25 January 2018
EMA/CHMP/434726/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BLINCYTO

International non-proprietary name: blinatumomab

Procedure No. EMEA/H/C/003731/II/0009

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Rapporteur(s)	
CHMP Rapporteur:	Alexandre Moreau
PRAC Rapporteur:	Eva Jirsová

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	28 November 2016	28 November 2016
☐	CHMP Rapporteur Assessment Report	3 January 2017	13 January 2017
☐	CHMP members comments	16 January 2017	16 January 2017
☐	Updated CHMP Rapporteur Assessment Report	19 January 2017	24 January 2017
☐	Request for Supplementary Information	26 January 2017	26 January 2017
☐	MAH responses	19 May 2017	19 May 2017
☐	CHMP Rapporteur Assessment Report	20 June 2017	29 June 2017
☐	PRAC Rapporteur Assessment Report	23 June 2017	23 June 2017
☐	PRAC members comments	28 June 2017	29 June 2017
☐	CHMP members comments	10 July 2017	10 July 2017
☐	Request for Supplementary Information	20 July 2017	20 July 2017
☐	MAH responses	13 October 2017	13 October 2017
☐	CHMP/PRAC joint Rapporteur assessment report	20 November 2017	29 November 2017
☐	SAG oncology	22 November 2017	22 November 2017
☐	CHMP members comments	4 December 2017	4 December 2017
☐	Request for Supplementary information	14 December 2017	14 December 2017
☐	MAH responses	19 December 2017	19 December 2017
☐	CHMP/PRAC joint Rapporteur Assessment Report	8 January 2018	9 January 2018
☐	Opinion	25 January 2018	25 January 2018
☒	Revision of CHMP opinion following request for clarification by the European Commission	22 March 2018	22 March 2018

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Abbreviations

ALL	Acute Lymphoblastic Leukemia
alloHSCT	allogeneic hematopoietic stem cell transplantation
ALLSS	Acute Lymphoblastic Leukemia Symptom Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CIOMS	Council for International Organizations of Medical Sciences
cIV	continuous intravenous
CL	clearance
CLS	capillary leak syndrome
CNS	central nervous system
CR	complete remission
CRF	case report form
CRh*	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRS	cytokine release syndrome
C_{ss}	steady state concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOI	event of interest
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FAS	full analysis set
FLAG (filgrastim)	fludarabine, cytarabine arabinoside, and granulocyte colonystimulating factor
FLAG-IDA	fludarabine, cytarabine arabinoside, and granulocyte colonystimulating factor (filgrastim) - idarubicin

GGT	gamma-glutamyltransferase
GvHD	graft versus host disease
HAMA	human antimurine antibodies
HiDAC	high-dose cytarabine arabinoside
HDMTX	high-dose methotrexate
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IRB	Institutional Review Board
IV	intravenous
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
OS	overall survival
PCR	polymerase chain reaction
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
protocol-specified therapy	blinatumomab or 1 of 4 SOC regimes
PT	preferred term
QoL	quality of life
R_0	infusion rate
SDV	source data verification
SOC	standard of care
SMQ	standardized MedDRA query
TLS	tumor lysis syndrome
ULN	upper limit of normal
WBC	white blood cells

1. Background information on the procedure

1.1. Requested 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 11 November 2016 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety information with the data from the study 103311. This study is fulfilling the specific obligation for the conditional MA. It is proposed to remove the SO. The Package Leaflet is updated accordingly.
The MAH takes this opportunity to amend the format of the preparation instructions to improve clarity. The content is not impacted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

1.2. Rationale for the proposed change

Blincyto (blinatumomab) was granted a conditional MA on 23/11/2015 in the indication of "Treatment of adult patients with Philadelphia chromosome-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (ALL)" based upon a phase 2 single arm study (MT103-211). As the Specific Obligation (SO) of the conditional approval, additional efficacy and safety data from the following phase 3 study were required to confirm the clinical B/R of blinatumomab, to better quantify the magnitude of its treatment effect and to help better differentiate between the AEs associated with blinatumomab and those associated with cytotoxic chemotherapy:

"Post-authorisation efficacy study (PAES): Study 00103311 (TOWER): A Study of BITE antibody blinatumomab *versus* standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL)."

The purpose of this type II variation is therefore to present the final efficacy and safety data from Study 00103311, propose updates to the product information to reflect the study data and request the CHMP to adopt the granting of a MA no longer subject to SO for Blincyto.

2. Overall conclusion and impact on the benefit/risk balance

As part of the CMA for Blincyto (blinatumomab) the results of the Specific Obligation (SO) on additional efficacy and safety data from the study 00103311 (TOWER) were submitted to confirm the clinical B/R of blinatumomab, to better quantify the magnitude of its treatment effect and to help better differentiate between the AEs associated with blinatumomab and those associated with cytotoxic chemotherapy:

The study showed statistically and clinically significant increases of OS, CR/CRh*/CRi and MRD negativity in the blinatumomab group as compared to the SOC chemotherapy group (7.7 months *versus* 4.0 months, 43.9% *versus* 24.3%, 23.6% *versus* 9.0% respectively).

However, the mortality rate following alloHSCT among all responders who did not receive anti-leukemic therapy was 10/38 (26.3%; 95% CI: 13.4, 43.1) in the Blincyto group and 3/12 (25%; 95% CI: 5.5, 57.2) in the SOC group; such mortality rate at 100 days post alloHSCT was 4/38 (12.4%; 95% CI: 4.8%, 29.9%) in the Blincyto group and 0/12 (0%; 95% CI: not estimable) in the SOC group.

Blinatumumab was associated with a clinically significant increase in OS in the target population regardless of subsequent therapies. The effect was consistent across subgroups, though the role of HSCT and long-term safety was not yet fully characterised. Importantly, it is currently impossible to explore the role of treatments such as allo HSCT in patients who received blinatumomab and important prognostic factors due to the likely selection bias as patients being offered alloHSCT had different characteristics depending on the treatment arm. Furthermore, the numbers were too small to assess this aspect (100-days post alloHSCT mortality was 4/38 in the blinatumomab group and 0/12 in the SOC group). To investigate the long-term effects of HSCT in this population, the CHMP recommended collecting relevant data concerning HSCT in this population depending on prior treatment with blinatumumab and other important prognostic factors. Although these data would not be expected to inform treatment decisions (a positive effect on OS has been observed in the target population regardless of subsequent therapies), these data may help in understanding the role of subsequent therapies and their association with important factors. Relevant endpoints should include EFS, OS, 100-day mortality postHSCT; incidence and severity of acute and chronic GvHD, rates of early (100-day) and late (> 100 days) infective AEs, overall “non-relapse” mortality (NRM) rates. There is an opportunity to use the existing transplant registries to collect this information (see study 20170610 in the RMP).

The safety profile of blinatumomab in 00103311 (TOWER) showed no unexpected findings and was consistent with the established blinatumomab safety profile. The SmPC was updated to reflect the results of study 00103311 with additional safety information.

Overall, taking into account statistically and clinically significant increases of OS as well as rates of CR/CRh* and MRD response observed in the blinatumomab arm compared to the SOC chemotherapy arm, the CHMP considered that the overall B/R of blinatumomab remains positive in adults with R/R ALL at the moment of treatment initiation for blinatumomab.

In view of the SAG advice, and given that this is the only relevant comparative study in this target population and that it is generally good practice to follow-up all patients until death, the MAH has been requested to collect as complete survival data as possible for the Phase 3 study 00103311 (Tower). The additional follow-up will provide more precise estimates and the possibility for further analyses (see RMP).

Additionally, the CHMP also considered that the ongoing studies in first line B-ALL and B-precursor paediatric ALL are of great interest to assess the B/R of blinatumomab and its real place in relation to HSCT in the management of childhood ALL (COG-AALL1331) and the direct benefit (OS) of chemotherapy combined with blinatumomab among MRD-positive subjects following front-line therapy (ECOG-E1910).

In conclusion, taking into account the controlled data of the Phase 3 study 00103311, the efficacy and safety of blinatumumab has been confirmed and the SOB is considered fulfilled as comprehensive data are now available in the authorised indications. Efficacy and safety have been comprehensively established on the basis of the available data. Further data to be collected from studies 00103311 (TOWER) and 20170610 are not considered critical for the efficacy and safety of the product in the approved indication, but are of interest to further describe aspects, such as exploring the long-term effects more precisely, as well as exploring the role of subsequent treatments like alloHSCT and their association with prior treatments and other factors. Such additional aspects are unrelated to the SOB as foreseen at the time of the granting of the conditional marketing authorisation. As a consequence, the

CHMP agreed on the granting of a marketing authorisation which was not subject to specific obligations.

Scientific Summary for the EPAR

In this variation the marketing authorisation holder submitted data from study 00103311 (TOWER): A Study of blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL). The primary endpoint was overall survival (OS) defined as the time of randomization until death due to any cause. Key secondary endpoints included complete remission (CR), complete remission with partial hematologic recovery (CRh*), complete remission with incomplete hematologic recovery (CRi) and minimal residual disease (MRD). In this study statistically and clinically significant increases of primary endpoint OS and secondary endpoints CR/CRh*/CRi and MRD negativity were observed in the blinatumomab arm as compared to the SOC chemotherapy arm (7.7 months vs 4.0 months, 43.9% vs 24.3%, 23.6% vs 9.0% respectively). In conclusion, the controlled data of the Phase 3 study 00103311 confirmed the efficacy and safety of blinatumumab and the CHMP agreed on the fulfilment of the specific obligation.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC, Annex II and Package Leaflet based on the clinical study 103311 (TOWER): a Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL). The RMP (version 7.0) has been updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took this opportunity to make editorials changes in section 6.6 of the SmPC. Finally, the CHMP recommends the granting of a marketing authorisation no longer subject to specific obligations.

☒ is recommended for approval.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

4. Scientific discussion

4.1. Introduction

Acute lymphoblastic leukaemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow and peripheral blood. Primary refractory ALL is defined by absence of complete remission (CR1) after standard induction therapy. A patient has relapsed ALL if they achieved a CR1 during upfront therapy and then relapse during or after therapy. A

similar classification is possible for salvage therapy. Refractory relapse is defined by lack of CR after first salvage therapy. Second relapse or later relapses are defined as relapse after achieving a second CR (CR2) in first salvage or later salvage therapies.

The detection of minimal residual disease (MRD) after induction therapy and/or consolidation therapy is an independent prognostic factor for poor outcome of ALL. Patients highly responsive to chemotherapy with an MRD level below 10-4 induced by induction treatment have a favourable prognosis. Patients with MRD that persists during induction and consolidation of front-line treatment or who become MRD-positive following treatment have poor leukaemia-free survival rates.

No chemotherapeutic regimens used in the treatment of adult R/R B-precursor ALL are clearly superior. Common treatment regimens include different combinations with fludarabine, cytarabine arabinoside, granulocyte-colony stimulating factor, and idarubicin (FLAG-IDA), high-dose cytarabine arabinoside (HiDAC), or methotrexate with L-asparaginase. Intrathecal chemotherapy may also be used to prevent central nervous system (CNS) relapse as part of the treatment regimen. The choice of standard of care (SOC) chemotherapeutic agent depends on several factors including the initial choice and response to treatment in the de novo setting, time since the chemotherapeutic regimen was last used (ie, early or late relapse), presence of adverse events, regional practice pattern, and physician preference.

Blincyto (blinatumomab) was granted a conditional MA on 23/11/2015 in the indication of "Treatment of adult patients with Philadelphia chromosome-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (ALL)" based upon a phase 2 single arm study (MT103-211) designed to evaluate efficacy and safety of blinatumomab in adult subjects with relapsed/refractory B-precursor ALL. As the Specific Obligation (SO) of the conditional approval, additional efficacy and safety data from the following phase 3 study were required to confirm the clinical B/R of blinatumomab, to better quantity the magnitude of its treatment effect and to help better differentiate between the AEs associated with blinatumomab and those associated with cytotoxic chemotherapy:

"Study 00103311 (TOWER): A Study of BITE antibody blinatumomab versus standard of care chemotherapy in adult subjects with relapsed/refractory b-precursor acute lymphoblastic leukaemia (ALL)."

4.2. Clinical

4.2.1. Pharmacokinetics

Study 00103311 was a phase 3 randomized, open-label study was designed to evaluate the efficacy and safety of blinatumomab vs SOC chemotherapy. Adult subjects with relapsed/refractory B-cell precursor ALL were randomized in a 2:1 ratio to receive blinatumomab or 1 of 4 pre-specified, investigator-chosen, SOC chemotherapy regimens. Randomization was stratified by age (< 35 years vs ≥ 35 years of age), prior salvage therapy (yes vs no), and prior alloHSCT (yes vs no) as assessed at the time of consent.

The study consisted of up to a 3-week screening and pre-phase period, a treatment period consisting of induction with 2 cycles of either blinatumomab or SOC chemotherapy (1 of 4 pre-specified, investigator-chosen regimens) a consolidation phase of up to 3 additional cycles of protocol-specified therapy, and a maintenance phase for up to an additional 12 months with protocol-specified therapy.

Blinatumomab was administered as a continuous intravenous (cIV) infusion at a constant flow rate for 4 weeks, followed by a 2-week treatment free interval, defined as 1 treatment cycle during the induction and consolidation cycles. During the maintenance phase, blinatumomab was administered as a cIV infusion at a constant flow rate for 4 weeks, followed by an 8-week treatment free interval. In the first induction cycle, the initial dose of blinatumomab was 9 µg/day for the first 7 days of treatment which was

escalated (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles, the blinatumomab dose remained at 28 µg/day for 4 weeks of cIV treatment.

Two PK samples were to be collected: 1) Cycle 1 D2, and 2) Cycle 1 D15. Both PK samples were to be taken during the infusion and at the same time as the other blood samples scheduled for that day.

271 subjects were randomized to Blinatumomab arm, 267 subjects were treated, and 247 were entered in the PK analysis set. Of note, 14 subjects withdrew consent.

The PK analysis set comprised 461 blinatumomab samples from 247 subjects. Of these samples, 114 (25%) were excluded from data analysis. Reasons for exclusion of samples were as follows:

Unscheduled (n = 5), collected during a retreatment phase (n = 7), concentrations of blinatumomab were below the LLOQ (n = 93) or exceeded 3 times of SD of mean (n = 1), subjects did not receive scheduled doses (e.g., recorded dose of 9 µg/day on cycle 1, day 15, while the scheduled dose should have been 28 µg/day (n = 8).

Table 1 Summary of PK results (Study 00103311)

Summary Statistic	9 µg/day C_{ss} (pg/mL)	28 µg/day C_{ss} (pg/mL)	Clearance (L/hr)
N	156	191	222
Mean	211	592	3.63
SD	413	553	3.12
Minimum	50.0	51.0	0.157
Median	122	447	2.82
Maximum	4400	4450	22.9
CV%	195.6	93.4	86.0
Geometric mean	139	431	2.73
Geometric mean CV%	84.9	96.6	89.7

cIV = continuous intravenous; CL = clearance; C_{ss} = steady state concentration; CV = coefficient of variation; PK = pharmacokinetics
Note: Clearance was estimated with dose-normalized C_{ss}

During a cIV infusion of 9 and 28 µg/day blinatumomab over 4 weeks, mean (standard deviation [SD]) serum Css of blinatumomab in cycle 1 were 211 (413) pg/mL and 592 (553) pg/mL, respectively. The mean Css values increased dose proportionally with a 2.81-fold increase in Css for a 3.1-fold increase in dose. The estimated mean (SD) clearance (CL) was 3.63 (3.12) L/hr and was consistent over time.

An exploratory analysis of this global study suggested that the blinatumomab CL was not affected by age, body weight, race, or sex.

4.2.2. Clinical efficacy

Study 00103311 was a phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of blinatumomab compared with the efficacy and safety of SOC chemotherapy in adult subjects with Philadelphia chromosome-negative relapsed/refractory B-cell precursor ALL.

Study participants

Main Inclusion Criteria

1. Subjects ≥ 18 years with Philadelphia negative B-precursor ALL, with any of the following:

- refractory to primary induction therapy or refractory to salvage therapy,
- in untreated first relapse with first remission duration < 12 months
- in untreated second or greater relapse
- or relapse at any time after allogeneic HSCT

2. Subject has received intensive combination chemotherapy for the treatment of ALL for initial treatment or subsequent salvage therapy.

3. Greater than 5% blasts in the bone marrow

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

Exclusion Criteria

1. History of malignancy other than ALL within 5 years prior to start of protocol-specified therapy with the exception of*:*

- Malignancy treated with curative intent and with no known active disease present for 5 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer.

2. Diagnosis of Burkitt´s Leukemia according to WHO classification

3. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

With the exception of history of CNS leukemia that is controlled with intrathecal therapy

4. Active ALL in the CNS (confirmed by CSF analysis) or testes (no clinical sign thereof)

5. Isolated extramedullary disease

6. Current autoimmune disease or history of autoimmune disease with potential CNS involvement

7. Autologous HSCT within 6 weeks before the start of protocol-specified therapy

8. Allogeneic HSCT within 12 weeks before the start of protocol-specified therapy

9. Any active acute Graft-versus-Host Disease (GvHD), grade 2-4 according to the Glucksberg criteria or active chronic GvHD requiring systemic treatment

10. Any systemic therapy against GvHD within 2 weeks before start of protocol-specified therapy

11. Known exclusion criteria to investigator choice of SOC chemotherapy (as per product insert).

12. Cancer chemotherapy within 2 weeks before start of protocol-specified therapy (intrathecal chemotherapy and dexamethasone are allowed until start of protocol-specified therapy). In addition, any subject whose organ toxicity (excluding hematologic) from prior ALL treatment has not resolved to no more than CTCAE grade 1

13. Radiotherapy within 2 weeks before the start of protocol-specified therapy

14. Immunotherapy (eg, rituximab) within 4 weeks before start of protocol-specified therapy

15. Subject received prior anti-CD19 therapy

16. Abnormal screening laboratory values as defined below:

- AST (SGOT) and/or ALT (SGPT) and/or ALP ≥ 5 x upper limit of normal (ULN)
- Total bilirubin (TBL) ≥ 1.5 x ULN (unless related to Gilbert´s or Meulengracht disease)
- Creatinine ≥ 1.5 ULN or Creatinine clearance < 60 ml/min (calculated)

17. Known infection with human immunodeficiency virus (HIV) or chronic infection with hepatitis B virus (HBsAg positive) or hepatitis C virus (anti-HCV positive)

18. Subject is pregnant or breastfeeding, or might become pregnant within 24 hours after the last dose of protocol-specified therapy (Note: Guidance regarding pregnancy, contraception, and breastfeeding for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)

19. Woman of childbearing potential and is not willing to use a highly effective method of contraception while receiving protocol-specified therapy and for an additional 24 hours after the last dose of protocol-specified therapy (Note: Contraception requirements for SOC and other protocol-mandated chemotherapy are based on local prescribing information.)

20. Currently receiving treatment in another investigational device or drug study or less than 30 days since ending treatment on another investigational device or drug study(s). Thirty days is calculated from Day 1 of protocol-specified therapy.

21. Other investigational procedures while participating in this study are excluded (except for participation in optional sub-studies to this protocol).

22. Subject has known sensitivity to immunoglobulins or any of the products or components to be administered during dosing.

23. Subject previously has randomized into this study or previous treatment with blinatumomab.

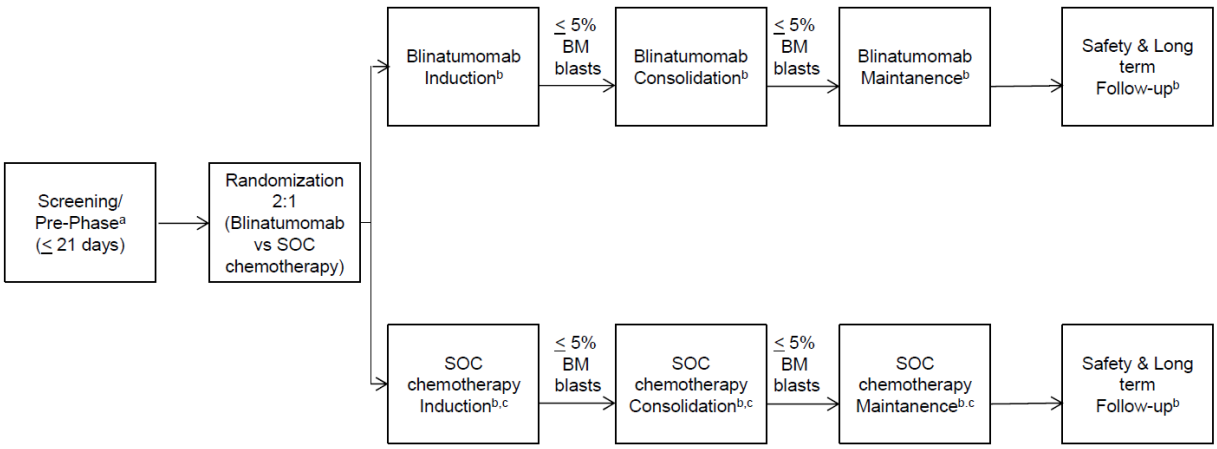
24. Subject likely to not be available to complete all protocol-required study visits or procedures, including follow-up visits, and/or to comply with all required study procedures to the best of the subject and Investigator's knowledge.

25. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Treatments

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

Figure 1 Study Design and Treatment Schema(Study 00103311)



BM = bone marrow; HSCT = hematopoietic stem cell transplantation; SOC = standard of care
a The prephase period during screening was permitted for the administration of dexamethasone to reduce tumor burden and the incidence of tumor lysis syndrome and cytokine release syndrome.
b Subjects who were eligible to receive allogeneic HSCT at any time after cycle 1 were required to discontinue protocol-specified therapy and complete a safety follow-up visit before the transplant was performed. These subjects continued to be followed during the long-term safety follow-up period.
c Standard of care chemotherapy options are described in Section 8.5.1.2

In the first induction cycle, the initial dose of blinatumomab will be 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 all other subsequent cycles.

The treatment-free period between cycles was 2 weeks in the induction and consolidation phases (cycles 1 to 5) and 8 weeks in the maintenance phase (cycles 6-9) of the study and was permitted to be prolonged by up to 7 days if the investigator deemed it to be necessary.

Subjects randomized to the *SOC chemotherapy* arm received one of the following chemotherapy regimens:

1. FLAG ± anthracycline based regimen (such as Idarubicin 10 mg/m^2 days 1, 3; fludarabine 30 mg/m^2 days 1-5; cytarabine 2g/m^2 days 1-5).

For subject's > 60 years of age: Idarubicin 5 mg/m^2 day 1,3; fludarabine 20 mg/m^2 days 1-5; cytarabine 1 g/m^2 days 1-5.

2. HiDAC based regimen: cytarabine arabinoside at least 1 g/m2 or greater per day ± anthracycline and/or in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.

3. High-dose methotrexate based regimen (such as 500 mg/m2 - 3 g/m2 HDMTX (infusion time up to 24 hours) in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents.

4. Clofarabine or clofarabine based regimens. Clofarabine use as a single agent should follow the recommended prescribing information. Clofarabine combination based regimens should use ≥ 20 mg/m2/day for up to 5 days.

The *core study duration* consisted of:

- A 3-week screening and pre-phase period allowing the administration of dexamethasone to reduce both tumor burden and the incidence of tumor lysis syndrome (TLS).
- Induction phase (2 induction cycles, 6w/cycle):

  Blinatumomab: each of 2 induction cycles consists of 4w of continuous IV infusion of blinatumomab followed by a 2w of treatment-free interval.

  SOC chemotherapy: 2 cycles of one of 4 protocol-specified, investigator-chosen, chemotherapy regimens.
- Consolidation phase (3 additional cycles, 6w/cycle): subjects who achieved a bone marrow response (≤ 5% of bone marrow blasts) or CR/CRh* (complete remission with partial hematologic recovery)/CRi (complete remission with incomplete hematologic recovery) within 2 induction cycles of treatment were permitted to continue to receive up to 3 additional consolidation cycles of their assigned protocol-specified therapy.
- Maintenance phase (4 additional cycles during 12 months, 12w/cycle): subjects who received 2 induction and up to 3 consolidation cycles of protocol-specified therapy and continued to have a bone marrow response (≤ 5% of bone marrow blasts or CR/CRh*/CRi) were allowed to continue to receive their assigned protocol-specified therapy for an additional 12 months (4 cycles). One cycle was defined as 12 weeks in duration, 4 weeks of blinatumomab cIV followed by an 8 week treatment-free period.

