hematologic CR in patients with B-precursor ALL who were at very high risk of relapse due to their MRD-positive status at study entry. In Study MT103-203, blinatumomab induced a complete MRD response within 1 treatment cycle in 77.9% of the subjects (88/113 subjects; 95% CI: 69.1 to 85.1); 2 additional subjects had a complete MRD response during cycle 2 of treatment, for an overall complete MRD response rate of 79.6% (95% CI: 71.0, 86.6). The median duration of complete MRD response was 17.3 months (95% CI: 12.6 to 23.3). The 18 month KM estimate for time to hematologic relapse (TTHR) (secondary analysis data cutoff date of 05 August 2015) was 67% (95% CI: 57, 76), and the median TTHR was not estimable (95% CI: 24.3 months, NE). The 18-month KM estimate for RFS, censored at HSCT or post-blinatumomab chemotherapy, was 54% (95% CI: 33, 70). The KM estimate for OS at 18 months was 65% (95% CI: 55, 73); the median OS was 36.5 months (95% CI: 19.2, NE). OS results were updated using longer follow-up time with a data cutoff date of 1 June 2017 (approximately 3 years of minimum follow-up time for those who survive that long). After 3 years of follow-up time, the median OS was 33.7 months (95% CI: 19.7 months to NE), with no new events reported between 40 and 60 months. According to the MAH, these results showed a plateau effect for OS after 3 years of follow up time.

The median OS was 17.4 months longer for subjects in CR1 compared with subjects in CR2/CR3 (CR1 median OS: 36.5 months; CR2/CR3 median OS: 19.1 months). The OS 18 month KM estimate was 0.69 for CR1 and 0.56 for CR2/CR3, with a hazard ratio using Cox proportion hazard model of 1.61 (95% CI: 0.93 to 2.77; p value = 0.087). However, stratified landmark analyses of OS at day 45 showed MRD responders had more favorable OS than MRD non-responders, regardless of baseline relapse history. According to the MAH, these additional post-hoc landmark analyses of RFS and OS by MRD response and relapse history suggested that improvements in RFS and OS are directly related blinatumomab's ability to induce a complete MRD response irrespective of relapse history.

The MAH furthermore argued that efficacy results from the earlier supportive phase 2 study MT103-202 were consistent with those reported in Study MT103-203. In addition, results from the historical comparator study 20120148 showed that 18-month RFS, censored at HSCT, was 37% (95% CI: 28, 46) and 18-month OS, uncensored at HSCT, was 56% (95% CI: 49, 64), which were lower than the results

observed in the pivotal study MT103-203, which showed 18-month RFS, censored at HSCT or post-blinatumomab chemotherapy, of 54% (95% CI: 33, 70) and 18-month OS, uncensored at HSCT or post-blinatumomab chemotherapy, of 65% (95% CI: 55, 73).

In conclusion, the MAH considered that blinatumomab does have strong, rapid, and sustained activity that induces MRD negativity in subjects in CR with MRD positive ALL. Therefore, this clear anti-tumor activity does represent a clinical benefit for patients with MRD-positive ALL, even in the absence of randomized controlled data.

Clinical Ground No.2 (Although an effect on MRD response has been quantified, a clinical benefit of MRD response is not established and surrogacy of MRD response to increased survival has not been established).

The MAH argued that although MRD negativity has not been validated as a surrogate endpoint, as pointed out above in clinical ground 1 and in the absence of survival data from randomized controlled trials, the data from Study MT103-203 clearly demonstrated that blinatumomab does have antitumor activity in patients with MRD positive B precursor ALL. The MAH considered that the magnitude of MRD negativity and the RFS and OS data from Study MT103-203 provided sufficient evidence that achieving complete MRD response with blinatumomab is reasonably likely to predict clinical benefit (ie, prolonged RFS and OS) in subjects with MRD-positive B-cell precursor ALL. The MAH argued that the SAG experts recommended that longer follow-up data on OS following HSCT should be collected and presented post approval to address some of the uncertainties about long-term outcomes. The MAH's proposals for confirmation via subsequent randomized controlled trials and a long-term post-approval follow-up study are in line with the experts' recommendations and regulatory guidance and are not uncommon for drugs with high anti-tumor activity.

The MAH highlighted that MRD is a direct measure of disease burden with cancer cells in the bone marrow and is not a tumor marker. Recurrent or resistant ALL exists along a continuum, with MRD (ie, molecular level disease) on one end and overt leukemia (ie, morphological disease) on the other end of the spectrum. Traditionally, evaluation of response to therapy has been limited to hematological CR (<5%) by microscopy. Advancement with more sensitive technologies (such as flow cytometry or PCR) allows leukemia to be detected at submicroscopic levels. After induction and/or consolidation treatment, patients who achieve hematologic CR but are MRD positive are very unlikely to achieve MRD negativity with additional rounds of chemotherapy, largely because these patients have already received SOC chemotherapy regimens for the treatment of ALL and these submicroscopic leukemia cells have already survived exposure to these treatments. As such, the presence of MRD indicates that a patient has not achieved a true disease-free state. However, there are no approved therapies specifically to treat MRD-positive patients, and there are no effective chemotherapies for these patients. Allogeneic HSCT is the only available treatment option for patients with MRD-positive ALL, but the outcome is far from optimal. Patients with MRD-positive disease may relapse while waiting for HSCT, and those who are MRD positive prior to HSCT have worse outcomes compared to patients who are MRD negative prior to HSCT (Bar et al, 2014; Gökbuget et al, 2012a).

Clinical Ground No. 3 (Ongoing studies to address uncertainties in the MRD-positive ALL population)

The MAH argued that the clinical program in ALL (Table 42) will address the uncertainties in the MRD-positive ALL population.

Table 42. Ongoing Studies to Address Uncertainties in the MRD-positive ALL Population

Study Number	Study Objectives	Study Design and Type of Control	Number of Patients	Key Entry Criteria	Relevant evidence	Study Status
E1910 Conducted by ECOG sponsored by NCI (Clinical-Trials.gov Identifier NCT02003222)	Efficacy Safety	Phase 3 • Lead-in/ Intensification therapy • Randomized • Controlled • Open-label • Multicenter	488	Adult subjects (30 to 70 years of age) who are newly diagnosed with Philadelphia chromosome-negative B-cell ALL	Compares the safety and efficacy of blinatumomab in conjunction with SOC chemotherapy to SOC chemotherapy alone. OS and RFS of patients who are MRD positive at randomization and then convert to MRD negative after blinatumomab will be compared to those who are MRD negative at randomization and remain so after blinatumomab or SOC chemotherapy. Primary endpoint: OS Patients who achieve CR1 and are MRD negative will be randomized to blinatumomab or SOC, and those who are MRD positive after achieving CR1 will receive blinatumomab. HSCT is at the recommendation of the investigator depending on a suitable donor. 2.5-year follow-up will provide long-term data for patients, including those who receive HSCT.	
AALL1331 Conducted by COG sponsored by NCI/CTEP (Clinical-Trials.gov Identifier NCT02101853)	Efficacy Safety	Phase 3 • Randomized • Controlled • Open-label • Multicenter • Risk-stratified	598 (195 HR/IR; 403 LR)	Subjects ≥ 1 to <31 years of age in first relapse of B-cell ALL with or without extramedullary disease	This study will provide extensive long-term follow-up data as patients will be followed for 10 years. This follow-up will allow for adequate assessment of OS and for survival after HSCT. The data generated from this study will also provide evidence of the survival by MRD-negativity status.	
20120215 Conducted by Amgen in cooperation with the I-BFM Study Group (EudraCT: 2014-002476-92 ClinicalTrials.gov Identifier NCT02393859)	Efficacy Safety	Phase 3 • Randomized • Open-label • Controlled • Adaptive Stratification: By age (1 to 9 years) andother (>28 days to <1 year and> 9 to < 18 years) By marrow/MRD	Up to 202	Pediatrics (age >28 days to <18 years) with Ph- high risk first relapse B-cell precursor ALL	EFS as primary endpoint; OS secondary endpoint. MRD status collected Compares blinatumomab to SOC chemotherapy Extensive LTFU (at least 3 years)	Enrolling; results expected in 2023

		(M1 with MRD levels ≥ 10-3, M1 with MRD levels ≥ 10-3, M2)				
20170610	Efficacy Safety	Observational study	Approx. 1000	Patients with refractory or relapsed B-cell ALL treated with blinatumomab or SOC chemotherapy immediately followed by allogeneic HSCT	Data on HSCT for patients with ALL, such as the type of HSCT, source of HSCT, donor-type, preparative regimen, functional status, and ALL disease characteristics.	Protocol Q2 2019; Interim CSR Q2 2022; Final CSR Q2 2025

ALL = acute lymphoblastic leukemia; COG = Children's Oncology Group; CR1 = first complete remission; CSR = clinical study report; CTEP = Cancer Therapy Evaluation Program; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; HR = high risk; HSCT = hematopoietic stem cell transplant;
I-BFM = International Berlin-Frankfurt-Munich; IR = intermediate risk; LR = low risk; LTFU = long-term follow up; MRD = minimal residual disease; NCI = National Cancer Institute; OS = overall survival; Ph- = Philadelphia chromosome-negative; Q = quarter; RFS = relapse-free survival; SOC = standard of care

- Study E1910, conducted by the Eastern Cooperative Oncology Group (ECOG) and sponsored by the National Cancer Institute (NCI), is a phase 3, randomized, controlled study to assess the effect of blinatumomab in combination with induction chemotherapy compared with induction chemotherapy alone for adult patients (≥ 30 through ≤ 70 years of age) with newly diagnosed Philadelphia chromosome-negative B-cell ALL. Patients who achieve CR1 and are MRD negative will be randomized to blinatumomab or SOC chemotherapy, and those who are MRD positive after achieving CR1 will receive blinatumomab. The primary objective of this study is to evaluate the OS associated with blinatumomab in conjunction with chemotherapy versus chemotherapy alone in patients with Philadelphia-negative B-cell ALL who are MRD negative after induction and intensification chemotherapy. A secondary objective is to compare OS and RFS of patients who are MRD positive at randomization/registration and then convert to MRD negative after 2 cycles of blinatumomab to patients who are MRD negative at randomization and remain so after 2 cycles of blinatumomab or consolidation chemotherapy.
- Study AALL1331, conducted by the Children's Oncology Group (COG) and sponsored by the NCI, is a phase 3, open-label, randomized, parallel group study to evaluate efficacy and safety of blinatumomab compared with standard combination chemotherapy in treating patients with B-cell ALL in first relapse. This is a group wide risk-stratified study to test whether incorporation of blinatumomab into the treatment of patients with childhood B-cell ALL at first relapse will improve DFS (the primary endpoint). Patients are randomized to blinatumomab or SOC chemotherapy arms based on level of risk. Risk stratification is determined based on site of relapse (marrow versus isolated extramedullary [IEM]), time to relapse, and MRD status following a uniform first block of chemotherapy. High and intermediate risk patients are randomized to either a control arm with 2 additional blocks of chemotherapy, or an experimental arm with 2 blocks of blinatumomab. Both arms will proceed to protocol-specified HSCT. Low risk patients are randomized to either a control arm with 2 blocks of chemotherapy followed by continuation and maintenance chemotherapy, or an experimental arm with 1 block of chemotherapy, 2 blocks of blinatumomab, each followed by continuation and a third additional block of blinatumomab followed by maintenance.