  Subjects must have discontinued treatment earlier if 1 of the following conditions occurred: received alloHSCT, investigator decided to stop therapy, needed excluded medications, or toxicity or relapse was experienced.
- Safety follow-up visit: clinic visit made 30 days after last dose of blinatumomab. This visit was required before the subject received alloHSCT or prohibited anticancer therapies were administered.
- Long-term safety follow-up period: contact between the investigator and subject either by clinic visit or telephone call continued every 3 months after the safety follow-up visit to assess disease status until 1 of the 3 following events occurred: a/ 330 deaths reported, b/ 12 months after the last subject randomized if only 300 to 329 deaths reported, c/ after 300 deaths reported with the duration of the long-term safety follow-up exceeded 12 months from the last subject randomized.

Doses Modifications

In case of CTCAE grade 4 adverse events, blinatumomab should be permanent discontinuation. CTCAE grade ≥ 3 cytokine release syndrome, tumor lysis syndrome and DIC/coagulopathy, treatment with blinatumomab was interrupted until the event resolves to at least grade 1. Blinatumomab could then be restarted at the lowest starting dose (9 µg/d) and possibly increased to the higher level if AE grade ≤ 1

for at least 7 days. If the AE lasts for ≥ 2 weeks, then blinatumomab is permanently discontinued. Patients who have been dose reduced will have an option to receive the higher dose.

In case of CTCAE grade ≥3 neurologic events, blinatumomab was stopped immediately and a physical exam, vital signs, and safety laboratory tests were performed. If the event has decreased to at least grade 1 within 1 week, treatment may be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped. A grade 3 neurologic event leading to treatment interruption at the dose of 9 µg/day or a neurologic event needing more than 1 week to resolve to grade ≤ 1 will result in permanent treatment discontinuation. In case of neurologic events CTCAE grade 4, or in case of occurrence of more than one seizure, the infusion of blinatumomab will have to be stopped immediately and treatment will be permanently discontinued.

Re-start of the infusion should be performed in the hospital after mandatory premedication with dexamethasone.

Prior and concomitant therapy:

Dexamethasone premedication before blinatumomab treatment

During the screening period, dexamethasone (10 mg/m^2/day) may have been administered for up to 5 days to prevent cytokine release and other events such as infusion reactions and fever (ie, pre-phase). This dose may have been increased to 24 mg/day if clinically indicated. Dexamethasone prephase was required during screening if the proportion of blasts was > 50% or if peripheral blood blast count was ≥15,000/µL. Prephase was recommended if lactate dehydrogenase (LDH) indicated rapidly progressing disease or if signs of extramedullary disease showed high tumor load.

In addition, administration of dexamethasone (20 mg IV) was mandatory for all subjects within 1 hour before the start of each cycle, within 1 hour of an increase in dose or after a treatment interruption >4 hours (ie, pre-dose) for the prevention of CRS resulting from blinatumomab. Dexamethasone was also administered to patients with neurologic adverse events at a dose of at least 24 mg/day for 3 days and then dose was reduced step-wise over 4 days. For subjects with signs of CRS, oral or IV dexamethasone was also administered at a dose of 8 mg/day thrice daily which was reduced stepwise over 4 days.

Intrathecal CNS prophylaxis before protocol-specified therapy

Within 10 days prior to randomized treatment and following each induction and consolidation treatment cycle, a mandatory cerebrospinal fluid (CSF) prophylaxis consisting of intrathecal therapy according to the institution or national guidelines.

Prohibited medications and therapies after the start of blinatumomab

Any other anti-tumor therapy (ie cytotoxic or cytostatic drugs, radiation therapy, immunotherapy), chronic systemic (>7 days) high dose corticosteroids (dexamethasone ≥24mg/day), any other immunosuppressive therapies and other investigational product.

Non-steroidal anti-inflammatory agents should have been avoided for fever management in order to avoid endothelial stress if possible.

Objectives

Primary objective:

- To evaluate the effect of blinatumomab on OS when compared to SOC chemotherapy

Secondary objectives:

- To evaluate haematological response induced by blinatumomab when compared to SOC chemotherapy
- To evaluate event free survival (EFS) induced by blinatumomab when compared to SOC chemotherapy
- To evaluate minimal residual disease (MRD) remissions induced by blinatumomab when compared to SOC chemotherapy
- To estimate the effect of blinatumomab on patient reported outcomes, global health status/quality of life (QoL) using the EORTC QLQ-C30.
- To evaluate the incidence of allogeneic hematopoietic stem cell transplantation (alloHSCT) and 100-day mortality following HSCT in blinatumomab treated subjects when compared to SOC chemotherapy
- To evaluate the safety of blinatumomab when compared to SOC chemotherapy

Exploratory objectives

- To evaluate blinatumomab exposure-response relationships for efficacy and safety
- To assess presence of ALL symptoms as measured by Acute Lymphoblastic Leukemia Symptom Scale (ALLSS)
- To assess the potential for mutations in the tumor DNA to predict resistance to blinatumomab treatment

Outcomes/endpoints

Primary Endpoint

- Overall survival (OS) defined as the time of randomization until death due to any cause.

Key Secondary Efficacy Endpoints

- Hematologic remission rate
    - Best response of CR within 12 weeks of treatment initiation: A CR was defined as having ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µl, and ANC > 1,000/µl. The CR must occur within 12 weeks of the first dose of protocol-specified therapy.
    - Best response of CR/CRh*/CRi within 12 weeks of treatment initiation: A CR/CRh*/CRi was defined as achieving any 1 of the following within 12 weeks of the first dose of protocol-specified therapy:
        - CR as defined above
        - CRh* which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts: platelets > 50,000/µl, and ANC > 500/µl
        - CRi which is defined as ≤ 5% blasts in the bone marrow, no evidence of disease and incomplete recovery of peripheral blood counts: platelets > 100,000/µl or ANC > 1000 (but not both)

When criteria are met for both CRh* and CRi, CRh* should be reported. When criteria are met for both CRi and blast-free marrow, CRi should be reported.

- Event Free Survival (EFS): EFS time was calculated from the time of randomization until the date of a disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever occurs first. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation will be considered treatment failures and assigned an EFS duration of 1 day. Subjects still alive and relapse-free will be censored on their last disease assessment date. If the last disease assessment date is after the date that triggers the analysis, the subject will be censored at the analysis trigger date.

Secondary Efficacy Endpoints

- Duration of CR: Time from CR until the date of a disease assessment indicating a relapse event or death, whichever occurs first
- Duration of CR/CRh*/CRi: Time from CR/CRh*/CRi until the date of a disease assessment indicating a relapse event or death, whichever occurs first
- MRD remission (defined as MRD level below 10^{-4} by PCR or flow cytometry) within 12 weeks of treatment initiation
- Time to a 10-point decrease from baseline in global health status and quality of life scale (QL2) using EORTC QLQ-C30, or EFS event (analyses described in a SSAP)
- AlloHSCT with or without blinatumomab treatment: subjects who underwent an allogeneic HSCT in remission after protocol treatment and without other intermittent treatment for ALL.

Secondary Safety Endpoints

- Incidence of adverse events
- 100-day mortality after alloHSCT
- Incidence of anti-blinatumomab antibody formation
- Changes in select vital sign and laboratory parameters

Exploratory Endpoints

- Blinatumomab steady state concentration (Css)
- ALLSS score at measured time points (analyses described in a SSAP)
- Investigation for mutations in the tumor DNA to predict resistance to blinatumomab treatment

Table 2. Hematologic Response Criteria Definitions (Study 00103311)

Response Criteria	Definition
CR	≤ 5% blasts in the bone marrow No evidence of disease Full recovery of peripheral blood counts: platelets > 100 000/µl, and ANC > 1000/µl
CRh*	≤ 5% blasts in the bone marrow No evidence of disease Partial recovery of peripheral blood counts: platelets > 50 000/µl, and ANC > 500/µl
CRi	≤ 5% blasts in the bone marrow No evidence of disease Incomplete recovery of peripheral blood counts: platelets > 100 000/µl or ANC > 1000/µl
Blast-free hypoplastic or aplastic bone marrow	≤ 5% blasts in the bone marrow No evidence of disease Insufficient recovery of peripheral blood counts: platelets ≤ 50 000/µl and/or ANC ≤ 500/µl
Partial remission	Bone marrow blasts 6% to 25% with at least a 50% reduction from baseline
Progressive disease	An increase from baseline of at least 25% of bone marrow blasts or an absolute increase of at least 5000 cells/µL in the number of circulating leukemia cells
Nonresponse	None of the above
Hematologic relapse	Proportion of blasts in bone marrow > 5% or blasts in peripheral blood after documented CR/CRh*/CRi
Extramedullary Disease	
Extramedullary disease	If clinical signs of extramedullary lesions are present, responses are assessed by modified Cheson criteria (Cheson et al, 2007).
Molecular Response	
MRD response	MRD < 10^{-4} measured by quantitative PCR (or flow cytometry)
MRD complete response	No detectable MRD by quantitative PCR (or flow cytometry)
MRD relapse	Reappearance of leukemic cells
MRD progression	Increase in MRD level by 1 log as compared to baseline level which is equal to a 10-fold increase in number of MRD cells

ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; CR = complete remission; CRh* = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; MRD = minimal residual disease; PCR = polymerase chain reaction.
Relapse was analyzed by immunophenotyping to determine whether the criteria for B-cell precursor ALL were fulfilled.
Note: An extramedullary relapse was assessed as a hematologic relapse. All hematologic assessments of bone marrow were reviewed in a central reference laboratory. When criteria were met for both CRh* and CRi, CRh* was reported. When criteria are met for both CRi and blast-free marrow, CRi was reported.

Sample Size

In the Full Analysis Set (FAS), if 330 deaths were observed, the study was powered at approximately 85% for a 2-sided log-rank test with an overall alpha of 0.05 with a 2:1 randomization ratio and an assumed hazard ratio of 0.70. Approximately 400 randomized subjects were needed to observe 330 deaths and assumed a control arm median of 4.2 months (Section 16.1.9, Section 3.2). If 300 deaths were observed in the study, the unconditional power decreased to approximately 80%.

Randomization

Patients were randomized in a 2:1 ratio to receive blinatumomab or 1 of 4 prespecified, investigator-chosen, SOC chemotherapy regimens as assigned by the IVRS.

Randomization was stratified by age (< 35 years vs ≥ 35 years), prior salvage therapy (yes vs no), and prior alloHSCT (yes vs no) as assessed at the time of consent.

Blinding (masking)

The study was open-label.

Statistical methods

Statistical hypothesis

This study was conducted to determine whether blinatumomab was superior to SOC chemotherapy with respect to the primary efficacy endpoint of OS. The null hypothesis indicated no difference between treatments arms with respect to OS vs an alternative hypothesis in which the treatment arms differ. The null hypothesis was rejected if the p-value from a 2-sided stratified log-rank test (stratified by randomization factors) was less than the value specified by the alpha spending function either at the interim analysis or the final analysis. The hypothesis would be rejected in favor of blinatumomab if the log-rank statistic is in the appropriate direction.

Analysis Sets

Primary Analysis Set: The primary analysis of efficacy was performed on all randomized subjects analysed according to their randomized treatment assignment, regardless of the treatment received (FAS, consistent with the intent-to-treat principle).

Safety Analysis Set: The primary analysis of safety was performed on the safety analysis set which included all subjects who received protocol-specified therapy analyzed according to the treatment they received.

PK Analysis Set: All subjects who received any infusion of blinatumomab and had at least 1 pharmacokinetic (PK) sample collected were included in the PK Analysis Set.

Interim Analysis Set: The formal interim analyses of efficacy included all subjects in the FAS who were randomized at the time of the database cutoff on 04 January 2016 which was triggered when 50% and 75% of the total of 330 deaths have been observed.

Covariates/Subgroup Analyses

Exploratory analyses examining the consistency of the treatment effect for the primary endpoint and key secondary endpoints consisted of performing subgroup analyses of each of the 8 stratum formed by the combination of stratification factors (eg, subjects < 35 years with prior salvage therapy and a prior alloHSCT) and for each level of a given stratification factor (eg, subjects < 35 years). Additional subgroup analyses were based on the following factors:

- Sex (male vs female)
- Race/ethnicity (categories depended on the data, all races with < 5% of the total enrolled subjects were pooled together for summary purposes)
- The primary analysis of efficacy was performed on all randomized subjects analysed according to their randomized treatment assignment, regardless of the treatment received (FAS, consistent with the intent-to-treat principle).
- Alternate age grouping (< 35 years vs 35 to 54 vs 55 to 64 vs ≥ 65 years)
- Number of prior salvage therapies (0 vs 1 vs ≥ 2)
- Repeated for subjects without a prior alloHSCT
- Provided adequate relapse data existed, relapse/refractory status (primary refractory or 1 prior relapse vs ≥ 2 prior relapses)
- Repeated for subjects without a prior alloHSCT
- Central laboratory baseline bone marrow blasts (< 50% vs ≥ 50%)
- Central laboratory baseline platelet count (< 50,000 vs 50,000 to 100,000 vs > 100,000/μL)
- Intended SOC chemotherapy regimen collected for all subjects before randomization
- CD20 status (positive vs negative)
- CD22 status (positive vs negative)
- Region (United States vs Europe vs rest of world)

Interim Analysis and Early Stopping Guidelines

Two formal interim analyses were planned and overseen by an external independent DMC. The DMC was scheduled to meet when approximately 50% (165 deaths) and 75% (248 deaths) of the total number of OS events were observed. In addition, the DMC assessed safety approximately every 6 months.

There were 3 planned reasons to stop the study:

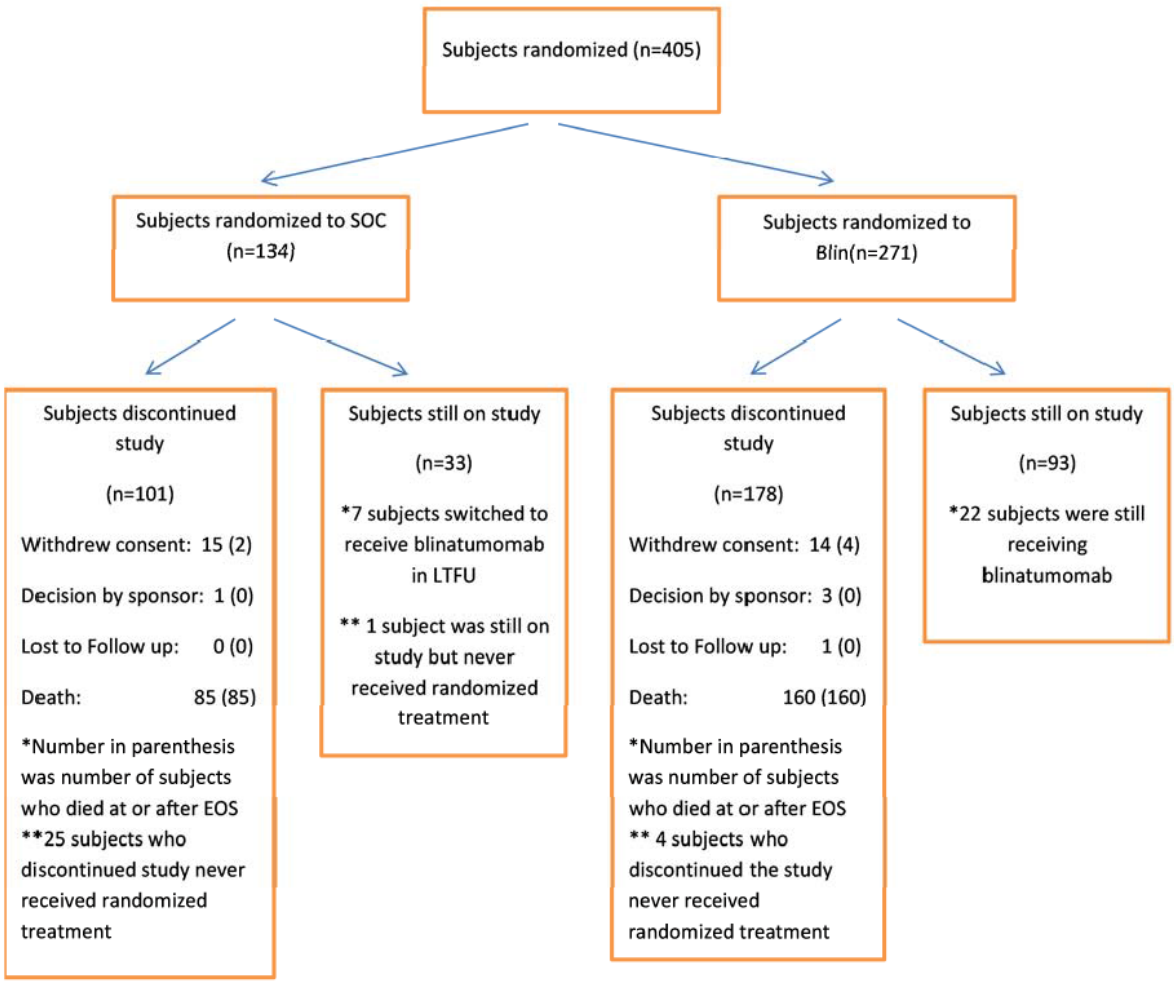
- For futility according to nonbinding boundaries from a Pampallona-Tsiatis-type (Pampallona and Tsiatis, 1994) beta spending function with a shape parameter of -0.5, safety
- Benefit based on an O'Brien-Fleming (1979)-type alpha-spending function (the critical p-values corresponding to this spending function were 0.0031 for the first interim analysis, 0.0183 for the second interim analysis, and 0.044 for the primary [ie, final] analysis if the interim analyses occurred precisely at 50% and 75% of deaths).
- Safety concerns

Efficacy Analyses

The primary analysis (OS) was performed on the FAS. A 2-sided stratified log-rank test, stratified by the randomization factors, was used to determine if OS was superior in the blinatumomab arm compared to SOC chemotherapy arm. In addition, a hazard ratio with a 95% CI was estimated from a stratified Cox regression model. The KM summaries (Kaplan and Meier, 1958) were performed by treatment arm. Sensitivity analyses were performed on a subset of subjects who received protocol-specified therapy. The KM summaries included KM curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Two-sided 95% CIs were provided for the estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980) and binomial properties (Clopper and Pearson, 1934).

4.2.2.1. ***Results***

Figure 2 Subject Disposition in Full Analyses Sets (Study 00103311)



alloHSCT = allogeneic hematopoietic stem cell transplantation; EOS = end of study; LTFU = long-term follow-up; SOC = standard of care

Note: Subjects discontinued treatment with the intent to receive an alternate therapy or alloHSCT. The end of maintenance was reached after 9 completed cycles of blinatumomab.

Conduct of the study

This study was conducted at 101 centers in 21 countries and 5 continents including Europe (65.4%), Latin America, North America (US 11.4%), Asia and Australia. The study was overseen by an independent data monitoring committee (DMC), established to monitor safety and efficacy. Central laboratories evaluated Human antimurine antibodies (HAMAs), lymphocyte subsets, pharmacogenetic, biomarker, bone marrow, and MRD assessments, while routine hematology, clinical chemistry, coagulation, urinalysis, immunoglobulin G (IgG), and pregnancy testing were performed at local laboratories.

On 28 January 2016, the DMC recommended that the study be stopped for benefit because the p-value = 0.011 was less than the prespecified threshold of 0.0183 for statistical significance testing for OS. Subsequently, on 4 February 2016, Amgen notified the regulatory authorities of the DMC recommendation and Amgen's decision to end the study early. Then, on 18 February 2016, the long-term follow-up part of the study was discontinued prematurely.

Table 3 Summary of Protocol Amendments (Study 00103311)

Amendment	Major Changes
Original Protocol 27 June 2013	
Amendment 1 15 September 2014	Clarify timing, scope, and applicability of study procedures to treatment arms Clarify criteria for discontinuation and withdrawal of blinatumomab-treated subjects, clarify terms and definitions used in protocol, clarify secondary endpoints and analyses, clarify study participation, clarify requirements for medical coverage and safety monitoring in an outpatient setting Increase the number of study sites globally Provide updated information on packaging, presentation, dose modifications, and overdose (> 10%) of blinatumomab Provide dose modification guidance for SOC chemotherapy regimen Update Amgen publication policy guidelines and team contact information to facilitate the enrollment of subjects, entry criteria were modified to allow for the screening of serum for potential drugs of abuse in subjects receiving hemodialysis with no urine output and to remove the requirement of "no detectable viral RNA" for subjects known to have had hepatitis C.
Amendment 2 10 March 2015	Clarify protocol-required procedures Updates made to align with current Amgen protocol templates
Amendment 3 09 September 2015	Update pregnancy, lactation, and contraception requirements to align with blinatumomab core risk and discomfort language Provide clarification on study design, and procedures for bone marrow aspirates, vital signs, and long-term follow-up
Amendment 4 20 April 2016	Update contraception timeframes to align with blinatumomab core risk and discomfort language Update sponsor contact information and definition of adverse events to align with current protocol template language

SOC = standard of care

Protocol deviation

Table 4 Summary of Subjects With Important Protocol Deviations (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 134) n (%)	Blinatumomab (N = 271) n (%)	Total (N = 405) n (%)
Number of subjects with at least 1 important protocol deviation	12 (9.0)	50 (18.5)	62 (15.3)
Randomized into study without meeting entry criteria	3 (2.2)	3 (1.1)	6 (1.5)
≤ 5% blasts in bone marrow	0	1 (0.4)	1 (0.2)
Allogeneic HSCT within 12 weeks	0	1 (0.4)	1 (0.2)
Serum chemistry out of range: bilirubin	1 (0.7)	0	1 (0.2)
Chemo within 2 weeks/unresolved > grade 1 toxicity	2 (1.5)	0	2 (0.5)
Provided informed consent	0	1 (0.4)	1 (0.2)
Received excluded concomitant medication	0	1 (0.4)	1 (0.2)
Received excluded medication	0	1 (0.4)	1 (0.2)
Subject not withdrawn after criteria met			
Failure to respond	0	1 (0.4)	1 (0.2)
Received wrong treatment or incorrect dose	0	22 (8.1)	22 (5.4)
Dose not reduced after grade ≥ 3 neurologic event	0	1 (0.4)	1 (0.2)
Overdose[a]	0	4 (1.5)	4 (1.0)
Compromised investigational product[b]	0	20 (7.4)	20 (4.9)
Other treatment compliance	0	1 (0.4)	1 (0.2)
Predose dexamethasone not administered	0	1 (0.4)	1 (0.2)
Missed bone marrow aspirate/biopsy	8 (6.0)	23 (8.5)	31 (7.7)
After 2 treatment cycles	5 (3.7)	8 (3.0)	13 (3.2)
At screening	3 (2.2)	16 (5.9)	19 (4.7)
Other deviations	1 (0.7)	2 (0.7)	3 (0.7)
Other GCP deviation	1 (0.7)	0	1 (0.2)
Reconsent not performed - level 1 or 2 risk	0	1 (0.4)	1 (0.2)
Reconsent not performed - level 3 risk	0	1 (0.4)	1 (0.2)

GCP = good clinical practice; HSCT = hematopoietic stem cell transplantation; SOC = standard of care
Note: A subject is counted once per category and once overall regardless of the number of deviations.
[a] An addition 7 subjects had an overdose with blinatumomab that was captured via Council for International Organizations of Medical Sciences (CIOMS) Forms. The likelihood of dosages errors is much greater with blinatumomab because of its continuous intravenous treatment regimen over 28 days vs a few hour duration with SOC chemotherapy.
[b] Administration of compromised investigational product with respect to stability or sterility or methods of preparation and administration not supported by stability.