  Overall survival is a key secondary endpoint for this study. The most relevant population to address the MRD-positive ALL population is the high-risk group, which includes MRD-positive patients in CR2. This study will provide extensive long-term follow-up data as patients will be followed for 10 years. This follow-up will allow for adequate assessment of OS and for survival after transplantation. The

data generated from this study will also provide evidence of survival by MRD-negativity status. To cover the age groups not included in the E1910 study, Study AALL1331 includes patients who are between the ages of 1 year to < 31 years. As of August 2018, approximately 16.3% of patients enrolled are young adults (ages 18 to 30 years of age) and 83.7% of patients enrolled are children. Although patients ≥ 31 years of age are not included in this study, Berry et al (2017) have shown that the value of achieving MRD negativity is substantial in both the pediatric and adult patients with ALL.

- Study 20120215, conducted by Amgen in cooperation with the International Berlin-Frankfurt-Munich (I-BFM) Study Group, is a randomized, open-label, controlled, phase 3 study to investigate the efficacy and safety of blinatumomab as consolidation therapy versus European consolidation therapy in pediatric patients (> 28 days to < 18 years of age) with high-risk first relapse B-cell precursor ALL. After induction therapy and 2 blocks of high-risk consolidation (HC) chemotherapy, pediatric patients with high-risk first relapse B-precursor ALL are randomized in a 1:1 ratio to either blinatumomab or a third block of standard HC3 chemotherapy. Randomization will be stratified by age, marrow status determined at the end of HC2, and MRD status determined at the end of induction. The primary endpoint is EFS with OS as a key secondary endpoint. The data from this study will also provide evidence of survival by MRD negativity status. This study will provide extensive long-term follow-up data as subjects will be followed for 3 years after allogeneic HSCT or until death, whichever occurs first. This follow-up will allow for adequate assessment of OS and for survival after transplantation. Although Study 20120215 is a robust study to assess the impact of blinatumomab compared with SOC chemotherapy, it is limited to studying patients who are less than 18 years of age. Although patients < 18 years of age are not included in Study MT103-203, Berry et al (2017) have shown that the value of achieving MRD negativity is substantial in both the pediatric and adult patients with ALL. Results for this study are expected in 2023.
- In addition to the ongoing randomized studies, Amgen is developing a long-term observational study to study (Study 20170610) that will characterize post-transplant outcomes of patients that were re/induced with blinatumomab. These outcomes will be compared to patients that received SOC chemotherapy in the relapse/refractory ALL setting. The protocol for this long-term observational study will also capture the MRD status of patients at the time of transplant. Patients may be followed for up to 10 years. This study will also help to better understand the questions surrounding outcomes related to post-transplant outcomes after blinatumomab treatment. Results for this study are expected in 2022.

Clinical Ground No. 4 (Indication limited to the Philadelphia chromosome-negative population). During the re-examination procedure and following the CHMP's request during the initial assessment of the extension of indication, the MAH applied for the following indication:

BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome-negative minimal residual disease (MRD) positive B-precursor ALL.

Clinical Ground No. 5 (Uncertainties regarding the impact of HSCT after blinatumomab on long-term outcomes). Based on the results of the analyses presented in the previous responses, the MAH considered that blinatumomab consistently showed a survival benefit in the transplant setting. After 3 years of follow-up time in Study MT103-203, subjects who achieved complete MRD response in cycle 1 and received HSCT while in hematologic CR had better OS than subjects who did not achieve complete MRD response in cycle 1 but were in hematologic CR at the time of HSCT. Using the updated data, the 100-day mortality rate following HSCT remains unchanged, because since the first follow up until 2015, no additional subjects underwent transplantation. The 100-day HSCT mortality rate for subjects who died

while in continuous CR after HSCT was < 10% (7.9%; 6/76 subjects), which is lower than the 100-day mortality rate of 28% observed in literature (Bishop et al, 2008).

In addition, the MAH considered that the high rate of HSCT in Study MT103-203, while partly attributable to a general increase in the rate of transplantation over time, is largely due to the success of blinatumomab in inducing complete MRD responses and the desire of investigators to transplant patients who achieved complete MRD response, which is a goal of therapy in order to prolong OS for these patients. An HSCT was planned for 81.9% of subjects in Study MT103-203. For 45.7% of subjects overall, an HSCT was planned regardless of whether the subject achieved an MRD response. This rate is similar to the overall rate of transplant in Study 20120148 (36.8% [49 of 133 subjects]. However, for an additional 31.0% of subjects, HSCT was planned only if the subject achieved an MRD response.

In the primary endpoint FAS in Study MT103-203, the rate of HSCT for subjects in CR was 71.6% (63 out of 88) in subjects who achieved a complete MRD response within cycle 1 compared to 40.0% (10 out of 25) in subjects who did not achieve a complete MRD response within cycle 1, which was similar to the HSCT rate in the historical comparator Study 20120148 (36.8% [49 of 133 subjects]. The MAH argued that given that 78% of subjects overall did achieve a complete MRD response in Study MT103-203, it can be concluded that the significant increase in the HSCT rate between the historical comparator study 20120148 and Study MT103-203, while partly attributable to a general increase in the rate of transplantation over time due to wider donor availability and improvements in transplant technology, is primarily due to the high complete MRD response rate in subjects who received blinatumomab in Study MT103-203. In addition, the fact that more and older subjects underwent HSCT in Study MT103-203 is supported by a substantial difference in age between subjects in Study MT103-203 and Study 20120148, and the median age of subjects who underwent HSCT was a decade higher in subjects in Study MT103-203 compared to subjects in Study 20120148. For example, in Study MT103-203, 4 subjects over 65 years of age underwent HSCT. Two of them were alive at the last follow-up visit. The high proportion of 33% of subjects with HSCT with mismatched donors also reflects enabling HSCT for subjects in Study MT103-203 who were probably otherwise not suitable for transplantation.