Baseline data

Table 5. Baseline Demographic Characteristics (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Total (N = 405)
Sex - n (%)			
Male	77 (57.5)	162 (59.8)	239 (59.0)
Female	57 (42.5)	109 (40.2)	166 (41.0)
Ethnicity - n (%)			
Hispanic/Latino	11 (8.2)	26 (9.6)	37 (9.1)
Not Hispanic/Latino	122 (91.0)	243 (89.7)	365 (90.1)
Unknown	1 (0.7)	2 (0.7)	3 (0.7)
Race - n (%)			
American Indian or Alaska Native	1 (0.7)	4 (1.5)	5 (1.2)
Asian	9 (6.7)	19 (7.0)	28 (6.9)
Black (or African American)	3 (2.2)	5 (1.8)	8 (2.0)
Multiple	0	2 (0.7)	2 (0.5)
Native Hawaiian or Other Pacific Islander, Other, White	0	1 (0.4)	1 (0.2)
Asian, Black (or African American)	0	1 (0.4)	1 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.4)	2 (0.5)
Other	8 (6.0)	12 (4.4)	20 (4.9)
White	112 (83.6)	228 (84.1)	340 (84.0)
Age (years)			
Mean	41.1	40.8	40.9
Standard deviation	17.3	17.1	17.2
Median	37.0	37.0	37.0
Quartile 1, quartile 3	26.0, 58.0	25.0, 54.0	26.0, 56.0
Minimum, maximum	18, 78	18, 80	18, 80
Age group - n (%)			
< 35 years	60 (44.8)	124 (45.8)	184 (45.4)
35 to 54 years	33 (24.6)	80 (29.5)	113 (27.9)
55 to 64 years	26 (19.4)	34 (12.5)	60 (14.8)
≥ 65 years	15 (11.2)	33 (12.2)	48 (11.9)
Geriatric age group - n (%)			
< 65 years	119 (88.8)	238 (87.8)	357 (88.1)
≥ 65 years	15 (11.2)	33 (12.2)	48 (11.9)
≥ 75 years	2 (1.5)	10 (3.7)	12 (3.0)

SOC = standard of care

Baseline characteristics

Table 6 Subject Baseline Characteristics (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Total (N = 405)
SOC chemotherapy regimens – n (%)			
FLAG ± anthracycline	56 (41.8)	Not applicable	56 (13.8)
High-dose methotrexate	30 (22.4)	Not applicable	30 (7.4)
Clofarabine	26 (19.4)	Not applicable	26 (6.4)
HIDAC	22 (16.4)	Not applicable	22 (5.4)
Eastern Cooperative Group Status - n (%)			
0	52 (38.8)	96 (35.4)	148 (36.5)
1	61 (45.5)	134 (49.4)	195 (48.1)
2	20 (14.9)	41 (15.1)	61 (15.1)
Unknown	1 (0.7)	0	1 (0.2)
B-cell precursor subtype - n (%)			
Pro-B-ALL	15 (11.2)	30 (11.1)	45 (11.1)
Pre-B-ALL	49 (36.6)	124 (45.8)	173 (42.7)
C-ALL	29 (21.6)	47 (17.3)	76 (18.8)
B-ALL with recurrent genetic abnormality	18 (13.4)	28 (10.3)	46 (11.4)
Unknown	23 (17.2)	42 (15.5)	65 (16.0)
MRD status following 1st line treatment – n (%)			
Negative ($< 10^{-4}$)	32 (23.9)	64 (23.6)	96 (23.7)
Positive ($\geq 10^{-4}$)	29 (21.6)	59 (21.8)	88 (21.7)
Unknown	73 (54.5)	148 (54.6)	221 (54.6)
Time to CR following 1st line treatment – n (%)			
Early (≤ 4 weeks)	40 (29.9)	77 (28.4)	117 (28.9)
Late (> 4 weeks)	53 (39.6)	98 (36.2)	151 (37.3)
Refractory	26 (19.4)	49 (18.1)	75 (18.5)
Unknown	15 (11.2)	47 (17.3)	62 (15.3)
Primary refractory – n (%)			
Yes	27 (20.1)	46 (17.0)	73 (18.0)
No	106 (79.1)	225 (83.0)	331 (81.7)
Unknown	1 (0.7)	0	1 (0.2)
Refractory to salvage treatment – n (%)			
Yes	34 (25.4)	87 (32.1)	121 (29.9)
No	99 (73.9)	182 (67.2)	281 (69.4)
Unknown	1 (0.7)	2 (0.7)	3 (0.7)

	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Total (N = 405)
First relapse with remission duration < 12 months – n (%)			
Yes	49 (36.6)	109 (40.2)	158 (39.0)
No	85 (63.4)	161 (59.4)	246 (60.7)
Unknown	0	1 (0.4)	1 (0.2)
In untreated second or greater relapse – n (%)			
Yes	21 (15.7)	46 (17.0)	67 (16.5)
No	113 (84.3)	225 (83.0)	338 (83.5)
Relapse after alloHSCT – n (%)			
Yes	45 (33.6)	91 (33.6)	136 (33.6)
No	88 (65.7)	180 (66.4)	268 (66.2)
Unknown	1 (0.7)	0	1 (0.2)
Prior alloHSCT - n (%)			
Yes	46 (34.3)	94 (34.7)	140 (34.6)
No	87 (64.9)	176 (64.9)	263 (64.9)
Unknown	1 (0.7)	1 (0.4)	2 (0.5)
Key ALL entry criterion - n (%)			
Refractory to primary or salvage therapy	54 (40.3)	115 (42.4)	169 (41.7)
In first relapse with first remission < 12 months	37 (27.6)	76 (28.0)	113 (27.9)
In untreated second or greater relapse (if none of the above)	16 (11.9)	32 (11.8)	48 (11.9)
Relapsed after alloHSCT (if none of the above)	27 (20.1)	46 (17.0)	73 (18.0)
No criteria met	0	2 (0.7)	2 (0.5)
Maximum of central/local bone marrow blasts - n (%)			
≤ 5%	0	0	0
> 5 to < 10%	7 (5.2)	9 (3.3)	16 (4.0)
10 to < 50%	23 (17.2)	60 (22.1)	83 (20.5)
≥ 50%	104 (77.6)	201 (74.2)	305 (75.3)
Unknown	0	1 (0.4)	1 (0.2)
Maximum central/local bone marrow blasts (%)			
n	134	270	404
Mean	70.5	70.0	70.2
SD	28.8	29.3	29.1
Median	83.0	81.0	81.0
Quartile 1, quartile 3	50.0, 94.0	47.0, 93.0	50.0, 93.0
Minimum, maximum	6, 100	6, 100	6, 100

	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Total (N = 405)
CD19 status – n (%)			
Positive	114 (85.1)	220 (81.2)	334 (82.5)
Partial positive	8 (6.0)	11 (4.1)	19 (4.7)
Weak positive	0	3 (1.1)	3 (0.7)
Negative	3 (2.2)	4 (1.5)	7 (1.7)
Not evaluable	5 (3.7)	11 (4.1)	16 (4.0)
Unknown	4 (3.0)	22 (8.1)	26 (6.4)
B cell: T cell ratio - n (%)			
< 0.125	32 (23.9)	101 (37.3)	133 (32.8)
≥ 0.125	51 (38.1)	144 (53.1)	195 (48.1)
Unknown	51 (38.1)	26 (9.6)	77 (19.0)

The randomization stratification in the FAS is presented in Table below.

Table 7 Randomization Stratification (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 134) n (%)	Blinatumomab (N = 271) n (%)	Total (N = 405) n (%)
Number of subjects with incorrect randomization stratification	16 (11.9)	30 (11.1)	46 (11.4)
Age			
< 35 years	60 (44.8)	123 (45.4)	183 (45.2)
≥ 35 years	74 (55.2)	148 (54.6)	222 (54.8)
Prior salvage therapy			
Yes	80 (59.7)	164 (60.5)	244 (60.2)
No	54 (40.3)	107 (39.5)	161 (39.8)
Prior alloHSCT			
Yes	46 (34.3)	94 (34.7)	140 (34.6)
No	88 (65.7)	177 (65.3)	265 (65.4)

AlloHSCT = allogeneic hematopoietic stem cell transplantation; SOC = standard of care

Numbers analysed

A summary of subject disposition in each analysis set is presented in Table below.

Table 8 Summary of Subject Disposition in Each Analysis Set (Study 00103311)

Subjects in Analysis Set	SOC Chemotherapy N = 134 n (%)	Blinatumomab N = 271 n (%)	Total N = 405 n (%)
Full Analysis Set (Randomized)	134 (100.0)	271 (100.0)	405 (100.0)
Post-baseline assessments	72 (53.7)	204 (75.3)	276 (68.1)
Safety Analysis Set (Treated)	109 (81.3)	267 (98.5)	376 (92.8)
Pharmacokinetic Analysis Set	0	247 (91.1)	247 (61.0)

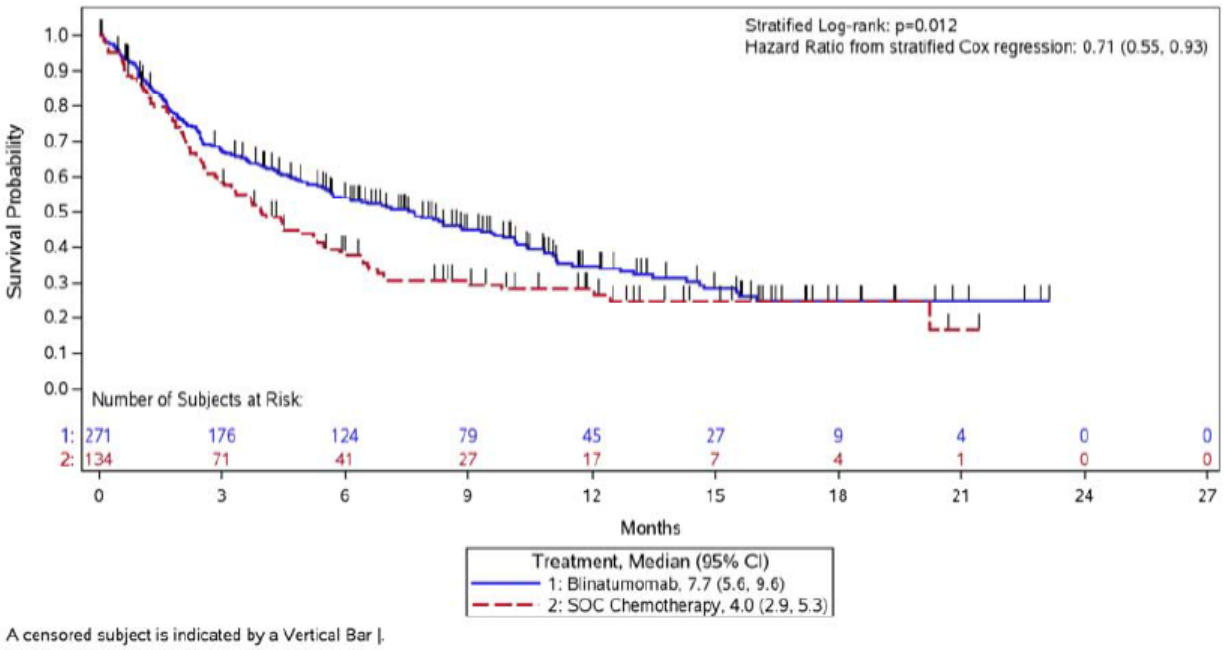
SOC = standard of care
Note: Reasons for exclusion from an analysis set were not mutually exclusive.
The full analysis set included subjects who were randomized but not treated similar to an intent-to-treat population

Outcomes and estimation

Primary efficacy endpoint

The median OS was 4.0 months (95% CI: 2.9, 5.3) in the SOC chemotherapy arm compared with 7.7 months (95% CI: 5.6, 9.6) in the blinatumomab arm with a p-value = 0.012 (stratified log-rank test). The hazard ratio was 0.71 (95% CI: 0.55, 0.93).

Table 9 Kaplan-Meier Curve of Overall Survival (Full Analysis Set) (Study 00103311)



A censored subject is indicated by a Vertical Bar |.

Of the 405 randomized subjects, 251 of 330 planned deaths from any cause were reported: 87 (64.9%) in the SOC chemotherapy arm and 164 (60.5%) in the blinatumomab arm. The median follow-up time was similar, 11.8 months in SOC chemotherapy am vs 11.7 months in the blinatumomab arm.

Table 10 Overall Survival (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)	Treatment Difference
Subject status			
Events - n (%)	87 (64.9)	164 (60.5)	
Deaths from any cause	87 (64.9)	164 (60.5)	
Censored - n (%)	47 (35.1)	107 (39.5)	
Alive at last follow-up	33 (24.6)	93 (34.3)	
Consent withdrawn	13 (9.7)	10 (3.7)	
Lost to follow-up	0 (0.0)	1 (0.4)	
Decision by sponsor	1 (0.7)	3 (1.1)	
Stratified log-rank test[a]			
Normal score[b]			-17.49
p-value			0.012
Unstratified log-rank test			
Normal score[b]			-16.24
p-value			0.022
Time to event (KM) (months)[c]			
Median	4.0	7.7	
95% CI (median)	(2.9, 5.3)	(5.6, 9.6)	
Q1, Q3	1.9, 12.4	2.1, 16.0	
Min, Max	0.1, 20.2	0.1, 16.0	
Time to censoring (months)[c,d]			
Median	11.8	11.7	
Q1, Q3	8.2, 14.2	7.5, 16.4	
Min, Max	0.0, 21.4	0.7, 23.1	
KM estimate - %			
At time 3 months[c]	58.4	67.3	
(95% CI)	(49.1, 66.5)	(61.3, 72.5)	
At time 6 months[c]	38.5	53.9	
(95% CI)	(29.8, 47.2)	(47.5, 59.7)	
At time 12 months[c]	28.3	34.7	
(95% CI)	(20.2, 36.9)	(28.1, 41.3)	
At time 18 months[c]	24.8	24.9	
(95% CI)	(16.7, 33.8)	(18.2, 32.2)	
At time 24 months[c]	NE	NE	
(95% CI)	(NE, NE)	(NE, NE)	
Stratified hazard ratio[e]			0.71
(95% CI)			(0.55, 0.93)

KM = Kaplan-Meier. CI=Confidence Interval. NE=not estimable

[a]Stratification factors are: age (<35 vs. ≥35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)
[b]A normal score < 0 indicates fewer than expected events for Blinatumomab relative to SOC Chemotherapy and therefore a longer survival time
[c]Months are calculated as days from randomization date to event/censor date, divided by 30.5
[d]Time to censoring measures follow-up time by reversing the status indicator for censored and events
[e]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 survival for Blinatumomab relative to SOC Chemotherapy

Sensitivity analyses are described in Table below and were performed as follows:

Table 11 Overall Survival (Primary Analysis and Sensitivity Analyses) (Study 00103311)

Overall Survival	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Treatment Difference
Primary analysis with all randomized subjects (FAS; Table 14-4.5.1)[a]			
Events - n (%)	87 (64.9)	164 (60.5)	-
Censored - n (%)	47 (35.1)	107 (39.5)	-
Stratified log-rank test[b]	-	-	-
p-value	-	-	0.012
Stratified hazard ratio[c]	-	-	0.71
(95% Confidence interval)	-	-	(0.55, 0.93)
Follow-up time (months)[d,e]	-	-	-
Median	11.8	11.7	-
Quartile 1, quartile 3	8.2, 14.2	7.5, 16.4	-
Minimum, maximum	0.0, 21.4	0.7, 23.1	-
Sensitivity Analysis 1: Subjects who were treated (safety analysis set; Table 14-4.5.2)			
Stratified log-rank test[b]	-	-	-
p-value	-	-	0.009
Stratified hazard ratio[c]	-	-	0.69
(95% Confidence interval)	-	-	(0.52, 0.91)
Sensitivity Analysis 2: Based on FAS and OS was censored at the time of alloHSCT (Table 14-4.5.3)			
Stratified log-rank test[b]	-	-	-
p-value	-	-	0.004
Stratified hazard ratio[c]	-	-	0.66
(95% Confidence interval)	-	-	(0.50, 0.88)
Sensitivity Analysis 3: Use of stratification values from case report forms for FAS (Table 14-4.5.4)			
Stratified log-rank test[b]	-	-	--
p-value	-	-	0.002
Stratified hazard ratio[c]	-	-	0.66
(95% Confidence interval)	-	-	(0.51, 0.87)
Sensitivity Analysis 4: With Gehan-Wilcoxon Test (Table 14-4.5.5)			
Stratified Gehan-Wilcoxon test[b]	-	-	-
p-value	-	-	0.028
Stratified hazard ratio[c]	-	-	0.71
(95% Confidence Interval)	-	-	(0.55, 0.93)

alloHSCT = allogenic hematopoietic stem cell transplantation; FAS = full analysis set; OS = overall survival; SOC = standard of care; - = not applicable

Note: The primary analysis and sensitivity analyses are described in Table 8-3

[a] A total of 251 deaths were reported from any cause; a total of 245 subjects discontinued the study because they died.

[b] Stratification factors: age (< 35 years; ≥ 35 years), prior salvage therapy and prior alloHSCT (yes; no).

[c] The hazard and hazard ratio estimates were obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicated a lower average event rate and longer survival time for blinatumomab relative to SOC chemotherapy.

[d] Time to censoring measured follow-up time by reversing the status indicator for censored and events.

[e] Months are calculated as days from randomization date to event/censor date, divided by 30.5.

Sensitivity analysis adjusted for potential bias introduced by the effect of drop-in (ie subjects randomized to SOC chemotherapy who subsequently received blinatumomab):

Table 12 Estimated Latent Treatment Effect on Overall Survival Without Subsequent Blinatumomab Drop-in by SOC Chemotherapy Arm (Full Analysis Set) (Study 00103311)

	n-subjects/ n-events[a]	Hazard ratio[b]	95% Confidence Interval for Hazard Ratio	P-value
n-subjects / events	405/251			
Treatment Blinatumomab vs. SOC Chemotherapy		0.72	0.54, 0.97	0.0293
Age <35 vs. ≥35 years old		0.75	0.58, 0.96	0.0249
Prior Salvage Therapy Yes vs. No		1.81	1.36, 2.39	<0.0001
Prior alloHSCT Yes vs. No		1.00	0.75, 1.34	0.9892

This method assumes a Weibull accelerated failure time model and a time-invariant treatment benefit at time of subsequent therapy that is the same as the blinatumomab treatment effect at randomization (Branson and Whitehead, 2002).

[a]Number of subjects and events in the parametric model.

[b]A hazard ratio < 1.0 indicates a lower average event rate and a longer survival for Blinatumomab relative to SOC Chemotherapy.

Table 13 Overall Survival: Censoring at Time of alloHSCT (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)	Treatment Difference
Subject status			
Events - n (%)	78 (58.2)	144 (53.1)	
Deaths from any cause	78 (58.2)	144 (53.1)	
Censored - n (%)	56 (41.8)	127 (46.9)	
Alive at last follow-up	11 (8.2)	49 (18.1)	
Consent withdrawn	13 (9.7)	10 (3.7)	
Lost to follow-up	0 (0.0)	1 (0.4)	
Decision by sponsor	0 (0.0)	2 (0.7)	
Received alloHSCT	32 (23.9)	65 (24.0)	
Stratified log-rank test[a]			
Normal score[b]			-18.62
p-value			0.004
Unstratified log-rank test			
Normal score[b]			-19.31
p-value			0.003
Time to event (KM) (months)[c]			
Median	3.9	6.9	
95% CI (median)	(2.8, 4.9)	(5.3, 8.8)	
Q1, Q3	1.9, 9.0	2.1, 14.6	
Min, Max	0.1, 12.4	0.1, 16.0	
Time to censoring (months)[c,d]			
Median	6.0	7.0	
Q1, Q3	2.8, 10.1	4.0, 11.8	
Min, Max	0.0, 15.9	0.7, 20.8	
KM estimate - %			
At time 3 months[c]	56.8	66.9	
(95% CI)	(47.3, 65.3)	(60.9, 72.3)	
At time 6 months[c]	32.0	52.8	
(95% CI)	(22.6, 41.8)	(46.0, 59.1)	
At time 12 months[c]	21.9	32.0	
(95% CI)	(12.8, 32.7)	(24.2, 40.1)	
At time 18 months[c]	NE	18.6	
(95% CI)	(NE, NE)	(10.6, 28.3)	
At time 24 months[c]	NE	NE	
(95% CI)	(NE, NE)	(NE, NE)	
Stratified hazard ratio[e]			0.66
(95% CI)			(0.50, 0.88)

Results of the subgroup analyses of OS are presented in table below.

Table 14 Subgroup Analysis of Overall Survival (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Age (per randomized strata)				0.67
<35 years	34/60 (56.7)	68/123 (55.3)	0.70 (0.46, 1.06)	
≥35 years	53/74 (71.6)	96/148 (64.9)	0.77 (0.55, 1.08)	
Prior salvage therapy (per randomized strata)				0.53
Yes	55/80 (68.8)	112/164 (68.3)	0.79 (0.57, 1.09)	
No	32/54 (59.3)	52/107 (48.6)	0.64 (0.41, 0.99)	
Prior alloHSCT (per randomized strata)				0.60
Yes	26/46 (56.5)	58/94 (61.7)	0.81 (0.51, 1.29)	
No	61/88 (69.3)	106/177 (59.9)	0.70 (0.51, 0.96)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Age/Prior salvage therapy/Prior alloHSCT				0.53
<35/Prior salvage/Prior alloHSCT	11/18 (61.1)	26/37 (70.3)	0.63 (0.30, 1.31)	
≥35/Prior salvage/Prior alloHSCT	5/10 (50.0)	15/20 (75.0)	1.59 (0.57, 4.44)	
<35/No prior salvage/Prior alloHSCT	3/8 (37.5)	7/16 (43.8)	0.78 (0.19, 3.15)	
≥35/No prior salvage/Prior alloHSCT	7/10 (70.0)	10/21 (47.6)	0.41 (0.15, 1.11)	
<35/Prior salvage/No prior alloHSCT	14/22 (63.6)	29/47 (61.7)	0.77 (0.41, 1.46)	
≥35/Prior salvage/No prior alloHSCT	25/30 (83.3)	42/60 (70.0)	0.66 (0.40, 1.08)	
<35/No prior salvage/No prior alloHSCT	6/12 (50.0)	6/23 (26.1)	0.40 (0.13, 1.25)	
≥35/No prior salvage/No prior alloHSCT	16/24 (66.7)	29/47 (61.7)	0.83 (0.45, 1.53)	
Sex				0.92
Male	50/77 (64.9)	102/162 (63.0)	0.72 (0.51, 1.01)	
Female	37/57 (64.9)	62/109 (56.9)	0.75 (0.50, 1.13)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Race				0.74
White	75/112 (67.0)	141/228 (61.8)	0.73 (0.55, 0.97)	
Asian	4/9 (44.4)	8/19 (42.1)	0.54 (0.16, 1.86)	
Other	8/13 (61.5)	15/24 (62.5)	0.93 (0.39, 2.21)	
Alternate age grouping				0.79
<35 years	34/60 (56.7)	69/124 (55.6)	0.71 (0.47, 1.07)	
35-54 years	22/33 (66.7)	49/80 (61.3)	0.67 (0.40, 1.11)	
55-64 years	21/26 (80.8)	24/34 (70.6)	0.77 (0.43, 1.39)	
≥65 years	10/15 (66.7)	22/33 (66.7)	1.04 (0.49, 2.19)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Number of prior salvage therapies				0.16
0	39/65 (60.0)	53/114 (46.5)	0.60 (0.39, 0.91)	
1	32/43 (74.4)	61/91 (67.0)	0.59 (0.38, 0.91)	
≥2	16/26 (61.5)	50/66 (75.8)	1.13 (0.64, 1.99)	
Number of prior salvage therapies - subjects without a prior alloHSCT				0.18
0	12/22 (54.5)	15/31 (48.4)	0.53 (0.24, 1.16)	
1	7/10 (70.0)	16/27 (59.3)	0.56 (0.23, 1.37)	
≥2	7/14 (50.0)	27/36 (75.0)	1.41 (0.61, 3.24)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Relapse/refractory status				0.16
Primary Refractory	14/27 (51.9)	24/46 (52.2)	1.00 (0.51, 1.97)	
1 Prior Relapse	30/44 (68.2)	58/93 (62.4)	0.73 (0.47, 1.14)	
≥2 Prior Relapses	15/20 (75.0)	28/45 (62.2)	0.32 (0.16, 0.64)	
Unknown	28/43 (65.1)	54/87 (62.1)	0.78 (0.49, 1.23)	
Relapse/refractory status - subjects without a prior alloHSCT				0.35
Primary Refractory	0/2 (0.0)	7/9 (77.8)	45116638 (0.00, NE)	
1 Prior Relapse	4/7 (57.1)	9/16 (56.3)	0.27 (0.08, 0.94)	
≥2 Prior Relapses	3/7 (42.9)	7/13 (53.8)	0.75 (0.19, 2.92)	
Unknown	19/30 (63.3)	35/56 (62.5)	0.80 (0.46, 1.40)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Central laboratory baseline bone marrow blasts				0.27
<50%	19/36 (52.8)	33/73 (45.2)	0.57 (0.33, 1.01)	
≥50%	63/93 (67.7)	113/170 (66.5)	0.85 (0.62, 1.16)	
Unknown	5/5 (100.0)	18/28 (64.3)	0.58 (0.21, 1.61)	
Baseline platelet count (/µl)				0.18
<50,000	50/66 (75.8)	104/136 (76.5)	0.76 (0.54, 1.07)	
50,000-100,000	15/20 (75.0)	32/64 (50.0)	0.34 (0.18, 0.65)	
>100,000	22/48 (45.8)	28/71 (39.4)	0.76 (0.43, 1.32)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Intended SOC chemotherapy regimen				0.072
Clofarabine or clofarabine based regimen	14/26 (53.8)	40/60 (66.7)	1.33 (0.72, 2.46)	
FLAG with or without anthracycline based regimen	38/56 (67.9)	59/113 (52.2)	0.52 (0.34, 0.79)	
HIDAC based regimen	13/22 (59.1)	27/44 (61.4)	0.92 (0.47, 1.80)	
High-dose methotrexate based regimen	22/30 (73.3)	38/54 (70.4)	0.68 (0.40, 1.15)	
Region				0.55
United States	11/15 (73.3)	24/31 (77.4)	1.00 (0.49, 2.06)	
Europe	56/85 (65.9)	109/180 (60.6)	0.75 (0.54, 1.04)	
Rest of the World	20/34 (58.8)	31/60 (51.7)	0.62 (0.35, 1.09)	
All subjects	87/134 (64.9)	164/271 (60.5)	0.71 (0.55, 0.93)	

The p-value is from a test of the interaction term in an unstratified Cox model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model. The hazard ratio estimate for all subjects was obtained from the Cox Proportional Hazard Model stratified by age group(<35 vs. ≥35), prior salvage status (yes vs. no), and prior alloHSCT status (yes vs. no).

Key secondary efficacy endpoints

- *Best hematologic response within 12 weeks*

Table 15 Best Response Within 12 Weeks of Treatment Initiation (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)	Treatment Difference
Subject Status			
CR - n (%)	21 (15.7)	91 (33.6)	17.9
(95% CI)	(10.0, 23.0)	(28.0, 39.5)	(9.6, 26.2)
p-value [a]			< 0.001
CRh* - n (%)	6 (4.5)	24 (8.9)	
(95% CI)	(1.7, 9.5)	(5.8, 12.9)	
CRi (without CRh*) - n (%)	6 (4.5)	4 (1.5)	
(95% CI)	(1.7, 9.5)	(0.4, 3.7)	
Blast free hypoplastic or aplastic bone marrow (without CRi) - n (%)	4 (3.0)	9 (3.3)	
(95% CI)	(0.8, 7.5)	(1.5, 6.2)	
Partial remission - n (%)	9 (6.7)	6 (2.2)	
(95% CI)	(3.1, 12.4)	(0.8, 4.8)	
Non-response - n (%)	15 (11.2)	41 (15.1)	
(95% CI)	(6.4, 17.8)	(11.1, 20.0)	
Progressive disease - n (%)	8 (6.0)	25 (9.2)	
(95% CI)	(2.6, 11.4)	(6.1, 13.3)	
Inevaluable/Missing post-baseline assessment within 12 weeks	65 (48.5)	68 (25.1)	
Reason for ending IP			
Adverse event	4 (3.0)	21 (7.7)	
Death	15 (11.2)	15 (5.5)	
Protocol specified criteria	21 (15.7)	28 (10.3)	
Failure to achieve CR/CRh*/CRi within 2 treatment cycles	0 (0.0)	1 (0.4)	
Intention to receive additional therapy other than allogeneic HSCT	6 (4.5)	5 (1.8)	
Intention to receive allogeneic HSCT	5 (3.7)	3 (1.1)	
Premature end to induction phase due to disease/clinical progression without prior CR/CRh*/CRi	10 (7.5)	19 (7.0)	
Subject request	25 (18.7)	4 (1.5)	
Never received IP	25 (18.7)	4 (1.5)	
CR/CRh*/CRi - n (%)	33 (24.6)	119 (43.9)	19.3
(95% CI)	(17.6, 32.8)	(37.9, 50.0)	(9.9, 28.7)
p-value [a]			< 0.001

CI = Confidence Interval. IP = Investigational Product.
aCochran-Mantel-Haenszel test adjusting for the stratification factors: age (<35 vs. ≥35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)

In the FAS, the CR rate (per investigator assessment) was 15.7% in the investigator's choice of SOC chemotherapy arm and 33.6% in blinatumomab arm (rate difference 17.9%; p-value < 0.001). The CR/CRh*/CRi rate was 24.6% in SOC chemotherapy arm and 43.9% in blinatumomab arm (rate difference 19.3%; p-value < 0.001).

Table 16 Subgroup Analysis of CR/CRh*/CRi Within 12 Weeks of Treatment Initiation (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/ Subjects (%)	Odds Ratio (95% CI)	p-value
Age (per randomized strata)				0.84
<35 years	15/60 (25.0)	53/123 (43.1)	2.27 (1.15, 4.50)	
≥35 years	18/74 (24.3)	66/148 (44.6)	2.50 (1.34, 4.66)	
Prior salvage therapy (per randomized strata)				0.18
Yes	12/80 (15.0)	62/164 (37.8)	3.44 (1.73, 6.87)	
No	21/54 (38.9)	57/107 (53.3)	1.79 (0.92, 3.49)	
Prior alloHSCT (per randomized strata)				0.055
Yes	5/46 (10.9)	38/94 (40.4)	5.56 (2.02, 15.36)	
No	28/88 (31.8)	81/177 (45.8)	1.81 (1.06, 3.09)	
Age/Prior salvage therapy/Prior alloHSCT				0.43
<35/Prior salvage/Prior alloHSCT	2/18 (11.1)	12/37 (32.4)	3.84 (0.76, 19.46)	
≥35/Prior salvage/Prior alloHSCT	0/10 (0.0)	6/20 (30.0)	12.56 (0.34, 459.15)	
<35/No prior salvage/Prior alloHSCT	2/8 (25.0)	8/16 (50.0)	3.00 (0.46, 19.59)	
≥35/No prior salvage/Prior alloHSCT	1/10 (10.0)	12/21 (57.1)	12.00 (1.28, 112.66)	
<35/Prior salvage/No prior alloHSCT	4/22 (18.2)	20/47 (42.6)	3.33 (0.98, 11.38)	
≥35/Prior salvage/No prior alloHSCT	6/30 (20.0)	24/60 (40.0)	2.67 (0.95, 7.49)	
<35/No prior salvage/No prior alloHSCT	7/12 (58.3)	13/23 (56.5)	0.93 (0.23, 3.82)	
≥35/No prior salvage/No prior alloHSCT	11/24 (45.8)	24/47 (51.1)	1.23 (0.46, 3.30)	
Sex				0.18
Male	19/77 (24.7)	61/162 (37.7)	1.84 (1.00, 3.38)	
Female	14/57 (24.6)	58/109 (53.2)	3.49 (1.72, 7.11)	
Race				0.71
White	28/112 (25.0)	100/228 (43.9)	2.34 (1.42, 3.87)	
Asian	1/9 (11.1)	8/19 (42.1)	5.82 (0.60, 56.29)	
Other	4/13 (30.8)	11/24 (45.8)	1.90 (0.46, 7.92)	
Alternate age grouping				0.069
<35 years	15/60 (25.0)	53/124 (42.7)	2.24 (1.13, 4.44)	
35-54 years	6/33 (18.2)	39/80 (48.8)	4.28 (1.59, 11.49)	
55-64 years	4/26 (15.4)	14/34 (41.2)	3.85 (1.09, 13.65)	
≥65 years	8/15 (53.3)	13/33 (39.4)	0.57 (0.17, 1.95)	
Number of prior salvage therapies				0.50
0	23/65 (35.4)	60/114 (52.6)	2.03 (1.08, 3.80)	
1	7/43 (16.3)	36/91 (39.6)	3.37 (1.35, 8.38)	
≥2	3/26 (11.5)	23/66 (34.8)	4.10 (1.11, 15.12)	
Number of prior salvage therapies - subjects without a prior alloHSCT				0.83
0	3/22 (13.6)	16/31 (51.6)	6.75 (1.65, 27.57)	
1	1/10 (10.0)	14/27 (51.9)	9.69 (1.07, 87.44)	
≥2	1/14 (7.1)	8/36 (22.2)	3.71 (0.42, 32.87)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/ Subjects (%)	Odds Ratio (95% CI)	p-value
Relapse/refractory status				0.099
Primary Refractory	12/27 (44.4)	19/46 (41.3)	0.88 (0.34, 2.30)	
1 Prior Relapse	13/44 (29.5)	40/93 (43.0)	1.80 (0.84, 3.87)	
≥2 Prior Relapses	3/20 (15.0)	22/45 (48.9)	5.42 (1.39, 21.10)	
Unknown	5/43 (11.6)	38/87 (43.7)	5.89 (2.12, 16.41)	
Relapse/refractory status - subjects without a prior alloHSCT				0.42
Primary Refractory	0/2 (0.0)	1/9 (11.1)	0.63 (0.01, 45.40)	
1 Prior Relapse	0/7 (0.0)	9/16 (56.3)	25.99 (0.69, 982.12)	
≥2 Prior Relapses	1/7 (14.3)	5/13 (38.5)	3.75 (0.34, 41.08)	
Unknown	4/30 (13.3)	23/56 (41.1)	4.53 (1.39, 14.73)	
Central laboratory baseline bone marrow blasts				0.10
<50%	12/36 (33.3)	50/73 (68.5)	4.35 (1.86, 10.18)	
≥50%	20/93 (21.5)	57/170 (33.5)	1.84 (1.02, 3.32)	
Unknown	1/5 (20.0)	12/28 (42.9)	3.00 (0.30, 30.39)	
Baseline platelet count (/µl)				0.074
<50,000	13/66 (19.7)	39/136 (28.7)	1.64 (0.80, 3.34)	
50,000-100,000	3/20 (15.0)	40/64 (62.5)	9.44 (2.50, 35.61)	
>100,000	17/48 (35.4)	40/71 (56.3)	2.35 (1.11, 5.01)	
Intended SOC chemotherapy regimen				0.20
Clofarabine or clofarabine based regimen	10/26 (38.5)	27/60 (45.0)	1.31 (0.51, 3.35)	
FLAG with or without anthracycline based regimen	17/56 (30.4)	54/113 (47.8)	2.10 (1.06, 4.14)	
HIDAC based regimen	2/22 (9.1)	21/44 (47.7)	9.13 (1.90, 43.86)	
High-dose methotrexate based regimen	4/30 (13.3)	17/54 (31.5)	2.99 (0.90, 9.91)	
Region				0.22
United States	6/15 (40.0)	11/31 (35.5)	0.82 (0.23, 2.93)	
Europe	20/85 (23.5)	83/180 (46.1)	2.78 (1.56, 4.97)	
Rest of the World	7/34 (20.6)	25/60 (41.7)	2.76 (1.04, 7.32)	
All subjects	33/134 (24.6)	119/271 (43.9)	2.40 (1.51, 3.80)	

To enable the estimation of an odds ratio when subgroups with zero events within a treatment group occurred, a continuity correction of 0.33 and 0.67 was added to the SOC Chemotherapy group and Blinatumomab group, respectively, which reflects the randomization.
The p-value is from a test of the interaction term in an unstratified logistic model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.

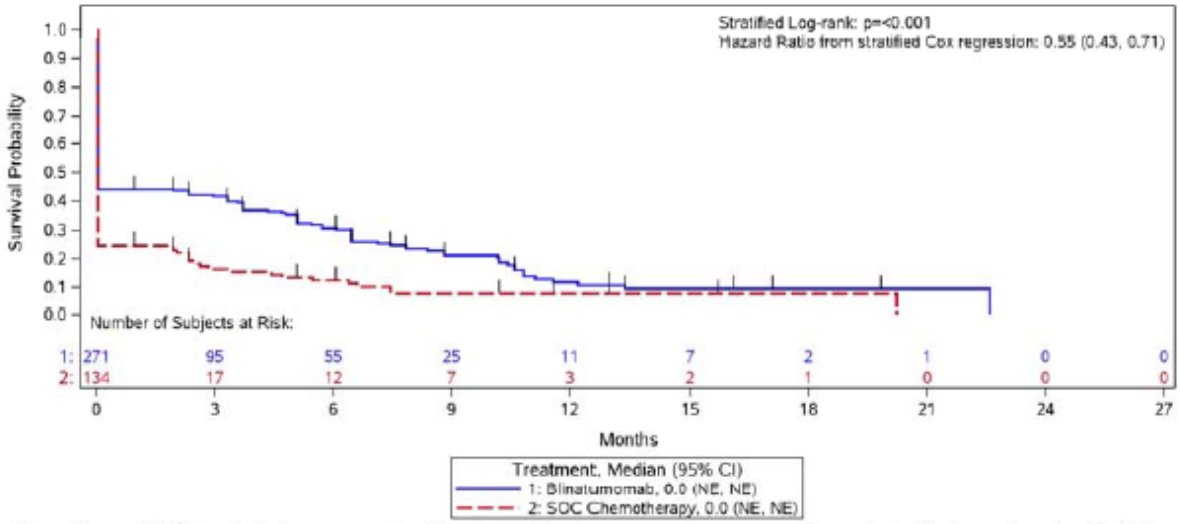
- *Event-free survival*

Table 17 Event Free Survival (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)	Treatment Difference
Subject status			
Events - n (%)	119 (88.8)	209 (77.1)	
No CR/CRh*/CRi	101 (75.4)	152 (56.1)	
Relapse	8 (6.0)	31 (11.4)	
Progressive disease	1 (0.7)	6 (2.2)	
Extramedullary relapse	0 (0.0)	2 (0.7)	
Death from any cause	9 (6.7)	18 (6.6)	
Censored - n (%)	15 (11.2)	62 (22.9)	
Alive w/o relapse	15 (11.2)	62 (22.9)	
Stratified log-rank test[a]			
Normal score[b]			-22.92
p-value			<0.001
Time to event (KM) (months)[c]			
Median	0.0	0.0	
95% CI (median)	(NE, NE)	(NE, NE)	
Q1, Q3	0.0, 0.0	0.0, 7.4	
Min, Max	0.0, 20.2	0.0, 22.6	
Time to censoring (months)[c,d]			
Median	10.2	7.8	
Q1, Q3	5.1, 13.0	5.1, 17.1	
Min, Max	1.0, 15.7	1.0, 19.8	
KM estimate - %			
At time 3 months[c]	16.4	41.6	
(95% CI)	(10.5, 23.5)	(35.6, 47.4)	
At time 6 months[c]	12.5	30.7	
(95% CI)	(7.2, 19.2)	(25.0, 36.5)	
At time 12 months[c]	7.9	11.8	
(95% CI)	(3.7, 14.2)	(7.0, 17.9)	
At time 18 months[c]	7.9	9.5	
(95% CI)	(3.7, 14.2)	(5.1, 15.6)	
At time 24 months[c]	0.0	0.0	
(95% CI)	(NE, NE)	(NE, NE)	
Stratified hazard ratio[e]			0.55
(95% CI)			(0.43, 0.71)

EFS is presented as a KM plot in Figure below.

Figure 3 Event-Free Survival (Full Analysis Set) (Study 00103311)



Observed/censored EFS times for both arms are assigned the scheduled time the assessment was supposed to occur in the blinatumomab arm to mitigate the potential bias associated with different treatment cycle lengths between arms;
Death events will still be reported as the actual death date. A censored subject is indicated by a Vertical Bar |.

Table 18 Subgroup Analysis of Event Free Survival (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Age (per randomized strata)				0.68
<35 years	53/60 (88.3)	92/123 (74.8)	0.67 (0.48, 0.95)	
≥35 years	66/74 (89.2)	117/148 (79.1)	0.58 (0.43, 0.79)	
Prior salvage therapy (per randomized strata)				0.48
Yes	77/80 (96.3)	138/164 (84.1)	0.56 (0.42, 0.75)	
No	42/54 (77.8)	71/107 (66.4)	0.70 (0.48, 1.03)	
Prior alloHSCT (per randomized strata)				0.012
Yes	45/46 (97.8)	72/94 (76.6)	0.44 (0.30, 0.66)	
No	74/88 (84.1)	137/177 (77.4)	0.76 (0.57, 1.01)	
Age/Prior salvage therapy/Prior alloHSCT				0.26
<35/Prior salvage/Prior alloHSCT	18/18 (100.0)	32/37 (86.5)	0.51 (0.27, 0.93)	
≥35/Prior salvage/Prior alloHSCT	10/10 (100.0)	18/20 (90.0)	0.47 (0.20, 1.07)	
<35/No prior salvage/Prior alloHSCT	8/8 (100.0)	9/16 (56.3)	0.37 (0.14, 1.01)	
≥35/No prior salvage/Prior alloHSCT	9/10 (90.0)	13/21 (61.9)	0.35 (0.14, 0.87)	
<35/Prior salvage/No prior alloHSCT	19/22 (86.4)	38/47 (80.9)	0.68 (0.39, 1.18)	
≥35/Prior salvage/No prior alloHSCT	30/30 (100.0)	50/60 (83.3)	0.55 (0.35, 0.88)	
<35/No prior salvage/No prior alloHSCT	8/12 (66.7)	13/23 (56.5)	1.25 (0.48, 3.22)	
≥35/No prior salvage/No prior alloHSCT	17/24 (70.8)	36/47 (76.6)	0.81 (0.45, 1.45)	
Sex				0.13
Male	67/77 (87.0)	134/162 (82.7)	0.73 (0.54, 0.98)	
Female	52/57 (91.2)	75/109 (68.8)	0.52 (0.36, 0.74)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Race				0.76
White	100/112 (89.3)	173/228 (75.9)	0.61 (0.48, 0.79)	
Asian	8/9 (88.9)	16/19 (84.2)	0.71 (0.30, 1.68)	
Other	11/13 (84.6)	20/24 (83.3)	0.74 (0.35, 1.56)	
Alternate age grouping				0.32
<35 years	53/60 (88.3)	93/124 (75.0)	0.68 (0.48, 0.95)	
35-54 years	29/33 (87.9)	60/80 (75.0)	0.50 (0.32, 0.79)	
55-64 years	25/26 (96.2)	27/34 (79.4)	0.53 (0.30, 0.93)	
≥65 years	12/15 (80.0)	29/33 (87.9)	0.98 (0.49, 1.94)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Number of prior salvage therapies				0.48
0	51/65 (78.5)	78/114 (68.4)	0.71 (0.50, 1.01)	
1	42/43 (97.7)	73/91 (80.2)	0.51 (0.35, 0.76)	
≥2	26/26 (100.0)	58/66 (87.9)	0.48 (0.29, 0.79)	
Number of prior salvage therapies - subjects without a prior alloHSCT				0.31
0	21/22 (95.5)	20/31 (64.5)	0.34 (0.18, 0.66)	
1	10/10 (100.0)	19/27 (70.4)	0.31 (0.13, 0.71)	
≥2	14/14 (100.0)	33/36 (91.7)	0.62 (0.33, 1.19)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Relapse/refractory status				0.047
Primary Refractory	19/27 (70.4)	34/46 (73.9)	1.16 (0.65, 2.06)	
1 Prior Relapse	38/44 (86.4)	75/93 (80.6)	0.74 (0.50, 1.10)	
≥2 Prior Relapses	20/20 (100.0)	38/45 (84.4)	0.38 (0.21, 0.68)	
Unknown	42/43 (97.7)	62/87 (71.3)	0.42 (0.28, 0.64)	
Relapse/refractory status - subjects without a prior alloHSCT				0.56
Primary Refractory	2/2 (100.0)	9/9 (100.0)	0.76 (0.16, 3.59)	
1 Prior Relapse	7/7 (100.0)	11/16 (68.8)	0.24 (0.08, 0.73)	
≥2 Prior Relapses	7/7 (100.0)	10/13 (76.9)	0.46 (0.17, 1.29)	
Unknown	29/30 (96.7)	42/56 (75.0)	0.46 (0.28, 0.76)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Central laboratory baseline bone marrow blasts				0.25
<50%	29/36 (80.6)	47/73 (64.4)	0.48 (0.30, 0.77)	
≥50%	85/93 (91.4)	141/170 (82.9)	0.72 (0.55, 0.94)	
Unknown	5/5 (100.0)	21/28 (75.0)	0.84 (0.29, 2.48)	
Baseline platelet count (/µl)				0.31
<50,000	66/66 (100.0)	117/136 (86.0)	0.64 (0.47, 0.88)	
50,000-100,000	18/20 (90.0)	48/64 (75.0)	0.38 (0.22, 0.67)	
>100,000	35/48 (72.9)	44/71 (62.0)	0.71 (0.45, 1.11)	

	SOC Chemotherapy Events/ Subjects (%)	Blinatumomab Events/Subjects (%)	Hazard Ratio (95% CI)	p-value
Intended SOC chemotherapy regimen				0.067
Clofarabine or clofarabine based regimen	20/26 (76.9)	47/60 (78.3)	1.14 (0.67, 1.95)	
FLAG with or without anthracycline based regimen	48/56 (85.7)	82/113 (72.6)	0.60 (0.42, 0.86)	
HIDAC based regimen	22/22 (100.0)	34/44 (77.3)	0.36 (0.20, 0.65)	
High-dose methotrexate based regimen	29/30 (96.7)	46/54 (85.2)	0.58 (0.35, 0.93)	
Region				0.073
United States	12/15 (80.0)	28/31 (90.3)	1.28 (0.63, 2.60)	
Europe	75/85 (88.2)	132/180 (73.3)	0.59 (0.44, 0.79)	
Rest of the World	32/34 (94.1)	49/60 (81.7)	0.53 (0.34, 0.85)	
All subjects	119/134 (88.8)	209/271 (77.1)	0.60 (0.47, 0.75)	

The p-value is from a test of the interaction term in an unstratified Cox model with terms for the covariate and treatment group also included; subjects with a missing value of the covariate were not included in the model.
The hazard ratio estimate for all subjects was obtained from the Cox Proportional Hazard Model stratified by age group(<35 vs. ≥35), prior salvage status (yes vs. no), and prior alloHSCT status (yes vs. no).

Other secondary efficacy endpoints:

Duration of hematologic response

The duration of the best hematologic response of CR and CR/CRh*/CRi were calculated only for subjects who achieve a CR or CR/CRh*/CRi, from the date a documented hematologic response until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. Subjects who do not have a relapse event will be censored on their last disease assessment date.

Of the 112 subjects who had a best response of CR within 12 weeks of treatment initiation, 49 subjects had an event and 63 subjects were censored. The median time to an event was 7.8 months (95% CI: 2.2, 19.0) in the SOC chemotherapy arm compared with 8.3 months (95% CI: 5.7, 10.7) in the blinatumomab arm.

Of the 152 subjects who had a best response of CR/CRh*/CRi within 12 weeks of treatment initiation, 75 subjects had an event and 77 subjects were censored. The median time to an event was 4.6 months (95% CI: 1.8, 19.0) in the SOC chemotherapy arm compared with 7.3 months (95% CI: 5.8, 9.9) in the blinatumomab arm.

All subjects were alive at the time of the data cutoff date of 4 January 2016. A summary of the duration of CR results is displayed in Table 19.