The MAH confirmed that in line with the advice given by experts at the SAG-O meeting in November 2017, transplant outcomes will be assessed in the observational study (Study 20170610) that will be conducted as part of the EMEA/H/C/003731/II/0009 variation (see RMP).

5.2. Scientific Advisory Group- consultation

Following a request from the MAH at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

The SAG should comment on the grounds for negative opinion in view of the grounds for re-examination submitted by the applicant:

- Therapeutic efficacy of Blincyto in the treatment of adults with minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) for BLINCYTO has not been established. Specifically, whilst an effect on MRD response has been quantified, a clinical benefit of MRD response is not established and surrogacy of MRD response to increased survival has not been established.
- In the absence of demonstrated efficacy, the benefit – risk of Blincyto in this setting is considered negative.

Based on the input from the experts on how MRD is measured and its validity in the tumour burden in ALL, the SAG unanimously agreed that MRD negativity is an important clinical objective in B-cell precursor ALL patients with residual disease.

Based on the pivotal study submitted, patients' residual disease level to enter the trial was high (10^{-3}). Such patients are at very high risk of frank relapse. Notably, the majority of patients did achieve MRD negativity after one course of Blincyto and had extended disease free survival.

Blincyto is approved for treatment of relapsed patients based on a randomized study that has shown improvement in overall survival. Thus, the effect of Blincyto of allowing patients with residual disease to obtain MRD negativity, delaying what would otherwise be imminent frank disease relapse, is considered clinically significant and important. The SAG considered that efficacy has been demonstrated and that the balance of benefits and risks is positive.

Given the clinical importance of reaching MRD negativity to avoid recurrence, demonstrating formal surrogacy with respect to overall survival is not considered necessary. In any case, following frank relapse, which is rapidly expected for MRD-positive patients in absence of treatment, Blincyto was associated with a positive effect on overall survival. Thus, apart from the clinically important effect of delaying recurrence, it is reasonable to assume that inducing MRD negativity in this high risk patient population will also result in survival benefit.

In addition, in the context of the re-examination procedure for this application, the SAG is asked to provide its views on the following issues:

1. **As MRD-positivity is reflective of chemo-resistant disease, does the SAG consider that the prognostic value of MRD conversion prior to HSCT reasonably may differ depending on the mechanism by which MRD-negativity is obtained, i.e. immunologically mediated (as with blinatumomab) vs chemotherapy-induced?**

There is no reason to believe that the prognostic value of MRD conversion would differ according to the mechanism involved. There is however the potential that immunologically-mediated MRD-negativity might translate into more durable disease control compared to chemotherapy, at least in some patients. The depth of remission after blinatumomab may be deeper as it has a different mechanism in these partially chemo-refractory patients. This possibility, if confirmed would be an additional very important goal, namely, achieving long-term remission and avoiding HSCT. Long-term follow-up through a registry and further biomarker identification would be of interest to explore this potential.

Concerning post-transplant mortality, the proportion observed in the pivotal study for Blincyto does not raise concerns given the patient characteristics, which highlight a poor prognosis, particularly in terms of age, type of donor (1/3 mismatched transplant) and stage of ALL (1/3 2nd CR and some CR3). Based on the non-randomized data with no protocol defined definitions on precise indications and specified "high dose regimens, with these caveats there is no concern about a possible adverse effect of Blincyto on HSCT.

2. **Does the SAG consider that the ongoing and planned studies cited by the applicant will adequately address the remaining outstanding uncertainties identified during the review, including the predictive role of blinatumomab-induced MRD conversion, not least in terms of longer-term outcomes, and the impact of HSCT after blinatumomab therapy?**

A number of important studies were discussed by the applicant. However, understandably, no study is primarily aiming to present a well-powered randomized comparison of overall survival of Blincyto v. no treatment in this high-risk disease population since Blincyto has been shown to be highly effective in inducing MRD negativity. Given that this important clinical goal is achieved and given that a detriment in

overall survival is unlikely based on the positive effect of survival in a slightly later stage of disease when patients formally meet the criteria for recurrence, a direct comparison is considered unnecessary. However, long-term follow-up through a registry and further biomarker identification would be of interest (see above).

3. **Please discuss whether available evidence supports the use of blinatumomab treatment in subjects deemed not fit for HSCT?**

Yes, available evidence supports the use of blinatumomab treatment in subjects deemed not fit for HSCT based on the ability of Blincyto to delay frank recurrence.

5.3. Discussion and overall conclusion on grounds for re-examination

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the MAH and considered the views of the Scientific Advisory Group.

Concerning clinical ground No. 1, the CHMP further discussed the MAH's arguments.

Based on the results of the study MT103-203, 77.9% of patients achieved MRD complete response. Two additional subjects had a complete MRD response at day 66 and day 77 respectively. The majority of these patients did achieve MRD negativity after one cycle of Blincyto and had extended disease free survival. Moreover, the percentage of patients with MRD $<10^{-4}$ was almost 87%. The MRD complete response achieved at cycle 1 was sustainable, with a median duration of 17.3 months. The CHMP concluded that these results suggest a strong, rapid and sustained pharmacodynamic activity of Blincyto in MRD-negativity in adult patients having Ph-negative ALL in CR/CRi.

Concerning clinical ground No.2, during the initial assessment of this application the CHMP noted that MRD response had not been established as surrogate endpoint of direct clinical benefit; differences in MRD negativity between randomised and interventional had not been shown to be predictive of the hazard ratio (HR) between arms for event free survival (EFS) or OS. The CHMP acknowledged that patients in CR that are MRD positive have a poor prognosis and an unmet medical need. Considering the residual disease level to enter the trial which was high (10^{-3}), the patients are at very high risk of frank relapse.