Table 19 Duration of CR (Subjects in the Full Analysis Set Who Achieved a CR within 12 weeks of treatment initiation) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)
Subject status		
Number of subjects	21	91
Events - n (%)	9 (42.9)	40 (44.0)
Relapse	5 (23.8)	25 (27.5)
Progressive disease	0 (0.0)	3 (3.3)
Extramedullary relapse	0 (0.0)	0 (0.0)
Death from any cause	4 (19.0)	12 (13.2)
Censored - n (%)	12 (57.1)	51 (56.0)
Alive w/o relapse	12 (57.1)	51 (56.0)
Time to event (KM) (months)[a]		
Median	7.8	8.3
95% CI (median)	(2.2, 19.0)	(5.7, 10.7)
Q1, Q3	3.8, 19.0	4.2, 12.3
Min, Max	1.6, 19.0	0.8, 12.3
Time to censoring (months)[a, b]		
Median	10.8	7.0
Q1, Q3	4.4, 13.0	2.8, 12.4
Min, Max	0.0, 15.2	0.0, 19.5
KM estimate - %		
At time 3 months [a]	75.6	78.2
(95% CI)	(47.3, 90.1)	(66.7, 86.1)
At time 6 months [a]	55.5	56.7
(95% CI)	(28.3, 75.9)	(43.3, 68.1)
At time 9 months [a]	48.5	45.1
(95% CI)	(22.7, 70.3)	(31.3, 57.9)
At time 12 months [a]	48.5	29.9
(95% CI)	(22.7, 70.3)	(16.7, 44.3)
At time 18 months [a]	48.5	23.3
(95% CI)	(22.7, 70.3)	(11.3, 37.8)
At time 24 months [a]	0.0	NE
(95% CI)	(NE, NE)	(NE, NE)

KM = Kaplan-Meier. CI=Confidence Interval. NE=not estimable
a Months are calculated as days from randomization date to event/censor date, divided by 30.5
b Time to censoring measures follow-up time by reversing the status indicator for censored and events

Table 20 Duration of CR/CRh*/Cri (Subjects in the Full Analysis Set Who Achieved a CR/CRh*/CRi within 12 weeks of treatment initiation) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)
Subject status		
Number of subjects	33	119
Events - n (%)	18 (54.5)	57 (47.9)
Relapse	8 (24.2)	31 (26.1)
Progressive disease	1 (3.0)	6 (5.0)
Extramedullary relapse	0 (0.0)	2 (1.7)
Death from any cause	9 (27.3)	18 (15.1)
Censored - n (%)	15 (45.5)	62 (52.1)
Alive w/o relapse	15 (45.5)	62 (52.1)
Time to event (KM) (months)[a]		
Median	4.6	7.3
95% CI (median)	(1.8, 19.0)	(5.8, 9.9)
Q1, Q3	1.7, 19.0	3.7, 12.0
Min, Max	0.9, 19.0	0.8, 20.1
Time to censoring (months)[a, b]		
Median	10.8	7.2
Q1, Q3	4.4, 13.0	3.9, 15.4
Min, Max	0.0, 15.6	0.0, 19.5
KM estimate - %		
At time 3 months [a]	59.7	80.4
(95% CI)	(38.9, 75.4)	(71.2, 86.9)
At time 6 months [a]	38.6	57.0
(95% CI)	(20.1, 56.8)	(45.8, 66.7)
At time 9 months [a]	33.7	43.6
(95% CI)	(16.2, 52.3)	(31.9, 54.7)
At time 12 months [a]	33.7	27.4
(95% CI)	(16.2, 52.3)	(16.3, 39.8)
At time 18 months [a]	33.7	22.4
(95% CI)	(16.2, 52.3)	(12.1, 34.8)
At time 24 months [a]	0.0	0.0
(95% CI)	(NE, NE)	(NE, NE)

Table 21 Subgroup Analysis of Best Hematologic Response and Duration of Response in Subjects with CR and CR/CRh*/CRi in Study 00103311 (Full Analysis Set Subjects Who Achieved a Response Within 12 Weeks of Treatment Initiation) (Study 00103311)

Subgroup	SOC Chemotherapy Responders/ Subjects (%)	Blinatumomab Responders/ Subjects (%)	Odds Ratio (95% CI)	SOC Chemotherapy Events[a]/ Subjects (%)	Blinatumomab Events[a]/ Subjects (%)	Hazard Ratio (95% CI)
	CR			Duration of CR		
All subjects	21/134 (15.7)	91/271 (33.6)	2.72 (1.60, 4.62)	9/21 (42.9)	40/91 (44.0)	1.08 (0.47, 2.48)
Primary refractory	8/27 (29.6)	16/46 (34.8)	1.27 (0.45, 3.53)	2/8 (25.0)	5/16 (31.3)	3.17 (0.36, 27.73)
Age ≥ 65 years	6/15 (40.0)	11/33 (33.3)	0.75 (0.21, 2.65)	3/6 (50.0)	7/11 (63.6)	0.49 (0.12, 2.03)
Intended SOC chemotherapy regimen: clofarabine or clofarabine-based regimen[b]	6/26 (23.1)	23/60 (38.3)	2.07 (0.72, 5.92)	1/6 (16.7)	10/23 (43.5)	NE (NE, NE)
Received ≥ 2 prior salvage therapies	0/26	15/66 (22.7)	22.87 (0.70, 743.28)	0/0	9/15 (60.0)	NE (NE, NE)
	CR/CRh*/CRi			Duration of CR/CRh*/CRi		
All subjects	33/134 (24.6)	119/271 (43.9)	2.40 (1.51, 3.80)	18/33 (54.5)	57/119 (47.9)	0.68 (0.38, 1.22)
Primary refractory	12/27 (44.4)	19/46 (41.3)	0.88 (0.34, 2.30)	4/12 (33.3)	7/19 (36.8)	1.55 (0.40, 6.06)
Age ≥ 65 years	8/15 (53.3)	13/33 (39.4)	0.57 (0.17, 1.95)	5/8 (62.5)	9/13 (69.2)	0.43 (0.13, 1.39)
Intended SOC chemotherapy regimen: clofarabine or clofarabine-based regimen[b]	10/26 (38.5)	27/60 (45.0)	1.31 (0.51, 3.35)	4/10 (40.0)	14/27 (51.9)	2.96 (0.84, 10.48)
Received ≥ 2 prior salvage therapies	3/26 (11.5)	23/66 (34.8)	4.10 (1.11, 15.12)	3/3 (100.0)	15/23 (65.2)	0.06 (0.01, 0.32)

HSCT = hematopoietic stem cell transplantation; CR = complete remission; CRh* = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; NE = not estimable; SOC = standard of care

To enable the estimation of an odds ratio when subgroups with zero events within a treatment group occurred, a continuity correction of 0.33 and 0.67 was added to the SOC chemotherapy arm and blinatumomab arm, respectively, which reflects the randomization.

[a] The subject had a disease assessment that indicated a relapse event or death.

[b] Selected by the investigator prior to randomization as the intended SOC chemotherapy regimen that would be administered if randomized to SOC chemotherapy.

MRD response within 12 weeks of treatment initiation

An MRD response was defined as an MRD level below 10^{-4} by PCR or flow cytometry. "Complete" MRD remission was defined as the occurrence of an MRD level below the limit of detection. The proportion of subjects who had an MRD response within 12 weeks of treatment initiation in the FAS is presented in Table 22.

Table 22 MRD Remission within 12 weeks of treatment initiation (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 134)	Blinatumomab (N = 271)	Treatment Difference
Number of subjects	134	271	
MRD remission - n (%)	19 (14.2)	81 (29.9)	15.7
(95% CI)	(8.8, 21.3)	(24.5, 35.7)	(7.7, 23.7)
p-value [a]			< 0.001
MRD complete remission - n (%)	12 (9.0)	64 (23.6)	14.7
(95% CI)	(4.7, 15.1)	(18.7, 29.1)	(7.7, 21.7)
p-value [a]			< 0.001
No MRD remission - n (%)	50 (37.3)	85 (31.4)	
No post-baseline MRD assessment - n (%)	65 (48.5)	105 (38.7)	
Number of subjects with a CR	21	91	
MRD remission - n (%)	11 (52.4)	57 (62.6)	10.3
(95% CI)	(29.8, 74.3)	(51.9, 72.6)	(-13.3, 33.8)
p-value [a]			0.32
MRD complete remission - n (%)	7 (33.3)	43 (47.3)	13.9
(95% CI)	(14.6, 57.0)	(36.7, 58.0)	(-8.7, 36.5)
p-value [a]			0.20
No MRD remission - n (%)	10 (47.6)	17 (18.7)	
No post-baseline MRD assessment - n (%)	0 (0.0)	17 (18.7)	
Number of subjects with a CR/CRh*/CRi	33	119	
MRD remission - n (%)	16 (48.5)	74 (62.2)	13.7
(95% CI)	(30.8, 66.5)	(52.8, 70.9)	(-5.4, 32.8)
p-value [a]			0.17
MRD complete remission - n (%)	10 (30.3)	58 (48.7)	18.4
(95% CI)	(15.6, 48.7)	(39.5, 58.1)	(0.4, 36.5)
p-value [a]			0.050
No MRD remission - n (%)	17 (51.5)	23 (19.3)	
No post-baseline MRD assessment - n (%)	0 (0.0)	22 (18.5)	

CI = Confidence Interval.
[a]Cochran-Mantel-Haenszel test adjusting for the stratification factors: age (<35 vs. ≥ 35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)

The proportion of subjects who had an MRD response within 12 weeks of treatment initiation and an evaluable postbaseline assessment in the FAS is presented in Table 23.

Table 23 MRD Response Evaluated Within 12 Weeks of Treatment Initiation and a Postbaseline Assessment (Study 00103311)

	SOC Chemotherapy	Blinatumomab	Treatment Difference
All randomized subjects with postbaseline assessment	69	166	
Number of subjects with CR/CRh*/CRi	33	97	
MRD response - n (%)	16 (48.5)	74 (76.3)	27.8
(95% Confidence interval)	(30.8, 66.5)	(66.6, 84.3)	(8.8, 46.8)
p-value[a]			0.007
MRD complete remission - n (%)	10 (30.3)	58 (59.8)	29.5
(95% Confidence interval)	(15.6, 48.7)	(49.3, 69.6)	(11.0, 48.0)
p-value[a]			0.004
PCR Assessment			
Randomized subjects with postbaseline assessment	56	138	
Number of subjects with CR/CRh*/CRi	24	82	
MRD response - n (%)	10 (41.7)	61 (74.4)	32.7
(95% Confidence interval)	(22.1, 63.4)	(63.6, 83.4)	(10.9, 54.6)
p-value[a]			0.008
MRD complete response - n (%)	4 (16.7)	45 (54.9)	38.2
(95% Confidence interval)	(4.7, 37.4)	(43.5, 65.9)	(19.8, 56.6)
p-value[a]			0.002
Flow cytometry assessment			
Randomized subjects with a postbaseline assessment	13	28	
Number of subjects with CR/CRh*/CRi	9	15	
MRD complete response[b] - n (%)	6 (66.7)	13 (86.7)	20.0
(95% Confidence interval)	(29.9, 92.5)	(59.5, 98.3)	(-15.3, 55.3)
p-value[a]			0.30

CR = complete remission; CRh* = complete remission with partial hematologic response; CRi = complete remission with incomplete hematologic response; MRD = minimal residual disease; PCR = polymerase chain reaction; SOC = standard of care
Note: complete MRD response is defined as unable to detect disease markers, MRD response is defined as MRD level < 10-4
a The Cochran-Mantel-Haenszel test was used to determine statistical significance after adjusting for stratification factors of age (< 35 years vs ☐ 35 years), prior salvage therapy (yes vs no), and prior allogeneic HSCT (yes vs no).
b The same number of subjects who achieved CR/CRh*/CRi had an MRD response and MRD complete response

The median duration of MRD response was 4.5 months (95% CI: 3.6, 9.0) in the blinatumomab arm and 3.8 months (95% CI: 1.9, 19.0) in the SOC chemotherapy arm.

Table 24.Duration of MRD Response at Any Time in Subjects who Achieved an MRDResponse at Any Time (Full Analysis Set)

Subject status – n (%)	SOC Chemotherapy (N = 21)	Blinatumomab (N = 84)
Events – n (%)	9 (42.9)	38 (45.2)
MRD relapse	2 (9.5)	17 (20.2)
Hematologic relapse	3 (14.3)	16 (19.0)
Death from any cause	4 (19.0)	5 (6.0)
Censored – n (%)	12 (57.1)	46 (54.8)
Alive without relapse	12 (57.1)	46 (54.8)
Kaplan-Meier time to event (months)[a]		
Median	3.8	4.5
95% confidence interval (median)	(1.9, 19.0)	(3.6, 9.0)
Quartile 1, quartile 3	2.0, 19.0	2.8, 12.0
Minimum, maximum	0.9, 19.0	0.2, 12.0
Kaplan-Meier time to censoring (months)[a,b]		
Median	12.6	5.5
Quartile 1, quartile 3	0.0, 19.5	1.6, 10.4
Minimum, maximum	0.0, 19.5	0.0, 15.7
Kaplan-Meier estimate – %		
3 months (95% confidence Interval)	60.0 (28.5, 81.2)	70.2 (57.5, 79.8)
6 months (95% confidence Interval)	42.9 (15.9, 67.7)	44.7 (31.0, 57.4)
9 months (95% confidence Interval)	34.3 (10.7, 59.5)	33.7 (19.5, 48.5)
12 months (95% confidence Interval)	34.3 (10.7, 59.9)	29.5 (15.5, 44.9)
18 months (95% confidence Interval)	34.3 (10.7, 59.9)	NE (NE, NE)

MRD = minimal residual disease; MRD response =≤ 1 x 10^{-4} disease; NE = not estimable
The MRD response rate was measured within the first 12 weeks of treatment initiation whereas the duration of MRD response was measured any time during the study.
[a] Months were calculated as days from the first onset of MRD response to events/censor date, divided by 30.5.
[b] Time to censoring measured follow-up time by reversing the status indicator for censored and events.

Postbaseline Allogeneic HSCT

The incidence of postbaseline alloHSCT is presented in Table 25.

Table 25 Subject Incidence of Post-baseline AlloHSCT (Full Analysis Set) (Study 00103311)

	SOC Chemotherapy (N=134)	Blinatumomab (N=271)	Treatment Difference
Subjects with AlloHSCT - n (%)	32 (23.9)	65 (24.0)	0.1
(95% CI)	(16.9, 32.0)	(19.0, 29.5)	(-8.7, 8.9)
p-value [a]			0.95
Subjects with AlloHSCT with a CR/CRh*/CRi within 12 weeks of treatment initiation without anti-cancer therapy prior to alloHSCT - n (%)	12 (9.0)	38 (14.0)	5.1
(95% CI)	(4.7, 15.1)	(10.1, 18.7)	(-1.3, 11.4)
p-value [a]			0.12
Subjects with AlloHSCT with a CR/CRh*/CRi within 12 weeks of treatment initiation with anti-cancer therapy prior to alloHSCT - n (%)	5 (3.7)	8 (3.0)	-0.8
(95% CI)	(1.2, 8.5)	(1.3, 5.7)	(-4.6, 3.0)
p-value [a]			0.69
Subjects with AlloHSCT not in remission after achieving a CR/CRh*/CRi within 12 weeks of treatment initiation - n (%)	1 (0.7)	4 (1.5)	0.7
(95% CI)	(0.0, 4.1)	(0.4, 3.7)	(-1.3, 2.8)
p-value [a]			0.54
Subjects with AlloHSCT without a CR/CRh*/CRi within 12 weeks of treatment initiation - n (%)	14 (10.4)	15 (5.5)	-4.9
(95% CI)	(5.8, 16.9)	(3.1, 9.0)	(-10.8, 0.9)
p-value [a]			0.071

CI = Confidence Interval.
aCochran-Mantel-Haenszel test adjusting for the stratification factors: age (<35 vs. ≥35), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no)

Table 26 Time to alloHSCT Following First Occurence of CR/CRh*/Cri (Subjects in the Full Analysis Set Achieving a CR/CRh*/CRi Within 12 Weeks of Treatment Initiation) (Study 00103311)

	SOC Chemotherapy (N=33)	Blinatumomab (N=119)
Subject status		
Number of subjects with CR/CRh*/CRi	33	119
Events - n (%)	18 (54.5)	50 (42.0)
alloHSCT	18 (54.5)	50 (42.0)
Censored - n (%)	15 (45.5)	69 (58.0)
No alloHSCT	15 (45.5)	69 (58.0)
Time to event (KM) (months)[a]		
Median	3.6	11.3
95% CI (median)	(2.3, 7.2)	(5.2, NE)
Q1, Q3	2.1, NE	3.2, NE
Min, Max	0.9, 7.2	0.3, 11.3
Time to censoring (months)[a,b]		
Median	5.2	7.8
Q1, Q3	4.4, 9.0	4.6, 13.1
Min, Max	0.9, 11.0	1.1, 19.8
KM estimate - %		
At time 1 month[a]	96.9	95.0
(95% CI)	(79.8, 99.6)	(89.1, 97.7)
At time 3 months[a]	52.4	75.7
(95% CI)	(33.1, 68.6)	(66.8, 82.6)
At time 6 months[a]	41.5	59.9
(95% CI)	(21.6, 60.3)	(49.8, 68.7)
At time 9 months[a]	27.6	53.8
(95% CI)	(10.0, 48.7)	(43.0, 63.4)
At time 12 months[a]	NE	45.8
(95% CI)	(NE, NE)	(33.4, 57.3)
At time 18 months[a]	NE	45.8
(95% CI)	(NE, NE)	(33.4, 57.3)

Survival status and 100-day mortality rate after alloHSCT

The survival status after alloHSCT in subjects who achieved CR/CRh*/CRi within 12 weeks of treatment and had an alloHSCT without anti-cancer therapy prior to alloHSCT is presented in Table 27.

Table 27 Survival Status Following alloHSCT (Subjects in the Full Analysis Set with anAlloHSCT following a CR/CRh*/Cri within 12 weeks of treatment initiation without anti-cancer therapy prior to alloHSCT) (Study 00103311)

	SOC Chemotherapy (N=12)	Blinatumomab (N=38)
Subject status		
Number of subjects with alloHSCT	12	38
Events - n (%)	3 (25.0)	10 (26.3)
Death from any cause	3 (25.0)	10 (26.3)
Censored - n (%)	9 (75.0)	28 (73.7)
Alive	9 (75.0)	28 (73.7)
Time to event (KM) (days)[a]		
Median	380.0	NE
95% CI (median)	(138.0, NE)	(252.0, NE)
Q1, Q3	380.0, NE	196.0, NE
Min, Max	123, 380	10, 339
Time to censoring (days)[a,b]		
Median	279.0	206.0
Q1, Q3	241.0, 379.0	119.0, 385.0
Min, Max	50, 532	1, 596
Mortality (KM estimate) - %		
At time 100 days[a]	0.0	12.4
(95% CI)	(NE, NE)	(4.8, 29.9)

KM = Kaplan-Meier. CI=Confidence Interval. NE=not estimable
a Days are calculated from alloHSCT date to death/censor date
b Time to censoring measures follow-up time by reversing the status indicator for censored and events

Global health status and quality of life

In TOWER study, Health related quality of life (HRQoL) reported by patients were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30). In a post-hoc sensitivity analysis, compared to SOC, Blincyto consistently delayed the time to clinically meaningful deterioration of HRQoL (≥ 10 point worsening from baseline) for global health status [median BLINCYTO versus SOC: 8.1 months versus 1.0 month; HR = 0.60 (95% CI = 0.42, 0.85)], functional scales, symptom scales and individual items.

Exploratory efficacy endpoints:

The C_{ss} of blinatumomab is described in section PK.

The following table summarises the efficacy results from the phase 3 study 00103311 (Tower).

Table 28 Summary of efficacy for Phase III study

Title: A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE Antibody Blinatumomab *Versus* Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukaemia (ALL)			
Study identifier	00103311, TOWER Study		
Design	Multicentre, open-label, parallel-groups, active-controlled, randomized in a 2:1 ratio,		
	Duration of main phase	22 to 25 months	
Hypothesis	Superiority		
Treatments groups	Blinatumomab N randomized =271		Continuous IV infusion, 9µg/d D1 to D7 in the 1st cycle then escalated to 28/µg/day for all subsequent doses and cycles. Induction phase: 2 cycles of 6w (4w on/2w off) Consolidation phase: 3 additional cycles (4w on/2w off) Maintenance phase: 4 additional cycles (4w on/8w off)
	SOC chemotherapy N randomized = 134		- FLAG ± anthracycline based regimen: eg Idarubicin 10 mg/m^2 days 1, 3; fludarabine 30 mg/m^2 days 1-5; cytarabine 2g/m^2 days 1-5. For subject's > 60 years: Idarubicin 5 mg/m^2 day 1,3; fludarabine 20 mg/m^2 days 1-5; cytarabine 1 g/m^2 days 1-5 - HiDAC based regimen: cytarabine arabinoside ≥ 1g/m2 /d ± anthracycline and/or in combination with other drugs eg native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents - High-dose methotrexate based regimen: eg 500 mg/m2 - 3 g/m^2 HDMTX (infusion time up to 24 hours) in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents. - Clofarabine or clofarabine based regimens. Clofarabine use as a single agent should follow the recommended prescribing information. Clofarabine combination based regimens should use ≥ 20 mg/m^2/day for up to 5 days.
Endpoints and definitions	Primary endpoint	OS	Duration from time of randomization until death due to any cause
	Key secondary endpoints	CR	CR: ≤ 5% blasts in the BM, no evidence of disease, and both platelets > 100,000/µl and ANC > 1,000/µl occurred within 12 w
		CR/CRh*/ CRi	Having either a CR, CRh*, or CRi within 12w: CRh*: ≤ 5% blasts in the BM, no evidence of disease and both platelets > 50,000/µl and ANC > 500/µl. CRi: ≤ 5% blasts in the BM, no evidence of disease and either platelets > 100,000/µl or ANC > 1000 (but not both).
		EFS	Duration from randomization until the date of a disease assessment indicating a relapse event or death, whichever occurs first.
	Other secondary endpoints	Duration of CR	Duration from the date a CR is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first.

		Duration of CR/CRh*/CR	Duration from the date a CR/CRh*/CR is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first.
		MRD remission	MRD level below 10^{-4} by PCR or flow cytometry. Complete MRD remission: an MRD level below the limit of detection.
		AlloHSCT	- subjects incidence of post-baseline alloHSCT - time to alloHSCT following first occurrence of CR/CRh*/CRi observed within 12w of treatment initiation - 100-day of mortality after alloHSCT
		Safety	Incidence of AE, Incidence of anti-blinatumomab antibody formation Changes in vital signs and laboratory parameters
Database lock	4 January 2016		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Primary analysis was performed on all randomised subjects (FAS, full analysis set consistent with the intent-to-treat principle) Safety analysis based was performed on all subjects who received protocol-specified therapy		
Descriptive statistics and estimate variability	Treatment group	Investigator's choice of SOC chemotherapy	Blinatumomab
	Number of subjects (FAS)	134	271
	Median OS (months)	4.0	7.7
	95% CI	2.9, 5.3	5.6, 9.6
	CR within 12w (%)	15.7	33.6
	95% CI	10.0, 23.0	28.0, 39.5
	CR/CRh*/Cri (%)	24.6	43.9
	95% CI	17.6, 32.8	37.9, 50.0
	Median EFS	0.0	0.0
	95% CI	NE, NE	NE, NE
	Duration of CR (months)	7.8	8.3
	95% CI	2.2, 19.0	5.7, 10.7
	Duration of CR/CRh*/Cri (months)	4.6	7.3
	95% CI	1.8, 19.0	5.8, 9.9
	MRD remission rate (%)	14.2	29.9
	95% CI	8.8, 21.3	24.5, 35.7
	AlloHSCT rate (%)	23.9	24.0
	95% CI	16.9, 32.0	19.0, 29.5

	Time to alloHSCT (months)	3.6	11.3
	95% CI	2.3, 7.2	5.2, NE
	100-day mortality rate after alloHSCT (%)	0.0	12.4
	95% CI	NE, NE	4.8, 29.9
Effect estimate per comparison	Primary endpoint: OS	Comparison groups	SOC chemotherapy vs blinatumomab (FAS)
		HR stratified analysis	0.71
		95% CI	0.55, 0.93
		P-value (2-sided)	0.012 < critical p-value 0.0194
	Secondary endpoint: CR rate	Comparison groups	SOC chemotherapy vs blinatumomab (FAS)
		CR rate difference	17.9
		95% CI	9.6, 26.2
		p-value	<0.001
	Secondary endpoint: CR/CRh*/CRi rate	Comparison groups	SOC chemotherapy vs blinatumomab (FAS)
		CR/CRh*/CRi rate difference	19.3
		95% CI	9.9, 28.7
		p-value	<0.001
	Secondary endpoint: EFS	Comparison groups	SOC chemotherapy vs blinatumomab (FAS)
		HR stratified analysis	0.55
		95% CI	0.43, 0.71
		p-value	<0.001
Notes	The primary analysis of OS between 2 arms used 2-sided log-rank test, stratified by 3 randomisation factors: age (<35 years vs >35 years), prior salvage therapy (yes vs no), and prior alloHSCT (yes vs no) OS primary analysis was triggered when 75% (248 subjects) of the total number of deaths (330) were observed. On 28/01/2016, the DMC recommended stopping the study because the p-value =0.011 less than threshold for statistical significance for OS p=0.0183		

Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Number of subjects with treatment-emergent adverse events	100 (91.7)	231 (86.5)
Febrile neutropenia	38 (34.9)	57 (21.3)
Anaemia	38 (34.9)	53 (19.9)
Neutropenia	29 (26.6)	47 (17.6)
Thrombocytopenia	30 (27.5)	39 (14.6)
Pyrexia	5 (4.6)	19 (7.1)
Alanine aminotransferase increased	9 (8.3)	15 (5.6)
Sepsis	7 (6.4)	13 (4.9)
White blood cell count decreased	6 (5.5)	12 (4.5)
Platelet count decreased	13 (11.9)	11 (4.1)
Pneumonia	11 (10.1)	11 (4.1)
Neutrophil count decreased	11 (10.1)	10 (3.7)
Hypokalaemia	11 (10.1)	9 (3.4)
Hyperglycaemia	7 (6.4)	8 (3.0)
Bacteraemia	6 (5.5)	2 (0.7)

MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care
Note: Adverse events were coded according to MedDRA version 18.1. Preferred terms were presented in descending order of subject incidence in the blinatumomab arm.
Source: Modified from Table 14-6-1.22

4.2.2.2. ***Discussion on clinical efficacy***

In FAS set, the median OS was 4.0 months (95% CI: 2.9, 5.3) in the SOC chemotherapy arm compared with 7.7 months (95% CI: 5.6, 9.6) in the blinatumomab arm with the hazard ratio 0.71 (95% CI: 0.55, 0.93) between treatment arms favoring blinatumomab. The median follow-up time was similar (11.8 months in SOC vs 11.7 months in blinatumomab arm). The KM survival curves started to separate between 2 arms around 3 months (58.4% in SOC vs 67.3% in blinatumomab) corresponding to 2-cycle induction phase of blinatumomab treatment (6 weeks/cycle). The largest difference was observed around 6 months of treatment (38.5% in SOC vs 53.9% in blinatumomab). KM survival estimates came near at 12 months and were similar at 18 months. Based on the stratified log-rank test, there was a statistically significant improvement in OS for blinatumomab as compared to defined investigator's choice of SOC chemotherapy (p = 0.012) according to the pre-specified threshold p-value <0.0194. This difference is considered clinically meaningful.

Consistent results were observed after censoring at the time of HSCT; median OS, censored at the time of HSCT, was 6.9 months (95% CI: 5.3, 8.8) in the blinatumomab arm and 3.9 months (95% CI: 2.8, 4.9) in the SOC arm (HR, 0.66; 95% CI: 0.50, 0.88; p value = 0.004). The mortality rate following alloHSCT among all responders who did not receive anti-leukemic therapy was 10/38 (26.3%; 95% CI: 13.4, 43.1) in the blinatumomab arm and 3/12 (25%; 95% CI: 5.5, 57.2) in the SOC group; such mortality rate at

100 days post alloHSCT was 4/38 (12.4%; 95% CI: 4.8%, 29.9%) in the blinatumomab arm and 0/12 (0%; 95% CI: not estimable) in the SOC group.

The receipt of an alloHSCT was based upon the investigator's discretion in this phase 3 study; subjects were not randomized by whether or when an HSCT was undertaken. Thus this trial could not distinguish the effect of HSCT on clinical benefit such as OS or RFS. The impact of blinatumomab as salvage induction therapy on HSCT could be confounded by different baseline and HSCT characteristics. In order to further characterise the effect of blinatumomab in patients following alloHSCT the MAH commited to evaluate the impact of blinatumomab compared to SOC chemotherapy on HSCT post-blinatumomab with careful collection of all relevant data concerning HSCT including a control group. Given that the benefit risk balance for the overall population was concluded as positive, this study was categorized as a Category 3 study in the RMP.

The submission of the draft protocol of this Study 20170610 "Overall survival and incidence of transplant-related adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: Induction with blinatumomab treatment versus induction with chemotherapy" is planned in November 2018, and the final report submission is expected in April 2025. Submission of interim results should be provided in Q2 2022.

The MAH will capture all SAEs related to infection, not only serious infections leading to/contributing to death, during routine post-transplant follow up and to collect efficacy and safety data on most patients who receive HSCT in the EU (see discussion on clinical safety).

Regarding the secondary endpoints, statistically and clinically significant increases of CR/CRh*/CRi and MRD negativity were observed in the blinatumomab arm as compared to the SOC chemotherapy arm (43.9% vs 24.3%, 23.6% vs 9.0% respectively).

Following the SAG advice, the MAH also is requested to re-open the Phase 3 study 00103311 (Tower) for collecting long-term efficacy and safety data to provide analysis of the effect of blinatumomab on OS when compared to standard of care chemotherapy for the complete population studied (see RMP).

In addition to the above, the CHMP also considered that the ongoing studies in first line B-ALL and B-precursor paediatric ALL are of great interest to assess the B/R of blinatumomab and how it would compare in relation to HSCT in the management of childhood ALL (COG-AALL1331) and the direct clinical benefit (eg.OS) of chemotherapy combined with blinatumomab among MRD-positive subjects following front-line therapy (ECOG-E1910).

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 22 November 2017 to provide advice on the following question:

After treatment with Blincyto, HSCT (which is normally the only potentially curative option) appears as negatively impacting outcomes (OS and RFS). Please discuss the target population for Blincyto, in particular if you foresee that the target population would be limited to patients never eligible to HSCT? If so, would you consider that this population is possible to define prospectively, before treatment?

The SAG experts concluded that for relapsed/refractory disease, the target population corresponds to the population treated in the prospective, randomized, phase 3 trial (TOWER) including patients with Ph-negative B-cell precursor ALL refractory to primary induction therapy or to salvage with intensive combination chemotherapy, first relapse with the first remission lasting less than 12 months, second or greater relapse, or relapse at any time after allogeneic stem-cell transplantation. Longer follow-up should

be requested post-approval to confirm in secondary (exploratory) analyses the long term efficacy and assess if a long-term benefit can be established or if the effect on OS is mainly transient. It is acknowledged that due to cross-over, treatment switching and other uncontrolled events the effect currently observed may be diluted in the long-term, but this can be explored using statistical techniques.

Conclusion on clinical efficacy

In view of the SAG advice, and given that this is the only relevant comparative study in this target population and that it is generally good practice to follow-up all patients until death, if feasible, the MAH has been requested to collect as complete survival data as possible for the Phase 3 study 00103311 (Tower). Although the difficulties of re-opening follow-up for a study are acknowledged, information on overall survival should be readily available. As it would be of interest to obtain a more precise estimation of the long-term effect, the MAH will investigate if there is an additional effect on survival affecting also events that occur later in the course of the disease. Information on this aspect will aid in exploring the effect size in terms of long-term efficacy in the context of the current established efficacy. Although no major differences are expected, the additional follow-up will provide more precise estimates and the possibility for further analyses (see RMP).

Statistically and clinically significant increases of OS, CR/CRh*/CRi and MRD negativity were observed in the blinatumomab arm as compared to the SOC chemotherapy arm (7.7 months vs 4.0 months, 43.9% vs 24.3%, 23.6% vs 9.0% respectively). The SmPC has been updated in section 5.1 with the data submitted. In conclusion, the Phase 3 study 00103311 data confirmed the efficacy of blinatumumab in adult patients with Philadelphia chromosome-negative relapsed/refractory B-cell precursor acute lymphoblastic leukaemia (ALL) and the CHMP agreed that the specific obligation has been fufilled.

4.2.3. Safety

Introduction

The primary analysis of safety was performed on the safety analysis set which included all subjects who received protocol-specified therapy analyzed according to the treatment they received.

Patient exposure

Blinatumomab exposure

Table 29 Summary of Blinatumomab exposure across all cycles (SafetyAnalysis Set) (Study 00103311)

	Blinatumomab (N = 267)
Number of cycles started - n (%)	
1	116 (43.4)
2	65 (24.3)
3	26 (9.7)
4	20 (7.5)
5	13 (4.9)
6 or more	27 (10.1)
Number of cycles started	
Mean	2.5
Standard Deviation	1.9
Median	2.0
Quartile 1, quartile 3	1.0, 3.0
Minimum, maximum	1, 9
Number of cycles completed	
0	70 (26.2)
1	62 (23.2)
2	59 (22.1)
3	22 (8.2)
4	20 (7.5)
5	10 (3.7)
6 or more	24 (9.0)
Mean number of cycles completed	
Mean	2.0
Standard Deviation	2.1
Median	2.0
Quartile 1, quartile 3	0.0, 3.0
Minimum, maximum	0, 9

	Blinatumomab (N = 267)
Duration of treatment (days)	
Mean	64.2
Standard Deviation	56.2
Median	54.1
Quartile 1, quartile 3	25.5, 84.0
Minimum, maximum	0, 258
Cumulative dose[a] (µg)	
Mean	1591.0
Standard Deviation	1543.5
Median	1264.9
Quartile 1, quartile 3	564.4, 2204.3
Minimum, maximum	4, 6935
Reasons for drug interruptions[b,c] - n (%)	
None	117 (43.8)
Adverse event	80 (30.0)
Noncompliance	1 (0.4)
Dose administration error	5 (1.9)
Subject request	4 (1.5)
Dose reinstated	5 (1.9)
Device complaint	12 (4.5)
Investigator decision	12 (4.5)
Withdrew from treatment	19 (7.1)
Infusion bag emptied prematurely	13 (4.9)
Other	46 (17.2)

a.Cumulative dose was the sum of (duration of each infusion) × (dose of each infusion).
b.A subject may have had more than 1 reason for an interruption.
c Adverse events that led to treatment interruption were obtained from 2 different case report forms, the adverse event case report form and the investigational product case report form . The numbers between the 2 case report forms do not match.
Note: All exposure records with the start date before the data cutoff date were included. Exposure was recorded from the treatment start date until the last dose date plus 30 days or before the data cutoff date (04 January 2016), whichever came first.

SOC chemotherapy exposure

Table 30 Summary of Standard of Care Chemotherapy Exposure Across AllCycles (SafetyAnalysis Set) (Study 00103311)

	SOC Chemotherapy (N = 109)
Type of SOC chemotherapy – n (%)	
FLAG ± anthracycline	49 (45.0)
HiDAC	19 (17.4)
High-dose methotrexate	22 (20.2)
Clofarabine	19 (17.4)
Number of cycles – n (%)	
1	81 (74.3)
2	25 (22.9)
3	1 (0.9)
4	2 (1.8)
Mean number of cycles	
Mean	1.3
Standard Deviation	0.6
Median	1.0
Quartile 1, quartile 3	1.0, 2.0
Minimum, maximum	1, 4
Reasons for drug interruptions[a] - n (%)	
None	100 (91.7)
Adverse event	5 (4.6)
Investigator decision	3 (2.8)
Other	1 (0.9)

FLAG = fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (filgrastim); HiDAC = high-dose cytarabine arabinoside; SOC = standard of care
a A subject may have had more than 1 reason for an interruption.
b Adverse events that led to treatment interruption were obtained from 2 different case report forms, the adverse event case report form and the investigational product case report form. The numbers between the 2 case report forms do not match most likely because other reasons may have been given for treatment interruption in the investigational product CRF rather than adverse event.

Adverse events

Treatment emergent adverse events (TEAE) regardless of causality

TEAE were collected from the first dose of study treatment until 30 days after the last dose or the safety follow-up visit. AEs starting before the start of treatment that worsened later (after start of treatment) are also defined as treatment-emergent.

As of the data cutoff date of 4 January 2016, 108/109 subjects (99.1%) in the SOC chemotherapy treatment arm and 263/267 subjects (98.5%) in the blinatumomab treatment arm had experienced at least 1 TEAE. Fatal TEAE were reported for 19 subjects (17.4%) in the SOC chemotherapy arm and 51 subjects (19.1%) in blinatumomab arm.

Table 31 Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set) (Study 00103311)

Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Treatment-emergent	108 (99.1)	263 (98.5)
Grade ≥ 2	106 (97.2)	256 (95.9)
Grade ≥ 3	100 (91.7)	231 (86.5)
Grade ≥ 4	67 (61.5)	133 (49.8)
Serious	49 (45.0)	165 (61.8)
Led to interruption of investigational product[a]	6 (5.5)	86 (32.2)
Serious	4 (3.7)	52 (19.5)
Led to discontinuation of investigational product	9 (8.3)	33 (12.4)
Serious	7 (6.4)	28 (10.5)
Life-threatening	26 (23.9)	55 (20.6)
Fatal	19 (17.4)	51 (19.1)
Treatment-related	92 (84.4)	214 (80.1)
Grade ≥ 2	89 (81.7)	195 (73.0)
Grade ≥ 3	78 (71.6)	143 (53.6)
Grade ≥ 4	51 (46.8)	57 (21.3)
Serious	34 (31.2)	74 (27.7)
Led to interruption of investigational product	6 (5.5)	58 (21.7)
Serious	4 (3.7)	33 (12.4)
Led to discontinuation of investigational product	8 (7.3)	19 (7.1)
Serious	6 (5.5)	14 (5.2)
Life-threatening	17 (15.6)	21 (7.9)
Fatal	8 (7.3)	8 (3.0)

CTCAE = Common Technical Criteria for Adverse Events; SOC = standard of care
Note: Severity grading was determined according to CTCAE v4.03
[a] Adverse events that led to treatment interruption were obtained from two different case report forms, the adverse event case report form and the investigational product case report form. The numbers between the 2 case report forms do not

match most likely because multiple other reasons may have been given for treatment interruption in the investigational product case report form rather than adverse event.

The incidence of treatment-emergent adverse events in ≥ 10% of subjects and the Exposure-adjusted rates for the safety analysis set are presented in Table 32.

Table 32 Incidence of Treatment-emergent Adverse Events in ≥ 10% of Subjects and Exposure-Adjusted Rates by Preferred Term (Safety Analysis Set) (Study 00103311)

	Subject Incidence Rates		Exposure-Adjusted Rates	
Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
No. of subjects with treatment-emergent adverse events	108 (99.1)	263 (98.5)	108 (2037) / 13763.5	263 (4108) / 4615.7
Pyrexia	49 (45.0)	159 (59.6)	49 (75) / 506.8	159 (335) / 376.4
Headache	32 (29.4)	77 (28.8)	32 (39) / 263.5	77 (101) / 113.5
Anaemia	46 (42.2)	69 (25.8)	46 (146) / 986.5	69 (204) / 229.2
Febrile neutropenia	43 (39.4)	64 (24.0)	43 (54) / 364.9	64 (83) / 93.3
Diarrhoea	38 (34.9)	58 (21.7)	38 (49) / 331.1	58 (72) / 80.9
Neutropenia	33 (30.3)	53 (19.9)	33 (52) / 351.4	53 (108) / 121.3
Nausea	46 (42.2)	51 (19.1)	46 (69) / 466.2	51 (71) / 79.8
Thrombocytopenia	32 (29.4)	47 (17.6)	32 (111) / 750.0	47 (112) / 125.8
Hypokalaemia	30 (27.5)	45 (16.9)	30 (44) / 297.3	45 (75) / 84.3
Cough	6 (5.5)	39 (14.6)	6 (7) / 47.3	39 (47) / 52.8
Oedema peripheral	16.0 (14.7)	39 (14.6)	16 (20) / 135.1	39 (48) / 53.9
Cytokine release syndrome	0	38 (14.2)	0	38 (49) / 55.1
Back pain	10 (9.2)	35 (13.1)	10 (14) / 94.6	35 (42) / 47.2
Constipation	28 (25.7)	34 (12.7)	28 (34) / 229.7	34 (45) / 50.6
Fatigue	14 (12.8)	34 (12.7)	14 (15) / 101.4	34 (43) / 48.3
Vomiting	26 (23.9)	33 (12.4)	26 (40) / 270.3	33 (35) / 39.3
Hypotension	13 (11.9)	32 (12.0)	13 (18) / 121.6	32 (37) / 41.6
Bone pain	8 (7.3)	30 (11.2)	8 (9) / 60.8	30 (40) / 44.9
Hypomagnesaemia	18 (16.5)	29 (10.9)	18 (20) / 135.1	29 (38) / 42.7
Insomnia	10 (9.2)	28 (10.5)	10 (12) / 81.1	28 (38) / 42.7
Alanine aminotransferase increased	11 (10.1)	24 (9.0)	11 (35)/236.5	24 (46)/51.7
Asthenia	11 (10.1)	21 (7.9)	11 (15)/101.4	21 (33)/37.1
Chills	12 (11.0)	19 (7.1)	12 (16)/108.1	19 (23)/25.8
Rash	13 (11.9)	19 (7.1)	13 (15)/101.4	19 (22)/24.7
Decreased appetite	15 (13.8)	18 (6.7)	15 (15)/101.4	18 (22)/24.7

Preferred Term	Subject Incidence Rates		Exposure-Adjusted Rates	
	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Stomatitis	14 (12.8)	18 (6.7)	14 (16)/108.1	18 (19)/21.3
Abdominal pain	19 (17.4)	17 (6.4)	19 (25)/168.9	17 (19)/21.3
Platelet count decreased	13 (11.9)	17 (6.4)	13 (73)/493.2	17 (54)/60.7
Pneumonia	16 (14.7)	16 (6.0)	16 (18)/121.6	16 (17)/19.1
Hypoalbuminaemia	11 (10.1)	13 (4.9)	11 (15)/101.4	13 (22)/24.7
Neutrophil count decreased	11 (10.1)	10 (3.7)	11(28)/189.2	10 (23)/25.8
Mucosal inflammation	14 (12.8)	9 (3.4)	14 (15)/101.4	9 (10)/11.2

MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted event rate per 100 subject years (n2*100/total exposure);
SOC = standard of care
Note: Adverse events were coded according to MedDRA version 18.1. Preferred terms were presented in descending order of subject incidence in the blinatumomab arm.
The units for exposure-adjusted event rates are number of events per 100 subject years.
Exposure time for each individual subject was the date at first dose until the last dose plus 30 days or data cutoff date, whichever came first. The total exposure was the sum of exposure time across subjects.

Treatment-related AE

Table 33 Summary of Subject Incidence of Treatment-Emergent Adverse Events (SafetyAnalysis Set) (Study 00103311)

	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
All treatment-related treatment-emergent adverse events	92 (84.4)	214 (80.1)
Grade ≥ 2	89 (81.7)	195 (73.0)
Grade ≥ 3	78 (71.6)	143 (53.6)
Grade ≥ 4	51 (46.8)	57 (21.3)
Serious adverse events	34 (31.2)	74 (27.7)
Leading to interruption of investigational product	6 (5.5)	58 (21.7)
Serious	4 (3.7)	33 (12.4)
Leading to discontinuation of investigational product	8 (7.3)	19 (7.1)
Serious	6 (5.5)	14 (5.2)
Life-threatening adverse events	17 (15.6)	21 (7.9)
Fatal adverse events	8 (7.3)	8 (3.0)

Adverse events coded using MedDRA version 18.1 .
Severity graded using CTCAE v4.03.

Table 34. Adverse Reactions in Study 00103311 Compared with Study MT103-211 (Safety Analysis Set)

System Organ Class Preferred Term	CIOMS Frequency (Very Common: ≥ 10% Common: 1% to < 10% Uncommon: 0.1% to <1%)	Phase 3 Tower Study				Phase 2 MT103-211	
		SOC Chemotherapy (N = 109) n (%)		Blinatumomab (N = 267) n (%)		Blinatumomab (N = 189) n (%)	
		Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3
Treatment-emergent adverse events	Very Common	105 (96.3)	95 (87.2)	258 (96.6)	215 (80.5)	188 (99.5)	136 (72.0)
Blood and lymphatic system disorders	Very Common	80 (73.4)	75 (68.8)	178 (66.7)	155 (58.1)	111 (58.7)	93 (49.2)
Anaemia [1,19]	Very Common	46 (42.2)	38 (34.9)	73 (27.3)	56 (21.0)	40 (21.2)	28 (14.8)
Febrile neutropenia [19]	Very Common	43 (39.4)	38 (34.9)	64 (24.0)	57 (21.3)	53 (28.0)	48 (25.4)
Thrombocytopenia [17,19]	Very Common	45 (41.3)	43 (39.4)	64 (24.0)	50 (18.7)	29 (15.3)	22 (11.6)
Neutropenia [12,19]	Very Common	42 (38.5)	38 (34.9)	62 (23.2)	56 (21.0)	39 (20.6)	36 (19.0)
Leukopenia [10,19]	Common	10 (9.2)	10 (9.2)	23 (8.6)	19 (7.1)	27 (14.3)	23 (12.2)
Leukocytosis [9]	Common	1 (0.9)	1 (0.9)	14 (5.2)	6 (2.2)	6 (3.2)	2 (1.1)
Lymphadenopathy	Common	0 (0.0)	0 (0.0)	6 (2.2)	1 (0.4)	1 (0.5)	0 (0.0)
Lymphopenia [11,19]	Common	4 (3.7)	4 (3.7)	5 (1.9)	4 (1.5)	5 (2.6)	4 (2.1)
Histiocytosis haematophagic	Common	0 (0.0)	0 (0.0)	4 (1.5)	4 (1.5)	0 (0.0)	0 (0.0)
Cardiac disorders	Very Common	16 (14.7)	1 (0.9)	35 (13.1)	3 (1.1)	24 (12.7)	1 (0.5)
Tachycardia [16,19]	Very Common	16 (14.7)	1 (0.9)	35 (13.1)	3 (1.1)	24 (12.7)	1 (0.5)
General disorders and administration site conditions	Very Common	69 (63.3)	10 (9.2)	191 (71.5)	28 (10.5)	148 (78.3)	21 (11.1)
Pyrexia [14]	Very Common	49 (45.0)	5 (4.6)	161 (60.3)	19 (7.1)	113 (59.8)	13 (6.9)
Oedema [13,19]	Very Common	19 (17.4)	1 (0.9)	46 (17.2)	3 (1.1)	64 (33.9)	5 (2.6)
Chills [19]	Common	12 (11.0)	3 (2.8)	19 (7.1)	1 (0.4)	29 (15.3)	0 (0.0)
Chest pain [2,19]	Common	10 (9.2)	2 (1.8)	18 (6.7)	0 (0.0)	23 (12.2)	2 (1.1)
Pain	Common	6 (5.5)	0 (0.0)	16 (6.0)	6 (2.2)	14 (7.4)	2 (1.1)
Hepatobiliary disorders	Common	11 (10.1)	4 (3.7)	20 (7.5)	10 (3.7)	21 (11.1)	11 (5.8)
Hyperbilirubinaemia [6,19]	Common	11 (10.1)	4 (3.7)	20 (7.5)	10 (3.7)	21 (11.1)	11 (5.8)
Immune system disorders	Very Common	1 (0.9)	0 (0.0)	42 (15.7)	9 (3.4)	27 (14.3)	5 (2.6)
Cytokine release syndrome	Very Common	0 (0.0)	0 (0.0)	38 (14.2)	9 (3.4)	22 (11.6)	2 (1.1)
Hypersensitivity [19]	Common	1 (0.9)	0 (0.0)	5 (1.9)	0 (0.0)	3 (1.6)	2 (1.1)
Cytokine storm [19]	Uncommon	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.1)	1 (0.5)

System Organ Class Preferred Term	CIOMS Frequency (Very Common: ≥ 10% Common: 1% to < 10% Uncommon: 0.1% to <1%)	Phase 3 Tower Study				Phase 2 MT103-211	
		SOC Chemotherapy (N = 109) n (%)		Blinatumomab (N = 267) n (%)		Blinatumomab (N = 189) n (%)	
		Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3
Infections and infestations	Very Common	79 (72.5)	57 (52.3)	171 (64.0)	91 (34.1)	118 (62.4)	67 (35.4)
Infections - pathogen unspecified [19]	Very Common	56 (51.4)	38 (34.9)	116 (43.4)	63 (23.6)	80 (42.3)	46 (24.3)
Bacterial infectious disorders [19]	Very Common	36 (33.0)	22 (20.2)	56 (21.0)	28 (10.5)	40 (21.2)	25 (13.2)
Viral infectious disorders	Very Common	17 (15.6)	1 (0.9)	43 (16.1)	7 (2.6)	23 (12.2)	9 (4.8)
Fungal infectious disorders [19]	Very Common	18 (16.5)	11 (10.1)	34 (12.7)	16 (6.0)	26 (13.8)	13 (6.9)
Injury, poisoning and procedural complications	Very Common	9 (8.3)	1 (0.9)	98 (36.7)	12 (4.5)	59 (31.2)	7 (3.7)
Infusion related reaction [18]	Very Common	9 (8.3)	1 (0.9)	91 (34.1)	9 (3.4)	55 (29.1)	7 (3.7)
Overdose	Common	0 (0.0)	0 (0.0)	8 (3.0)	0 (0.0)	5 (2.6)	0 (0.0)
Accidental overdose	Common	0 (0.0)	0 (0.0)	3 (1.1)	3 (1.1)	2 (1.1)	0 (0.0)
Investigations	Very Common	20 (18.3)	12 (11.0)	69 (25.8)	32 (12.0)	58 (30.7)	20 (10.6)
Hepatic enzyme increased [5]	Very Common	16 (14.7)	12 (11.0)	45 (16.9)	26 (9.7)	31 (16.4)	17 (9.0)
Decreased immunoglobulins [3]	Common	2 (1.8)	0 (0.0)	26 (9.7)	7 (2.6)	21 (11.1)	2 (1.1)
Weight increased [19]	Common	4 (3.7)	0 (0.0)	8 (3.0)	1 (0.4)	16 (8.5)	0 (0.0)
Blood alkaline phosphatase increased	Common	4 (3.7)	0 (0.0)	7 (2.6)	3 (1.1)	7 (3.7)	3 (1.6)
Metabolism and nutrition disorders	Common	1 (0.9)	1 (0.9)	10 (3.7)	8 (3.0)	8 (4.2)	3 (1.6)
Tumour lysis syndrome	Common	1 (0.9)	1 (0.9)	10 (3.7)	8 (3.0)	8 (4.2)	3 (1.6)
Musculoskeletal and connective tissue disorders	Very Common	23 (21.1)	2 (1.8)	81 (30.3)	13 (4.9)	59 (31.2)	10 (5.3)
Back pain	Very Common	10 (9.2)	2 (1.8)	35 (13.1)	4 (1.5)	26 (13.8)	4 (2.1)
Bone pain	Very Common	8 (7.3)	0 (0.0)	30 (11.2)	6 (2.2)	19 (10.1)	5 (2.6)
Pain in extremity	Common	8 (7.3)	0 (0.0)	25 (9.4)	3 (1.1)	21 (11.1)	2 (1.1)