MRD negativity at the end of induction therapy is a strong and independent prognostic indicator for relapse risk. A profound reduction of tumour load is therefore the key factor for durable remission. The CHMP agreed with the SAG experts that given the clinical importance of reaching MRD negativity to avoid recurrence, demonstrating formal surrogacy with respect to overall survival is not considered necessary. In absence of treatment with Blincyto, MRD-positive patients will relapse. Therefore if these high risk patients are treated with Blincyto and reach MRD negativity, this may impact overall survival. This assumption is also supported by the demonstration of an OS gain over standard of care when treating patients in the relapsed/refractory setting. Furthermore, there is a lack of any available specific therapy.

Concerning clinical ground No. 3 and the ongoing clinical studies, the CHMP agreed that while it is not expected that the surrogacy of MRD will be established, these studies are important to further characterise long-term outcomes in patients treated with Blincyto and to provide data on outcomes after HSCT in patients treated with Blincyto.

Concerning clinical ground No. 4 regarding the proposed indication, the CHMP agreed with the MAH that the indication should specify ''Philadelphia chromosome-negative''. In addition to this, the CHMP considered that the indication should define that patients should be in first or second complete remission,

as was 98% of the study population. Therefore the indication has been revised as follows: BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

Concerning clinical ground No.5 the CHMP acknowledged that the increased HSCT rate between the historical comparator study 20120148 and Study MT103-203, is partly due to a general increase in the rate of transplantation over time but primarily due to the high MRD conversion rate seen in MT103-203, and also a higher number of older subjects were transplanted in this study as compared to the historical controls. The CHMP highlighted that, 23 deaths (out of 53 deaths) occurred while the subjects were in CR after HSCT (23 out of a total of 90 subjects who received HSCT after starting Blincyto, 25.6%), and only 3 deaths occurred in subjects achieving a CR without undergoing HSCT (3 out of a total of 26 subjects who did not receive HSCT, 11.5%). Based on the above, the CHMP concluded that the proportion of deaths observed in the pivotal study for Blincyto did not raise concerns given the poor prognosis of the studies population. Both studies AALL1331 and E1910 described above will provide data on outcomes after HSCT in patients treated with Blincyto.

5.4. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

Safety concerns

Table 42. Summary of the safety concerns

Important identified risks	Neurologic events
	Infections
	Cytokine release syndrome
	Infusion reactions
	Tumor lysis syndrome
	Capillary leak syndrome
	Elevated liver enzymes
	Medication errors
	Febrile neutropenia and neutropenia
	Decreased immunoglobulin
	Pancreatitis
Important potential risks	Off-label use
	Leukoencephalopathy (including PML)
	Thromboembolic events (including DIC)

	Immunogenicity
	Worsening of hepatic impairment in patients with hepatic impairment
	Use in patients with active or a history of high risk CNS pathology including patients with untreated ALL in CNS
	Hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines)
	Hematopoietic stem cell transplantation-related toxicity in children
Missing information	Use in pregnancy and breastfeeding
	Use in elderly
	Use in patients with renal impairment
	Use in patients with ethnic differences
	Use in patients with active uncontrolled infections
	Use in patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus
	Use in patients after recent HSCT
	Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)
	Recent or concomitant treatment with other immunotherapy
	Effects on fertility
	Long-term safety and efficacy
	Development impairment in children including neurological, endocrine, and immune system
	Subsequent relapse of leukemia in children including in the central nervous system
	Long-term toxicity in children
	Secondary malignant formation in children

Pharmacovigilance Plan

Table 43 Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Study MT103-211 (extension cohort only): An open-label, multicenter, phase 2 study to evaluate efficacy and safety of the bi-specific T-cell engager (BiTE®) antibody blinatumomab in adult subjects with relapsed/ refractory B-precursor acute lymphoblastic	• To evaluate CNS symptoms and explore potential predictive factors for CNS events associated with blinatumomab	Neurologic events	Ongoing	Final CSR: June 2018

leukemia (ALL) Category 3				
Study 20120215: A Randomized, Open-Label, Controlled Phase 3 Adaptive Trial to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab as Consolidation Therapy Versus Conventional Chemotherapy in Pediatric Patients with High-Risk First Relapse of B-precursor Acute Lymphoblastic Leukemia (ALL) Category 3	• To evaluate event-free survival (EFS) in the blinatumomab arm versus EFS in the standard consolidation chemotherapy arm	Long-term safety and efficacy	Ongoing	Final CSR anticipated: July 2024

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Study 20150136: An observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices Category 1	Primary objective: • To characterize the safety profile of blinatumomab in routine clinical practice in countries in the EU • To estimate the frequency and types of blinatumomab medication errors identified in patient charts Secondary objectives: • To estimate the incidence of other serious adverse events, ie, serious adverse events not included in the primary objective • To evaluate safety and effectiveness	Selected identified risks, potential risks, and missing information, as well as other serious adverse events	Planned	Enrollment update will be provided in each PSUR Annual interim reports will be provided with corresponding PSUR/PBRER starting with PSUR/PBRER #3 Final CSR: anticipated Q4 2021

	endpoints among patient subgroups defined by demographic and clinical factors • To characterize the effectiveness of blinatumomab in routine clinical practice • To describe blinatumomab utilization and select healthcare resource use in routine clinical practice			
Study 20150163: Survey of physicians, pharmacists, and nurses involved in the prescribing, preparation and administration of blinatumomab in Europe to evaluate the effectiveness of additional risk minimization measures Category 3	Primary objective: • To evaluate the distribution, knowledge and impact on behavior of additional risk minimization measures for physicians, pharmacists and nurses	Neurologic events, medication errors	Planned	Final CSR: anticipated Q2 2019
Study 20150228: A cross-sectional survey of patients and caregivers receiving blinatumomab in routine clinical practice in Europe to evaluate the effectiveness of additional risk minimization measures Category 3	Primary objective: • To assess knowledge about and receipt of the educational materials Secondary objective: • To determine the level of understanding of the information in the educational materials • To evaluate adherence to the instructions in the patient educational materials	Neurological events, medication errors	Planned	Final CSR: anticipated Q3 2019
Study 20170610: Overall survival and incidence of transplant-related adverse events in relapsed/refractory B-cell acute	Primary objective: • To generate data on HSCT for patients with ALL, such as the type of HSCT, source	Long-term safety and efficacy	Planned	Final Protocol: Q2 2019 Interim CSR: Q2 2022 Final CSR: Q2 2025

lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: Induction with blinatumomab treatment versus induction with chemotherapy Category 3		of HSC, donor-type, preparative regimen, functional status, and ALL disease characteristics.			
Study number to be determined: A retrospective study to determine follow-up overall survival of subjects with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab versus standard of care chemotherapy in the phase 3 open label, randomized 00103311/TOWER study. Category 3	Primary	objective: • To determine follow-up overall survival of subjects with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab versus standard of care chemotherapy in the phase 3 open-label, randomized 00103311/TOWER study	Long-term safety and efficacy	Planned	Final Protocol: Q1 2019 Final CSR: Q4 2019

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Study 20180130: Long-term follow-up for developmental, HSCT, and secondary malignancy toxicity in pediatric high-risk patients enrolled in Study 20120215 Category 1	Primary objective: • To identify incidence of developmental impairment, including neurological, endocrine and immune system • To identify incidence of HSCT-related toxicity • To identify incidence of subsequent relapse of leukemia including in the central nervous system (CNS) • To identify incidence of long term toxicity • To identify incidence of secondary malignant formation	Hematopoietic stem cell transplantation-related toxicity in children Long-term safety and efficacy Development impairment in children including neurological, endocrine, and immune system Subsequent relapse of leukemia in children including in the central nervous system Long-term toxicity in children Secondary malignant formation in children	Planned	Final Protocol: Q1 2019 Interim Analyses: Every 2 years from start of data collection Final CSR: Q4 2036
Study 20130320 An open-label, multi-center, expanded access protocol of blinatumomab for the treatment of pediatric and adolescent subjects with relapsed and/or refractory B-precursor acute lymphoblastic leukemia (ALL) Category 3	Primary objective: To estimate the incidence of treatment-emergent and treatment-related adverse events during treatment with blinatumomab in pediatric and adolescent subjects with B-precursor ALL in second or later bone marrow relapse, in any marrow relapse after alloHSCT, or refractory to other treatments	Long-term safety and efficacy	Ongoing	Protocol: 07 June 2018 Final CSR: Q2 2034

Risk minimisation measures

Table 44. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Neurologic events	Relevant text is provided in the following section of the SmPC: • Section 4.2 Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.7, Effects on ability to drive and use machines • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	Educational materials for physicians, nurses, and patients (including caregivers) (Annex 11 of the RMP).
Infections	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 3, How to use blinatumomab • Section 4, Possible side effects	None
Cytokine release syndrome	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties • Section 5.3, Preclinical safety data Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks (continued)		
Infusion reactions	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 3, How to use blinatumomab	None
Tumor lysis syndrome	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Capillary leak syndrome	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Elevated liver enzymes	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.2, Pharmacokinetic properties Relevant text is provided in the following section of the SmPC: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Medication errors	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.9, Overdose • Section 6.6, Special precautions for disposal and other handling	Educational material will be distributed to pharmacists[a], physicians, nurses, and patients (including caregivers). In addition, patients will also receive a patient alert card (Annex 11 of the RMP).

Febrile neutropenia and neutropenia	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab • Section 4, Possible side effects	None
Decreased immunoglobulin	Relevant text is provided in the following section of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Pancreatitis	Proposed relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Proposed relevant text is provided in the following sections of the PL: • Section 2, Warnings and precautions • Section 4, Possible side effects	A DHPC was distributed to communicate the changes to the prescribing information.
Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risk		
Off-label use	Relevant text is provided in the following section of the SmPC: • Section 4.1, Therapeutic indications • Section 5.1, Pharmacodynamics properties	None
Leukoencephalopathy (including PML)	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following section of the PIL: • Section 4, Possible side effects	None
Thromboembolic events (including disseminated intravascular coagulation)	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use	None
Immunogenicity	Relevant text is provided in the following section of the SmPC: • Section 4.8, Undesirable effects	None

Worsening of hepatic impairment in patients with hepatic impairment	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 5.2, Pharmacokinetic properties	None
Use in patients with active or a history of high risk CNS pathology including patients with untreated ALL in CNS	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use	None
Hematological disorders in newborn exposed in utero to blinatumomab (particularly B-cell depletion and risk of infections in case of vaccination with live virus vaccines)	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy, and lactation	None
Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hematopoietic stem cell transplantation-related toxicity in children	No risk minimization activities are proposed.	None
Missing Information		
Use in pregnancy and breastfeeding	Relevant text is provided in the following section of the SmPC: • Section 4.3, Contraindications (lactation) • Section 4.4, Special warnings and precautions for use • Section 4.6, Fertility, pregnancy and lactation Relevant text is provided in the following section of the PIL: • Section 2, What you need to know before you use blinatumomab	None
Use in elderly	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties	None
Use in patients with renal impairments	Relevant text is provided in the following section of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.2, Pharmacokinetic properties	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Use in patients with ethnic differences	No risk minimization activities are proposed at this time, given the lack of clinical evidence for any risks associated with patients of different race or ethnic origins who are treated with blinatumomab.	None
Use in patients with active uncontrolled infections	Relevant text is provided in the following section of the SmPC: • Section 4.4, Special warnings and precautions for use	None
Use in Patients with HIV positivity or chronic infection with hepatitis B virus or hepatitis C virus	No risk minimization activities are proposed.	None
Use in patients after recent HSCT	No risk minimization activities are proposed.	None
Recent or concomitant treatment with other anti-cancer therapies (including radiotherapy)	No risk minimization activities are proposed.	None
Recent or concomitant treatment with other immunotherapy	No risk minimization activities are proposed.	None
Effects on fertility	Relevant text is provided in the following section of the SmPC: • Section 4.6, Fertility, pregnancy and lactation	None
Long-term safety and efficacy	No risk minimization activities are proposed.	None
Development impairment in children including neurological, endocrine, and immune system	No risk minimization activities are proposed.	None
Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Subsequent relapse of leukemia in children including in the central nervous system	No risk minimization activities are proposed.	None
Long-term toxicity in children	No risk minimization activities are proposed.	None
Secondary malignant formation in children	No risk minimization activities are proposed.	None

5.5. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the new indication and its relevant posology and to update the safety information. The Package Leaflet is updated accordingly.