System Organ Class Preferred Term	CIOMS Frequency (Very Common: ≥ 10% Common: 1% to < 10% Uncommon: 0.1% to <1%)	Phase 3 Tower Study				Phase 2 MT103-211	
		SOC Chemotherapy (N = 109) n (%)		Blinatumomab (N = 267) n (%)		Blinatumomab (N = 189) n (%)	
		Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3	Any Grades	Grade ≥ 3
Nervous system disorders	Very Common	38 (34.9)	6 (5.5)	126 (47.2)	14 (5.2)	107 (56.6)	18 (9.5)
Headache [19]	Very Common	32 (29.4)	3 (2.8)	77 (28.8)	1 (0.4)	65 (34.4)	7 (3.7)
Tremor	Common	0 (0.0)	0 (0.0)	26 (9.7)	1 (0.4)	33 (17.5)	1 (0.5)
Dizziness [19]	Common	8 (7.3)	0 (0.0)	18 (6.7)	1 (0.4)	26 (13.8)	1 (0.5)
Somnolence	Common	1 (0.9)	0 (0.0)	14 (5.2)	3 (1.1)	9 (4.8)	1 (0.5)
Paraesthesia	Common	1 (0.9)	0 (0.0)	13 (4.9)	0 (0.0)	7 (3.7)	0 (0.0)
Hypoaesthesia	Common	0 (0.0)	0 (0.0)	7 (2.6)	0 (0.0)	6 (3.2)	0 (0.0)
Memory impairment [19]	Common	0 (0.0)	0 (0.0)	5 (1.9)	0 (0.0)	3 (1.6)	0 (0.0)
Seizure [19]	Common	4 (3.7)	3 (2.8)	5 (1.9)	2 (0.7)	4 (2.1)	1 (0.5)
Aphasia [19]	Common	0 (0.0)	0 (0.0)	4 (1.5)	1 (0.4)	7 (3.7)	2 (1.1)
Cognitive disorder [19]	Common	0 (0.0)	0 (0.0)	4 (1.5)	2 (0.7)	3 (1.6)	1 (0.5)
Encephalopathy	Common	0 (0.0)	0 (0.0)	4 (1.5)	4 (1.5)	10 (5.3)	6 (3.2)
Speech disorder [19]	Uncommon	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	Very Common	13 (11.9)	0 (0.0)	39 (14.6)	4 (1.5)	46 (24.3)	3 (1.6)
Insomnia [19]	Very Common	10 (9.2)	0 (0.0)	28 (10.5)	1 (0.4)	29 (15.3)	0 (0.0)
Confusional state	Common	3 (2.8)	0 (0.0)	9 (3.4)	3 (1.1)	14 (7.4)	3 (1.6)
Disorientation [19]	Common	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)	7 (3.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Very Common	16 (14.7)	3 (2.8)	58 (21.7)	9 (3.4)	53 (28.0)	11 (5.8)
Cough	Very Common	6 (5.5)	0 (0.0)	39 (14.6)	0 (0.0)	35 (18.5)	0 (0.0)
Dyspnoea [4,19]	Common	13 (11.9)	3 (2.8)	24 (9.0)	8 (3.0)	29 (15.3)	11 (5.8)
Productive cough	Common	1 (0.9)	0 (0.0)	11 (4.1)	1 (0.4)	5 (2.6)	0 (0.0)
Skin and subcutaneous tissue disorders	Very Common	22 (20.2)	0 (0.0)	38 (14.2)	2 (0.7)	35 (18.5)	4 (2.1)
Rash [15,19]	Very Common	22 (20.2)	0 (0.0)	38 (14.2)	2 (0.7)	35 (18.5)	4 (2.1)
Vascular disorders	Very Common	21 (19.3)	5 (4.6)	52 (19.5)	8 (3.0)	41 (21.7)	13 (6.9)
Hypotension [8,19]	Very Common	13 (11.9)	3 (2.8)	33 (12.4)	3 (1.1)	23 (12.2)	5 (2.6)
Hypertension [7,19]	Common	9 (8.3)	2 (1.8)	18 (6.7)	5 (1.9)	12 (6.3)	8 (4.2)
Flushing [19]	Common	1 (0.9)	0 (0.0)	6 (2.2)	0 (0.0)	9 (4.8)	0 (0.0)

CIOMS = Council for International Organizations of Medical Sciences; SOC = standard of care

The classification of CIOMS frequency is based on the cutoff percentages that were applied to adverse event incidence in the 'All Grades' column of the 'Blinatumomab' group in Study 00103311.

[1] Anaemia includes anaemia and hemoglobin decreased

[2] Chest pain includes Chest discomfort, Chest pain, Musculoskeletal chest pain, and Non-cardiac chest pain

[3] Decreased immunoglobulins includes Blood immunoglobulin G decreased, Globulins decreased, Hypogammaglobulinaemia, Hypoglobulinaemia, and Immunoglobulins decreased

[4] Dyspnoea includes Acute respiratory failure, Dyspnoea, Dyspnoea exertional, Respiratory failure, and Wheezing

[5] Hepatic enzyme increased includes lanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, and Transaminases increased

[6] Hyperbilirubinaemia includes Blood bilirubin increased and Hyperbilirubinaemia

[7] Hypertension includes Blood pressure increased and Hypertension

[8] Hypotension includes Blood pressure decreased and Hypotension

[9] Leukocytosis includes Leukocytosis and White blood cell count increased

[10] Leukopenia includes Leukopenia and White blood cell count decreased

[11] Lymphopenia includes Lymphocyte count decreased and Lymphopenia

[12] Neutropenia includes Neutropenia and Neutrophil count decreased

[13] Oedema includes Face oedema, Generalised oedema, Oedema, and Oedema peripheral

[14] Pyrexia includes Body temperature increased and Pyrexia

[15] Rash includes Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, and Rash pruritic

[16] Tachycardia includes Sinus tachycardia, Supraventricular tachycardia, and Tachycardia

[17] Thrombocytopenia includes Platelet count decreased and Thrombocytopenia

[18] Infusion-related reactions is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and event lasted ≤ 2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous

[19] These terms did not meet the above criteria but are added in the table because they are biologically plausible.

Grade ≥ 3 TEAE

The incidence of grade ≥ 3 TEAEs in the safety analysis set in ≥ 5% of subjects in either of treatment arms is presented in Table 35.

In the SOC chemotherapy arm, the most frequently reported grade ≥ 3 TEAE (subject incidence rate ≥ 5%) included: febrile neutropenia and anemia (34.9% for each); thrombocytopenia (27.5%); neutropenia (26.6%); platelet count decreased (11.9%); pneumonia, neutrophil count decreased, and hypokalaemia (10.1% for each); alanine aminotransferase (ALT) increased (8.3%); sepsis (6.5%), and hyperglycaemia (6.4%); white blood cell count (WBC) decreased and bacteraemia (5.5% for each); the most frequently reported grade 4 TEAE included neutropenia (20.2%), thrombocytopenia (21.1%), platelet count decreased (11.0%), neutrophil count decreased (10.1%), and WBC count decreased (5.5%).

In the blinatumomab arm, the most frequently reported grade ≥ 3 TEAE (subject incidence rate ≥ 5%) included: febrile neutropenia (21.3%); anemia (19.9%); neutropenia (17.6%); thrombocytopenia (14.6%); pyrexia (7.1%); ALT increased (5.6%); the most frequently reported grade 4 TEAE included thrombocytopenia (11.6%) and neutropenia (11.2%).

Table 35 Incidence of Grade ≥3 Treatment-emergent Adverse Events by Preferred Term that Occurred in ≥ 5% of Subjects (Safety Analysis Set) (Study 00103311)

Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Number of subjects with treatment-emergent adverse events	100 (91.7)	231 (86.5)
Febrile neutropenia	38 (34.9)	57 (21.3)
Anaemia	38 (34.9)	53 (19.9)
Neutropenia	29 (26.6)	47 (17.6)
Thrombocytopenia	30 (27.5)	39 (14.6)
Pyrexia	5 (4.6)	19 (7.1)
Alanine aminotransferase increased	9 (8.3)	15 (5.6)
Sepsis	7 (6.4)	13 (4.9)
White blood cell count decreased	6 (5.5)	12 (4.5)
Platelet count decreased	13 (11.9)	11 (4.1)
Pneumonia	11 (10.1)	11 (4.1)
Neutrophil count decreased	11 (10.1)	10 (3.7)
Hypokalaemia	11 (10.1)	9 (3.4)
Hyperglycaemia	7 (6.4)	8 (3.0)
Bacteraemia	6 (5.5)	2 (0.7)

Events of interest

Events of special interest for blinatumomab included central neuropsychiatric events due to direct neurotoxicities (neurologic events), CRS, infections, elevated liver enzymes, infusion reactions considering duration, TLS, acute pancreatitis, embolic and thrombotic events, medication errors and product use issues, cytopenias (including febrile neutropenia and neutropenia), lymphopenias, decreased immunoglobulins, and events suggestive of leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML]).

Neurologic Event

Treatment-emergent neurologic events and serious neurologic events were more frequently reported in the blinatumomab arm than in the SOC chemotherapy arm (61.0% vs 49.5%, 6.7% vs 1.8% respectively). One subject (0.4%) who was treated with blinatumomab had a fatal neurologic event preferred term (PT: completed suicide). More subjects interrupted or discontinued study treatment in blinatumomab arm than in SOC arm due to central neurologic events (0.9% vs 6.4%, 0.9% vs 3.7% respectively).

Table 36 Treatment-emergent Central Neuropsychiatric Event Rates Due to Direct Neurotoxicities and Exposure-adjusted Rates with a Subject Incidence ≥ 2% (Safety Analysis Set) Subject Incidence Rates Exposure-adjusted (Study 00103311)

	Subject Incidence Rates		Exposure-adjusted Rates	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109)	Blinatumomab (N = 267)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Central neuropsychiatric events due to direct Neurotoxicities	54 (49.5)	163 (61.0)	54 (110)/743.2	163 (420)/471.9
Headache	32 (29.4)	77 (28.8)	32 (39)/263.5	77 (101)/113.5
Insomnia	10 (9.2)	28 (10.5)	10 (12)/81.1	28 (38)/42.7
Tremor	0	26 (9.7)	0	26 (36)/40.4
Dizziness	8 (7.3)	18 (6.7)	8 (8)/54.1	18 (20)/22.5
Somnolence	1 (0.9)	14 (5.2)	1 (1)/6.8	14 (19)/21.3
Anxiety	6 (5.5)	13 (4.9)	6 (6)/40.5	13 (13)/14.6
Paraesthesia	1 (0.9)	13 (4.9)	1 (1)/6.8	13 (15)/16.9
Confusional state	3 (2.8)	9 (3.4)	3 (3)/20.3	9 (10)/11.2
Hypoaesthesia	0	7 (2.6)	0	7 (8)/9.0
Seizure	4 (3.7)	5 (1.9)	4 (4)/27.0	5 (5)/5.6
Agitation	4 (3.7)	3 (1.1)	4 (4)/27.0	3 (3)/3.4
Syncope	3 (2.8)	0	3 (4)/27.0	0

MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted rate per 100 subject years (n2*100/total exposure); SOC = standard of care
Note: Adverse events were coded according to MedDRA version 18.1. Subject incidence of ☐ 2% in either treatment arm was reported.
Exposure time for each individual subject was the date at first dose until the last dose plus 30 days or data cutoff date, whichever came first. The total exposure was the sum of exposure time across subjects. The units for

exposure-adjusted event rates are number of events per 100 subject years. Treatment-emergent adverse events occurred between date at first dose until the last dose plus 30 days or data cutoff date, whichever occurred first. Rows were sorted by preferred term in descending order of frequency in the blinatumomab arm.

Serious neurologic events for blinatumomab included encephalopathy (n=4), aphasia (n=3), and all other events occurred in 1 subject.

The median time to first onset of neurologic events was 7.0 days for both treatment arms; however, the mean (SD) time to first onset of neurologic events was earlier for SOC chemotherapy (11.4 [10.6] days) compared with blinatumomab (18.5 [29.0] days). The median time (range) to first onset of grade ≥ 3 neurologic events was also earlier for subjects who received SOC chemotherapy (12.0 days; 1 to 34 days) compared with subjects who received blinatumomab (18.0 days; 1 to 401 days). The duration of treatment-emergent direct neurotoxicities (neurologic events) is presented in Table 37.

Table 37Duration of Treatment-emergent Serious Central Neuropsychiatric Events Due to Direct Neurotoxicities (Safety Analysis Set) (Study 00103311)

	SOC Chemotherapy (N = 109)	Blinatumomab (N = 267)
Subjects with any Central Neuropsychiatric Events due to Direct Neurotoxicities – n (%)	54 (49.5)	163 (61.0)
Subjects with any resolved event – n (%)	41 (37.6)	143 (53.6)
Number of resolved events	82	339
Number of days experiencing resolved events (days)		
Mean (Standard Deviation)	19.0 (58.8)	24.7 (51.3)
Median (quartile 1, quartile 3)	5.0 (1.0, 18.0)	6.0 (2.0, 26.0)
Minimum, maximum	1, 380	1, 313
Subjects with any unresolved event – n (%)	22 (20.2)	58 (21.7)
Number of unresolved events	28	81
Subjects with grade ≥ 3 Central Neuropsychiatric Events due to Direct Neurotoxicities – n (%)	9 (8.3)	25 (9.4)
Subjects with any grade ≥ 3 resolved event – n (%)	7 (6.4)	19 (7.1)
Number of grade ≥ 3 resolved events	10	23
Number of days experiencing grade ≥ 3 resolved events (days)		
Mean (Standard Deviation)	4.4 (5.9)	9.7 (29.9)
Median (quartile 1, quartile 3)	1.0 (1.0, 9.0)	2.0 (2.0, 4.0)
Minimum, maximum	1, 16	1, 133
Subjects with any unresolved event – n (%)	4 (3.7)	9 (3.4)
Number of unresolved events	4	11

CTCAE: Common Technical Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory

Activities; SOC = standard of care

All neurologic events resolved for 32 of 54 subjects in SOC arm (59.3%; 32/54) and for 105 subjects of 163 subjects in the blinatumomab arm (64.4%; 105/163). The median time to resolution for any grade was 5.0 days (range: 1 to 380 days) and 6.0 days (1 to 313 days) for SOC chemotherapy and blinatumomab respectively.

Leukoencephalopathy (including progressive multifocal leukoencephalopathy [PML])

In the phase 3 study, events suggestive of leukoencephalopathy only occurred in 2 subjects (0.7%) who received blinatumomab. Both events (1 event reported as grade 4 leukoencephalopathy and 1 event reported as grade 3 PML) were serious and led to treatment discontinuation; however, neither event was fatal nor was the diagnosis of PML confirmed in either subject

Cytokine Release Syndrome (CRS)

CRS was specific to subjects who received blinatumomab (16.1%; 43 subjects), no case was reported in SOC chemotherapy arm.

The most frequently identified CRS event (preferred term) was CRS (38 subjects) followed by histiocytosis hematophagic (4 subjects) and cytokine storm (1 subject).

Serious CRS events occurred in 10 subjects (3.7%): 7 subjects experienced CRS and 3 subjects experienced histiocytosis hematophagic. Treatment was manageable, the cases were not fatal, and 1 subject resumed treatment.

Thirteen subjects (4.9%) experienced grade $\geq$ 3 CRS events and 1 subject (0.4%) experienced a grade 4 CRS event. CRS events led to treatment interruption for 13 subjects (4.9%) and treatment discontinuation for 3 subjects (1.1%).

The median time (range) to first onset of any CRS events was 2.0 days (1 to 254 days) and the median time to first onset of grade $\geq$ 3 CRS was 4.0 days (1 to 246 days).

Of 43 subjects experienced CRS in blinatumomab arm events, all events resolved for 39 subjects (90.7%; 39/43). The median time (range) to CRS resolution was 4.0 days (1 to 21 days).

Infections

More infections were reported in subjects receiving SOC chemotherapy than in the blinatumomab arm (72.5% vs 64.0%). Serious infections were similar between treatment arms (SOC chemotherapy 30.3% vs blinatumomab 28.1%). Fatal infections were also similar between 2 arms (SOC chemotherapy: 11.9% [13 subjects]; blinatumomab: 11.2% [30 subjects]). Infections leading to treatment interruptions were lower in SOC arm than in blinatumomab arm (1.8% vs 7.5%). Infections leading to treatment discontinuations were similar between treatment arms (SOC chemotherapy: 4.6%; blinatumomab: 3.4%).

The incidences of upper respiratory tract infection (0.9% vs 7.1%), nasopharyngitis (0.0% vs 4.9%), and urinary tract infection (1.8% vs 4.9%) were lower in SOC arm than in blinatumomab arm (>2% difference). All other identified infections were similar (< 2% difference) or lower for the blinatumomab arm compared with the SOC chemotherapy arm.

Table 38 Treatment-emergent Infections and Exposure-adjusted Rates by Preferred TermWith a Subject Incidence ≥ 2% (Safety Analysis Set) (Study 00103311)

	Subject Incidence Rates		Exposure-adjusted Rates	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Infections	79 (72.5)	171 (64.0)	79 (180)/1216.2	171 (388)/436.0
Upper respiratory tract infection	1 (0.9)	19 (7.1)	1 (1)/6.8	19 (27)/30.3
Device related infection	6 (5.5)	16 (6.0)	6 (6)/40.5	16 (20)/22.5
Pneumonia	16 (14.7)	16 (6.0)	16 (18)/121.6	16 (17)/19.1
Oral herpes	9 (8.3)	15 (5.6)	9 (10)/67.6	15 (16)/18.0
Sepsis	8 (7.3)	14 (5.2)	8 (10)/67.6	14 (15)/16.9
Nasopharyngitis	0	13 (4.9)	0	13 (15)/16.9
Urinary tract infection	2 (1.8)	13 (4.9)	2 (2)/13.5	13 (16)/18.0
Fungal infection	3 (2.8)	9 (3.4)	3 (3)/20.3	9 (9)/10.1
Septic shock	5 (4.6)	8 (3.0)	5 (5)/33.8	8 (8)/9.0
Bacterial sepsis	2 (1.8)	7 (2.6)	2 (2)/13.5	7 (8)/9.0
Conjunctivitis	1 (0.9)	7 (2.6)	1 (1)/6.8	7 (8)/9.0
Bronchopulmonary aspergillosis	1 (0.9)	6 (2.2)	1 (1)/6.8	6 (7)/7.9
Cellulitis	2 (1.8)	6 (2.2)	2 (3)/20.3	6 (6)/6.7
Herpes simplex	0	6 (2.2)	0	6 (7)/7.9
Herpes virus infection	1 (0.9)	6 (2.2)	1 (1)/6.8	6 (6)/6.7
Staphylococcal infection	2 (1.8)	6 (2.2)	2 (2)/13.5	6 (7)/7.9
Bacteraemia	9 (8.3)	5 (1.9)	9 (10)/67.6	5 (6)/6.7
Enterococcal bacteraemia	3 (2.8)	5 (1.9)	3 (3)/20.3	5 (5)/5.6
Oral candidiasis	5 (4.6)	5 (1.9)	5 (7)/47.3	5 (5)/5.6
Sinusitis	6 (5.5)	5 (1.9)	6 (6)/40.5	5 (7)/7.9
Candida infection	3 (2.8)	4 (1.5)	3 (3)/20.3	4 (4)/4.5
Folliculitis	4 (3.7)	4 (1.5)	4 (4)/27.0	4 (4)/4.5
Pneumonia fungal	3 (2.8)	1 (0.4)	3 (3)/20.3	1 (1)/1.1
Staphylococcal sepsis	3 (2.8)	1 (0.4)	3 (3)/20.3	1 (1)/1.1
Device related sepsis	3 (2.8)	1 (0.4)	3 (3)/20.3	1 (1)/1.1
Streptococcal bacteraemia	3 (2.8)	0	3 (3)/20.3	0

The incidences of serious pneumonia (1.8% in SOC vs 3.7% in blinatumomab) and serious device related infection (0.9% in SOC vs 2.2% in blinatumomab) were higher for blinatumomab than for SOC chemotherapy. All other identified infections were similar (< 1% difference) or lower for the blinatumomab arm compared with the SOC chemotherapy arm.

Table 39Treatment-emergent Serious Infections by Preferred Term With a Subject Incidence ≥ 1% (Safety Analysis Set) (Study 00103311)

Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Infections	33 (30.3)	75 (28.1)
Sepsis	7 (6.4)	13 (4.9)
Pneumonia	2 (1.8)	10 (3.7)
Septic shock	3 (2.8)	8 (3.0)
Bacterial sepsis	2 (1.8)	6 (2.2)
Device related infection	1 (0.9)	6 (2.2)
Bronchopulmonary aspergillosis	1 (0.9)	4 (1.5)
Neutropenic sepsis	1 (0.9)	3 (1.1)
Pseudomonal sepsis	1 (0.9)	3 (1.1)
Pseudomonas infection	1 (0.9)	3 (1.1)
Bacteraemia	3 (2.8)	2 (0.7)
Device related sepsis	2 (1.8)	1 (0.4)
Pneumonia fungal	2 (1.8)	1 (0.4)

Elevated liver enzymes

Similar incidences of elevated liver enzyme events were identified in subjects from both treatment arms: SOC chemotherapy, 24.8%; blinatumomab, 21.7%.

Serious elevated liver enzyme events (n=3) were identified exclusively in subjects who received blinatumomab: 2 subjects had blood bilirubin increased and 1 subject had transaminases increased. Grade ≥3 elevated liver enzyme events were similar between 2 arms (14.7% SOC, 12.7% blinatumomab).

No subjects in either treatment arm were identified with fatal liver enzyme events. Elevated liver enzyme events that led to treatment interruptions (1.5%; 4 subjects) and treatment discontinuations (0.4%; 1 subject) were identified in the blinatumomab arm with no interruptions or discontinuation reported in the SOC chemotherapy arm.

Transaminases increased (% difference: 3.7%) and hepatic enzyme increased (% difference: 2.1%) were higher in blinatumomab than in SOC arm. All other elevated liver enzyme events were similar (< 2% difference) or higher for the SOC chemotherapy arm compared with blinatumomab arm.

Table 40 Treatment-emergent Elevated Liver Enzyme Events and Exposure-adjusted Rates by Preferred Term (Safety Analysis Set) (Study 00103311)

	Subject Incidence Rates		Exposure-adjusted Rates	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 109) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Elevated liver enzyme	27 (24.8)	58 (21.7)	27 (102)/689.2	58 (176)/197.8
ALT increased	11 (10.1)	24 (9.0)	11 (35)/236.5	24 (46)/51.7
AST increased	10 (9.2)	15 (5.6)	10 (24)/162.2	15 (30)/33.7
GGT increased	4 (3.7)	12 (4.5)	4 (5)/33.8	12 (25)/28.1
Blood bilirubin increased	9 (8.3)	11 (4.1)	9 (23)/155.4	11 (21)/23.6
Transaminases increased	0	10 (3.7)	0	10 (12)/13.5
Hyperbilirubinaemia	2 (1.8)	9 (3.4)	2 (4)/27.0	9 (12)/13.5
Hepatic enzyme increased	1 (0.9)	8 (3.0)	1 (1)/6.8	8 (20)/22.5
Hepatosplenomegaly	1 (0.9)	6 (2.2)	1 (1)/6.8	6 (6)/6.7
Hepatic function abnormal	0	2 (0.7)	0	2 (2)/2.2
Ascites	3 (2.8)	1 (0.4)	3 (3)/20.3	1 (1)/1.1
Hepatomegaly	3 (2.8)	1 (0.4)	3 (3)/20.3	1 (1)/1.1
Liver function test abnormal	3 (2.8)	0	3 (3)/20.3	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted rate per 100 subject years (n2100/total exposure);

SOC = standard of care

Infusion reactions considering duration

The incidence of suggestive infusion reactions (ie events starts within 48h of infusion initiation with no duration restriction) was lower in the SOC chemotherapy arm (8.3%; n=9) compared with the blinatumomab arm (34.1%; n=91). Regardless of treatment, no subjects were identified with serious infusion reactions. No infusion reactions led to treatment discontinuation or were life-threatening (grade 4) or fatal.

Infusion reactions leading to treatment interruption were specific to 9 subjects (3.4%) who received blinatumomab.