5.5.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

6. Benefit-risk balance

6.1. Therapeutic Context

6.1.1. Disease or condition

Blincyto as monotherapy is proposed for the treatment of adults with Philadelphia chromosome-negative CD19 positive B precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

6.1.2. Available therapies and unmet medical need

Persistent MRD-positivity in adult patients after induction therapy and/or consolidation therapy in complete haematological remission (e.g. CR1) is considered an unmet medical need. The main goal in these patients is inducing MRD-negativity of sufficient duration to allow for stem-cell transplantation, the only potentially curative option in this setting with otherwise very poor prognosis.

6.1.3. Main clinical studies

The MAH submitted a single pivotal open-label non-comparative (Study MT103-203, n=116)) which was supported by a supportive study (MT103-202, n=20) and a retrospective historical study (study 20120148). Indirect comparisons with historical studies by propensity score analysis were also submitted. The primary efficacy endpoint was the proportion of subjects who achieved a complete MRD response. RFS, OS, duration of MRD response, TTHR, mortality within 100-day after alloHSCT were analysed as secondary endpoints. The pivotal study enrolled 116 adult subjects with MRD-positive B-cell precursor ALL in complete hematological remission with the presence of MRD at a level of ≥10-3, without prior HSCT. The majority of studied population was Ph-negative (111/116) and in first CR (CR1 64.7%).

6.2. Favourable effects

A complete MRD response rate was observed within the first cycle in 77.9% (88/113; 95% CI: 69.1, 85.1) of subjects. 2 additional subjects had a complete MRD response at day 66 and day 77 respectively. The overall complete response rate for the Prim EP FAS was 79.6% (90/113; 95% CI: 71.0, 86.6), with a median time to complete MRD response of 29.0 days (range: 5 to 71 days). The MRD complete response achieved at cycle 1 was sustainable, with a median duration of 17.3 months.

These results suggest a strong, rapid and sustained activity of Blincyto in MRD-negativity in subjects in CR with MRD+ ALL.

RFS was calculated from initiation of Blincyto in this study in Ph-negative subjects at 18 months. The 18-month KM estimate for haematological RFS, censored at HSCT or post-Blincyto chemotherapy, was 54%

(95% CI: 33% to 70%) with not estimable median RFS (95% CI: 6.3 months to not estimable [n.e.]). The RFS was 17.9 months longer in MRD complete responders than in MRD non-responders (23.6M vs 5.7M) according to a landmark analysis from day 45. RFS (not censored at HSCT or post-Blincyto chemotherapy) was 13.6 months longer in patients in CR1 than in CR2 or CR3 (24.6M vs 11.0M).

After at least 18M follow-up, the median of OS, calculated from initiation of Blincyto, was not estimable. Nearly twice as many subjects who had an MRD complete response than MRD non-responders were alive as of the data cut-off date (62.5% vs 33.3%). The median OS was 28.4m longer for complete MRD responder at C1 compared with MRD non-responder. The 18-months OS uncensored at HSCT or post blinatumomab chemotherapy is 65%. MRD non-responder at C1 had a median TTHR clearly shorter than in MRD complete responder (13.6m vs NE).

6.3. Uncertainties and limitations about favourable effects

The appropriateness of MRD response as a validated surrogate endpoint of direct clinical benefit was not established by robust evidence based on a documented and measurable correlation between MRD status and validated endpoints such as OS or EFS (see below, section 6.7.1.).

Of a total of 53 deaths, 23 occurred while the subjects were in CR after HSCT (23 out of a total of 90 subjects who received HSCT after starting Blincyto, 25.6%), and only 3 deaths occurred in subjects achieving a CR without undergoing HSCT (3 out of a total of 26 subjects who did not receive HSCT, 11.5%). Some transplanted patients died even 30 months after their HSCT. The CHMP concluded that the proportion of deaths observed in the pivotal study for Blincyto did not raise specific concerns given the poor prognosis of the studies population and the small numbers. Furthermore studies AALL1331 and E1910 will provide data on outcomes after HSCT in patients treated with Blincyto.

6.4. Unfavourable effects

A total of 843 subjects from 8 clinical studies received blinatumomab. Of these 843 subjects, 706 subjects with relapsed/refractory ALL are included in the total relapsed/refractory ALL population from 6 of the 8 clinical studies and 137 subjects are included in the adult MRD-positive ALL population from pivotal study MT103-203 (N = 116) or supportive study MT103-202 (N = 21).

The highest incidences (≥ 50%) of TEAE by system organ class (SOC) were General Disorders and Administration Site Conditions (94.8%; 110/116), Nervous System Disorders (68.1%; 79/116), and Gastrointestinal Disorders (53.4%; 62/116). The most frequently reported TEAEs (preferred terms in > 20% of subjects) were pyrexia (88.8%; 103/116), headache (37.9%; 44/116), tremor (30.2%; 35/116), chills (25.9%; 30/116), fatigue (24.1%; 28/116), nausea (23.3%; 27/116), and vomiting (22.4%; 26/116).

Treatment-emergent grade ≥ 3 adverse events (preferred term in ≥ 5% of subjects) included neutropenia (15.5%; 18/116), pyrexia (7.8%; 9/116), leukopenia (6%; 7/116), and alanine aminotransferase (ALT) increased and tremor (5.2%; 6/116 for each).

Events of interest (EOI) for the blinatumomab program include neurologic events, infections, CRS, drug related hepatic disorders, infusion reactions, tumor lysis syndrome (TLS), thromboembolic events, medication errors, cytopenias, decreased immunoglobulins, capillary leak syndrome (CLS), pancreatitis and leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

6.5. Uncertainties and limitations about unfavourable effects

Although data are limited due to the small size of the trial and hampered by the open-label design, safety was generally in line with the known safety profile of Blincyto; therefore no specific uncertainties have arisen in the present study.

There is some uncertainty about the impact of Blincyto on the outcome of HSCT, as randomized data are not available (and are not feasilble to obtain). However the CHMP recommended the applicant to submit the results from the studies AALL1331 and E1910 in order to get more data on outcomes after HSCT in patients treated with Blincyto.

6.6. Effects Table

Table 45. Effects table for Blincyto in the treatment of adults with MRD positive B-cell precursor ALL – pivotal study MT103-203 (data cut-off: 05 August 2015)

Effect	Short Description	Unit	Blincyto N=116	Uncertainties/ Strength of evidence
Favourable Effects				
MRD	proportion of subjects who achieved a complete MRD response defined by the absence of MRD after 1 cycle of Blincyto	% (95% CI)	77.9 (69.1, 85.1)	Similar high MRD response rate was also observed in supportive study. The MRD response was sustainable 45.0 months (95% CI: 6.5, 45.0) with censored at HSCT or post-Blincyto chemotherapy 17.3 months (95% CI: 12.6, 23.3) not censored at HSCT or post-Blincyto chemotherapy.
RFS	haematological RFS rate at 18 months following initiation of Blincyto, evaluated in Ph-negative ALL subjects censored at HSCT or post-Blincyto chemotherapy	Months (KM median; 95% CI) RFS (KM rate; 95% CI)	Median RFS not estimable (6.3, NE) Landmark from 3M: HSCT 16.1M, No HSCT 22.1M Landmark from 6M: HSCT 29.2M, No HSCT n.e. 54% (33%, 70%) with censored at HSCT or post-Blincyto chemotherapy 53% (44%, 62%) not censored at HSCT or post-Blincyto chemotherapy with HSCT	
OS	Time from treatment start with Blincyto until death	Months (KM median; 95% CI) OS (KM rate; 95% CI)	NE (NE, NE) with censored at HSCT or post-Blincyto chemotherapy 36.5 months (19.2, NE) not censored at HSCT or post-Blincyto chemotherapy Landmark from 3M: HSCT 21.2M, No HSCT 33.5M Landmark from 6M: HSCT 30.5M, No HSCT n.e. 83% (55%, 94%) with censored at HSCT or post-Blincyto chemotherapy 65% (55%, 73%) not	

Effect	Short Description	Unit	Blincyto N=116	Uncertainties/ Strength of evidence
			censored at HSCT or post-Blincyto chemotherapy	
Unfavourable Effects				
AEs	Incidence as percentage of patients involved	Percentage	All grades 100% ≥grade 3 AE: 61.2% (primarily: pyrexia, headache, tremor, chills, fatigue, nausea, vomiting)	
SAEs	Incidence as percentage of patients involved	Percentage	62.9% (primarily: pyrexia, tremor, aphasia and encephalopathy)	
Discontinuation	Incidence as percentage of patients involved	Percentage	Discontinuation 17.2% (primarily: tremor, seizure, aphasia and encephalopathy)	

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

While the surrogacy of MRD for RFS and OS has not been established, MRD in the present scenario is a sensitive marker for residual disease, which is illustrated by the fact MRD positive patients will generally experience imminent relapse without further intervention. Furthermore, there is a lack of any available specific therapy. Therefore patients with CR that are MRD positive have a highly unmet medical need.

Study MT103-203 demonstrated a compelling 78% rate of MRD negativisation ($<10^{-4}$), as well as a clinically relevant DoR with a median of 17 months. Hence the CHMP concluded that, given these results and the clinical importance of reaching MRD negativity to avoid recurrence, demonstrating formal surrogacy with respect to overall survival is not considered necessary.

The high proportion of subjects who achieved a complete MRD response (77.9%) with blinatumomab regimen in the pivotal study was considered clinically meaningful and significant, especially in the population studied with very poor prognosis. Other endpoints like duration of response and RFS were consistent with the notion of clinical benefit.

The safety profile for the adult MRD-positive ALL population is consistent with the known safety profile of blinatumomab in relapsed/refractory ALL.

6.7.2. Balance of benefits and risks

The activity of Blincyto in MRD-negativity in subjects with MRD positive B-cell precursor ALL observed is clinically relevant. In such a setting, the available demonstration of outstanding pharmacodynamic activity in the presence of a manageable safety profile may be considered to establish clinical benefit. Therefore, the benefit risk for blinatumomab as monotherapy for the treatment of adults with Philadelphia chromosome-negative CD19 positive B precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% for BLINCYTO monotherapy is considered positive.

6.8. Conclusions

The overall B/R of Blincyto is positive.

7. Recommendations following re-examination

Final outcome

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation acceptable and therefore recommends, by a majority of 29 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change to therapeutic indication - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB

Extension of indication to include the treatment of adults with Philadelphia chromosome-negative CD19 positive B precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% for BLINCYTO monotherapy; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 9.1) are updated in accordance. In addition, the Marketing authorisation holder took the opportunity to update the contact details of the Portuguese and Irish local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Blincyto is not similar to Xaluprine, Incusig and Besponsa within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.