Table 41Treatment-emergent Adverse Events Suggestive of InfusionReactions Considering Duration and Exposure-adjusted Rates by Preferred Term (Safety Analysis Set) (Study 00103311)

	Subject Incidence Rates		Exposure-adjusted Rates	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Infusion reaction considering duration	9 (8.3)	91 (34.1)	9 (11)/74.3	91 (119)/133.7
Pyrexia	7 (6.4)	73 (27.3)	7 (7)/47.3	73 (95)/106.7
Cytokine release syndrome	0	14 (5.2)	0	14 (15)/16.9
Hypotension	3 (2.8)	4 (1.5)	3 (3)/20.3	4 (4)/4.5
Myalgia	0	2 (0.7)	0	2 (2)/2.2
Acute kidney injury	0	1 (0.4)	0	1 (1)/1.1
Hypertension	1 (0.9)	1 (0.4)	1 (1)/6.8	1 (1)/1.1
Rash erythematous	0	1 (0.4)	0	1 (1)/1.1

Tumor Lysis Syndrome (TLS)

The subject incidence of TLS was 0.9% (1 subject) in the SOC chemotherapy arm and 3.7% (10 subjects) in the blinatumomab arm and all events were reported as the preferred term TLS.

Treatment-emergent serious TLS was identified exclusively for 3 subjects (1.1%) who received blinatumomab. Grade ≥3 treatment-emergent TLS was identified in 1 subject (0.9%) in the SOC chemotherapy arm and 8 subjects (3.0%) in the blinatumomab arm.

Regardless of treatment, no subjects were identified with fatal TLS.

Treatment-emergent TLS leading to treatment interruption and treatment discontinuation occurred in 1 subject each (0.4%) who received blinatumomab.

Acute pancreatitis

In the phase 3 study, treatment-emergent pancreatitis was reported for 2 subjects, 1 subject from each treatment arm. Both events were grade 3 in severity. For the subject who received SOC chemotherapy, the event was serious, led to treatment interruption, and was considered by the investigator as related to SOC chemotherapy.

Embolic and thrombotic events

The subject incidence rates for treatment-emergent embolic and thrombotic events were similar with SOC chemotherapy (8.3%) compared with blinatumomab (6.0%). Subjects who received SOC chemotherapy had subject incidence rates of serious, grade ≥ 3 and grade ≥ 4 embolic and thrombotic events of 1.8% (2 subjects) for each. Subjects who received blinatumomab had subject incidence rates of serious, grade

≥ 3, and grade ≥ 4 events of 1.1%, 1.5%, and 0.7%, respectively. One subject who received blinatumomab experienced a fatal embolic and thrombotic event of hemorrhagic stroke.

One subject each was identified with embolic and thrombotic events that led to treatment interruption (0.4%; 1 subject) or treatment discontinuation (0.4%; 1 subject) specific to the blinatumomab arm.

By preferred term, in the SOC chemotherapy arm, device occlusion was identified for 3 subjects (2.8%); all other embolic and thrombotic events were identified for 1 subject (0.9%) each. In the blinatumomab arm, 2 subjects each (0.7%) were identified with deep vein thrombosis, device occlusion, thrombosis, and transient ischemic attack; all other embolic and thrombotic events were identified for 1 subject each (0.4%).

Serious embolic and thrombotic events were identified for 2 subjects (1.8%) who received SOC chemotherapy including hemiplegia and peripheral artery thrombosis, and for 3 subjects (1.1%) who received blinatumomab including acute myocardial infarction, hemorrhagic stroke, and hemiparesis.

Table 42 Treatment-emergent Embolic and Thrombotic Events and Exposure-adjusted Rates by Preferred Terms (Safety Analysis Set) (Study 00103311)

	Subject Incidence Rates		Exposure-adjusted Rates	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Embolic and thrombotic events	9 (8.3)	16 (6.0)	9 (10)/67.6	16 (20)/22.5
Deep vein thrombosis	0	2 (0.7)	0	2 (2)/2.2
Device occlusion	3 (2.8)	2 (0.7)	3 (4)/27.0	2 (2)/2.2
Thrombosis	0	2 (0.7)	0	2 (2)/2.2
Transient ischaemic attack	0	2 (0.7)	0	2 (3)/3.4
Acute myocardial infarction	0	1 (0.4)	0	1 (1)/1.1
Cerebral ischaemia	0	1 (0.4)	0	1 (1)/1.1
Haemorrhagic stroke	0	1 (0.4)	0	1 (1)/1.1
Hemiparesis	1 (0.9)	1 (0.4)	1 (1)/6.8	1 (3)/3.4
Thrombophlebitis superficial	0	1 (0.4)	0	1 (1)/1.1
Thrombosis in device	0	1 (0.4)	0	1 (2)/2.2
Venous thrombosis	0	1 (0.4)	0	1 (1)/1.1
Venous thrombosis limb	0	1 (0.4)	0	1 (1)/1.1
Amaurosis	1 (0.9)	0	1 (1)/6.8	0
Embolism	1 (0.9)	0	1 (1)/6.8	0
Hemiplegia	1 (0.9)	0	1 (1)/6.8	0
Peripheral artery thrombosis	1 (0.9)	0	1 (1)/6.8	0
Thrombophlebitis	1 (0.9)	0	1 (1)/6.8	0

Medication errors and product use issues

For this study, a dose of > 10% higher than the intended blinatumomab dose was considered to be clinically important, reported as a serious adverse event, and categorized as “other medically important serious event” regardless of outcome (with or without associated adverse events).

All medication errors occurred exclusively in the blinatumomab arm, 12 subjects (4.5%) were identified with medication errors in which all were deemed serious events per protocol-specified requirements. Of the 12 subjects who experienced medications, 11 of these events involved blinatumomab administration and 1 event involved another chemotherapy agent. None of the 11 subjects who experienced

blinatumomab administration errors experienced other adverse events in temporal relation to the medication error. No medication errors were fatal or led to discontinuation.

Medication errors (preferred terms) included overdose (8 subjects; 3.0%), accidental overdose (3 subjects, 1.1%), and medication error (1 subject; 0.4%). Grade ≥ 3 medication errors included accidental overdose (3 subjects; 1.1%) and medication error (1 subject; 0.4%).

Cytopenias (including febrile neutropenia and neutropenia)

In the phase 3 study, the subject incidence rate of treatment-emergent cytopenia events was higher with SOC chemotherapy (72.5%) compared with blinatumomab (59.9%). Serious cytopenia events were similar between treatment arms: 15.6% with SOC chemotherapy; 12.7% with blinatumomab. Grade ≥ 3 and grade ≥ 4 treatment-emergent cytopenia events occurred at higher subject incidence rate with SOC chemotherapy (67.9% and 52.8%, respectively) compared with blinatumomab (45.9% and 28.8%, respectively). Cytopenias that led to interruptions or discontinuation were similar between SOC chemotherapy (2.8% and 3.0%, respectively) and blinatumomab arms (1.8% versus or 0.7%, respectively).

Four subjects (1.5%) had fatal cytopenia events in the blinatumomab arm (2 subjects experienced neutropenic sepsis, and 1 subject each experienced pancytopenia and febrile bone marrow aplasia), while no subjects in the SOC chemotherapy arm had fatal cytopenia events.

The subject incidences of all identified cytopenia events were higher or similar (< 2% difference) for the SOC chemotherapy arm compared with the blinatumomab arm.

Table 43 Treatment-emergent Cytopenia by Preferred Term (Safety Analysis Set) (Study 00103311)

	Treatment-emergent		Exposure-adjusted	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Cytopenia	79 (72.5)	160 (59.9)	79 (355) / 2398.6	160 (467) / 524.7
Febrile neutropenia	43 (39.4)	64 (24.0)	43 (54) / 364.9	64 (83) / 93.3
Neutropenia	33 (30.3)	53 (19.9)	33 (52) / 351.4	53 (108) / 121.3
Thrombocytopenia	32 (29.4)	47 (17.6)	32 (111) / 750.0	47 (112) / 125.8
Platelet count decreased	13 (11.9)	17 (6.4)	13 (73) / 493.2	17 (54) / 60.7
White blood cell count decreased	6 (5.5)	14 (5.2)	6 (12) / 81.1	14 (36) / 40.4
Leukopenia	5 (4.6)	10 (3.7)	5 (5) / 33.8	10 (30) / 33.7
Neutrophil count decreased	11 (10.1)	10 (3.7)	11 (28) / 189.2	10 (23) / 25.8
Pancytopenia	4 (3.7)	7 (2.6)	4 (4) / 27.0	7 (7) / 7.9
Lymphocyte count decreased	4 (3.7)	3 (1.1)	4 (8) / 54.1	3 (3) / 3.4
Neutropenic sepsis	2 (1.8)	3 (1.1)	2 (2) / 13.5	3 (3) / 3.4
Lymphopenia	0	2 (0.7)	0	2 (3) / 3.4
Bone marrow failure	0	1 (0.4)	0	1 (1) / 1.1
Cyclic neutropenia	0	1 (0.4)	0	1 (1) / 1.1
Cytopenia	0	1 (0.4)	0	1 (1) / 1.1
Febrile bone marrow aplasia	0	1 (0.4)	0	1 (1) / 1.1
Neutropenic infection	0	1 (0.4)	0	1 (1) / 1.1
Agranulocytosis	2 (1.8)	0	2 (3) / 20.3	0
Reticulocyte count decreased	1 (0.9)	0	1 (3) / 20.3	0

MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted rate per 100 subject years (n2*100/total exposure);
SOC = standard of care

Adverse events were coded according to MedDRA version 18.1.

Lymphopenia

A similar subject incidence of treatment-emergent lymphopenia was identified between treatment arms: 3.7% (4 subjects) in the SOC chemotherapy arm and 1.9% (5 subjects) in the blinatumomab arm. No subjects were identified with serious or fatal lymphopenia and no treatment-emergent events were identified that led to treatment interruption or treatment discontinuation. The incidence of identified treatment-emergent grade ≥ 3 and grade ≥ 4 lymphopenia was similar between treatment arms (SOC chemotherapy: grade ≥ 3 [3.7%], grade ≥ 4 [2.8%]; blinatumomab: grade ≥ 3 [1.5%], grade ≥ 4 [0.7%]).

Decreased immunoglobulins

In the phase 3 study, the subject incidence rates for decreased immunoglobulin events were lower with SOC chemotherapy (1.8%) compared with blinatumomab (9.7%) principally due to hypogammaglobulinemia (0.9% vs 6.0%). No decreased immunoglobulins events were deemed serious or were fatal in either treatment arm. Grade ≥ 3 events of decreased immunoglobulin events were only observed in blinatumomab arm (2.6%, 7 subjects), 1 of which was grade 4 in severity.

	Treatment-emergent		Exposure-adjusted	
Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Decreased immunoglobulins	2 (1.8)	26 (9.7)	2 (2)/13.5	26 (31)/34.8
Hypogammaglobulinaemia	1 (0.9)	16 (6.0)	1 (1)/6.8	16 (18)/20.2
Blood immunoglobulin G decreased	0	5 (1.9)	0	5 (7)/7.9
Immunoglobulins decreased	1 (0.9)	4 (1.5)	1 (1)/6.8	4 (4)/4.5
Globulins decreased	0	1 (0.4)	0	1 (1)/1.1
Hypoglobulinaemia	0	1 (0.4)	0	1 (1)/1.1

MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted rate per 100 subject years (n2*100/total exposure);

SOC = standard of care

Table 44 Grade ≥ 3 Treatment-emergent Decreased Immunoglobulin Events (Safety Analysis Set) (Study 00103311)

Event of Interest Category Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Decreased immunoglobulins	0	7 (2.6)
Hypogammaglobulinaemia	0	5 (1.9)
Blood immunoglobulin G decreased	0	1 (0.4)
Immunoglobulins decreased	0	1 (0.4)

Vital Signs, Physical Findings, and Other Observations Related to Safety

Table 45 Abnormal Changes in Vital Signs (Safety Analysis Set)

Vital Signs	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Pulse rate		
> 120 bpm	13 (11.9)	35 (13.1)
< 50 bpm	2 (1.8)	3 (1.1)
Systolic blood pressure		
≥ 160 mmHg	4 (3.7)	19 (7.1)
≤ 90 mmHg	16 (14.7)	42 (15.7)
Diastolic blood pressure		
≥ 105 mmHg	2 (1.8)	5 (1.9)
≤ 50 mmHg	10 (9.2)	46 (17.2)
Weight		
Decrease ≥ 10% from baseline	9 (8.3)	13 (4.9)
Increase ≥ 10% from baseline	1 (0.9)	30 (11.2)
Body temperature		
> 39°C	2 (1.8)	29 (10.9)

In the phase 3 study, blood pressure was the most frequently reported abnormal vital sign change. In subjects who received SOC chemotherapy, the most frequent change was low systolic blood pressure (≤ 90 mmHg; 14.7%); whereas, in subjects who received blinatumomab, the most frequent change was low diastolic blood pressure (≤ 50 mmHg; 17.2%).

In the phase 3 study, there is no evidence of increased risk associated vital sign changes from baseline for subjects who received blinatumomab compared with subjects who received SOC chemotherapy. Changes in vital signs observed for blinatumomab in the phase 3 study are consistent with those observed in the phase 2 study.

Serious adverse events and death

Treatment-emergent SAE

The incidence of SAEs (regardless of relationship to study treatment) was higher in blinatumomab arm than in SOC chemotherapy arm (61.8%, 165/267 versus 45.0%, 49/109) (Table 12-4). In both arms, the most affected system organ class was “Infections and Infestations” (30.3%, 33/109 in SOC vs 28.1% 75/267 blinatumomab arm). The most frequent SAE events in the SOC chemotherapy treatment arm were febrile neutropenia (11.0%; 12/109), sepsis (6.4%; 7/109), and septic shock (2.8%; 3/109); whereas, in the blinatumomab arm they were febrile neutropenia (8.6%; 23/267), pyrexia (6.0%; 16/267), and sepsis (4.9%; 13/267).

As compared to SOC arm, SAEs in “General disorders and administration site conditions” (1.8% vs 10.1%), “Nervous system disorders” (3.7% vs 7.1%), “Injury, poisoning and procedural complications” (0.9% vs 5.6%), Immune system disorders (0.0% vs 4.1%) were more frequently reported in subjects receiving blinatumomab.

Table 46 Incidence of Treatment-emergent Serious Adverse Events in ≥ 2% of Subjects and Exposure-Adjusted Rates (Safety Analysis Set)

	Subject Incidence Rates		Exposure-Adjusted Rates	
Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)	SOC Chemotherapy (N = 109) n1 (n2)/r	Blinatumomab (N = 267) n1 (n2)/r
Total exposure in years	Not applicable	Not applicable	14.8	89.0
Number of subjects with treatment-emergent serious adverse events	49 (45.0)	165 (61.8)	49 (95/641.9)	165 (311)/349.4
Febrile neutropenia	12 (11.0)	23 (8.6)	12 (12)/81.1	23 (28)/31.5
Pyrexia	1 (0.9)	16 (6.0)	1 (1)/6.8	16 (20)/22.5
Sepsis	7 (6.4)	13 (4.9)	7 (9)/60.8	13 (13)/14.6
Pneumonia	2 (1.8)	10 (3.7)	2 (2)/13.5	10 (10)/11.2
Overdose	0	8 (3.0)	0	8 (8)/9.0
Septic shock	3 (2.8)	8 (3.0)	3 (3)/20.3	8 (8)/9.0
Cytokine release syndrome	0	7 (2.6)	0	7 (7)/7.9
Bacterial sepsis	2 (1.8)	6 (2.2)	2 (2)/13.5	6 (6)/6.7
Device related infection	1 (0.9)	6 (2.2)	1 (1)/6.8	6 (8)/9.0
Bacteraemia	3 (2.8)	2 (0.7)	3 (3)/20.3	2 (2)/2.2

MedDRA = Medical Dictionary for Regulatory Activities; n1 = number of subjects with event; n2 = number of events reported; r = exposure-adjusted event rate per 100 subject years (n2*100/total exposure);

SOC = standard of care

Deaths

In the phase 3 study, a total of 19 subjects (17.4%) in the SOC chemotherapy arm and 51 subjects (19.1%) in the blinatumomab arm had fatal TEAE. For both arm, Infections and Infestations was the most affected system organ class (SOC chemotherapy: 11.9%; blinatumomab: 11.2%), principally due to fatal sepsis (SOC chemotherapy: 3.7%; blinatumomab: 3.0%).

In this open label study, fatal TEAE were considered related to study drug by investigators for 7.3% (8/109) of subjects in the SOC treatment arm and 3.0% (8/267) of subjects in the blinatumomab treatment arm. In the blinatumomab arm, 7 of the 8 deaths were in the setting of severe infections and 1 death was reported as respiratory failure, in an unspecified setting as limited information was provided on treatments administered, imaging, or blood culture results. Although the deaths were deemed related

to blinatumomab, infectious deaths occurring in the setting of active disease would not be unexpected in this patient population, regardless of the administration of blinatumomab. Similarly in the SOC chemotherapy arm, 7 of the 8 deaths deemed related to the SOC chemotherapy arm were attributed to infections and occurred in the setting of active disease. The remaining death was reported as acute kidney injury, with limited information provided.

Table 47 Treatment-emergent Fatal Adverse Events by System Organ Classand PreferredTerm (Safety Analysis Set)

System Organ Class Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Number of subjects with treatment-emergent fatal adverse events	19 (17.4)	51 (19.1)
Blood and lymphatic system disorders	0	3 (1.1)
Febrile bone marrow aplasia	0	1 (0.4)
Leukocytosis	0	1 (0.4)
Pancytopenia	0	1 (0.4)
Cardiac disorders	1 (0.9)	2 (0.7)
Cardiac arrest	0	1 (0.4)
Cardiopulmonary failure	0	1 (0.4)
Cardiac tamponade	1 (0.9)	0
General disorders and administration site conditions	0	5 (1.9)
Multi-organ failure	0	3 (1.1)
Death	0	1 (0.4)
General physical health deterioration	0	1 (0.4)
Infections and infestations	13 (11.9)	30 (11.2)
Sepsis	4 (3.7)	8 (3.0)
Septic shock	0	6 (2.2)
Bacterial sepsis	0	2 (0.7)
Bronchopulmonary aspergillosis	0	2 (0.7)
Fungal sepsis	0	2 (0.7)
Neutropenic sepsis	0	2 (0.7)
Pneumonia	1 (0.9)	2 (0.7)
Bacterial infection	0	1 (0.4)
Infection in an immunocompromised host	0	1 (0.4)
Lower respiratory tract infection	0	1 (0.4)
Lung infection	0	1 (0.4)
Mucomycosis	0	1 (0.4)
Sepsis syndrome	0	1 (0.4)
Bacteraemia	2 (1.8)	0

System Organ Class Preferred Term	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
Brain abscess	1 (0.9)	0
Enterococcal infection	1 (0.9)	0
Fusarium infection	1 (0.9)	0
Pneumonia fungal	1 (0.9)	0
Pseudomonas infection	1 (0.9)	0
Systemic candida	1 (0.9)	0
Metabolism and nutrition disorders	1 (0.9)	0
Metabolic acidosis	1 (0.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.7)
Acute lymphocytic leukaemia	0	1 (0.4)
Leukaemic infiltration extramedullary	0	1 (0.4)
Nervous system disorders	1 (0.9)	2 (0.7)
Cerebral haemorrhage	0	1 (0.4)
Haemorrhagic stroke	0	1 (0.4)
Haemorrhage intracranial	1 (0.9)	0
Psychiatric disorders	0	1 (0.4)
Completed suicide	0	1 (0.4)
Renal and urinary disorders	1 (0.9)	1 (0.4)
Acute kidney injury	1 (0.9)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	2 (1.8)	5 (1.9)
Acute respiratory failure	0	2 (0.7)
Pneumonitis	0	1 (0.4)
Respiratory arrest	0	1 (0.4)
Respiratory failure	2 (1.8)	1 (0.4)

CTCAE = Common Technical Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = standard of care

Laboratory findings

In the phase 3 study, shifts from grade 0 or 1 to grade 4 were noted in serum chemistry parameters in subjects from both treatment arms. The shifts in serum hematology parameters occurred at a higher subject incidence rate for subjects who received SOC chemotherapy compared with subjects who received blinatumomab. For subjects who received SOC chemotherapy, the highest number of shifts from grade 0 or 1 to grade 4 occurred in lymphocytes (60 subjects; 55.0%), WBC count (35 subjects; 32.1%), and platelets (34 subjects; 31.2%); whereas, in subjects who received blinatumomab the highest number of shifts occurred in WBC count (73 subjects; 27.3%), neutrophils (56 subjects; 21.0%), and lymphocytes (46 subjects; 17.2%). Median decreases in immunoglobulin levels from baseline to cycle 1 and cycle 2 were less pronounced with SOC chemotherapy compared with blinatumomab treatment

(-0.30 and -1.13 versus -1.35 and -2.25, respectively); a response that has been reported previously for blinatumomab (Zugmaier et al, 2014).

In the phase 3 study, there is no evidence of increased risk associated with serum chemistry or hematology changes from baseline for subjects who received blinatumomab compared with subjects who received SOC chemotherapy. The types and frequencies of serum chemistry and hematology changes from baseline, and decreased immunoglobulins observed in the phase 3 study for blinatumomab were consistent with those observed in the phase 2 study.

Safety in special population

A summary of TEAE by race, sex, and age in the safety analysis set are presented in Table 48.

Table 48 Treatment-emergent Adverse Events by Race, Sex, and Age (Safety Analysis Set)

Treatment-emergent Adverse Events	SOC Chemotherapy (N = 109) n (%)	Blinatumomab (N = 267) n (%)
All events	108 (99.1)	263 (98.5)
Race		
White	90 (100.0)	222 (98.2)
Non-white	18 (94.7)	41 (100.0)
Sex		
Male	63 (98.4)	156 (98.1)
Female	45 (100.0)	107 (99.1)
Age in years		
< 35	49 (98.0)	124 (100.0)
35 to 54	25 (100.0)	76 (98.7)
55 to 64	22 (100.0)	32 (97.0)
≥ 65	12 (100.0)	31 (93.9)

SOC = standard of care

Immunological events

In the phase 3 study, subjects who were randomized to blinatumomab were tested for anti-blinatumomab antibodies before the first dose of blinatumomab on day 1 of cycle 1, on day 29 of cycle 2, and at the safety follow-up visit.

At the time of the data cutoff data, data for immunogenicity were available for 247 subjects. Of these 247 subjects, 4 subjects (1.6%) who received blinatumomab tested positive for anti-blinatumomab antibodies: 1 subject tested positive for binding antibodies, 2 subjects tested positive for both binding and neutralizing antibodies and 1 subject had no results for the binding antibody, but tested positive for

neutralizing antibody. Review of the hematologic response in these 4 subjects showed that 3 subjects achieved a CR and 1 developed progressive disease. No conclusions can be made from these data.

According to information in "Anti-Blinatumomab Antibody Assays Report", valid results of paired samples from pre-dose and post-dose were available for 171 patients. In 5 of these patients (2.9%) anti-blinatumomab immune response was detected in serum after at least 2 treatments respectively but still in low levels (titer ranged from < 10 to 21870). Using the blinatumomab neutralizing assay it could be demonstrated that the ADAs had neutralizing effects on the bioactivity of blinatumomab (except in two patients but this is likely resulted from the poorer sensitivity of the Nab assay). Two patients who showed very low titers at time point C2D29 (<10) were classified as negative for the presence of ADAs at SFU. Thus, in the context of clinical study 00103311, blinatumomab has been shown to cause the formation of anti-drug-antibodies in 2.9% of patients treated with blinatumomab and analyzed in this immunogenicity study.

Interruption/Discontinuation due to AES

Regardless of treatment, a treatment interruption was defined as lasting more than 7 days, but less than 14 days. Treatment restarted within the same cycle in subjects who had interruptions less than 7 days in length. Treatment was discontinued in subjects who had an interruption more than 14 days in length.

AE leading to treatment interruption

TEAE leading to treatment interruption regardless of relationship were reported in 5.5% (6/109) of subjects receiving SOC chemotherapy and 32.2% (86/267) of subjects receiving blinatumomab.

Two highest subject incidence of TEAE leading to SOC chemotherapy interruption was in Blood and Lymphatic System Disorders and Gastrointestinal Disorders (2.8%; 3/109 each) in SOC arm; and in Infections and Infestations (7.5%; 20/267), Nervous system disorders and General disorders and administration site conditions (7.1%, 19/267 each) for blinatumomab. By preferred term, in the SOC chemotherapy arm, only febrile neutropenia led to treatment interruption in more than 1 subjects (n=2). In the blinatumomab arm, TEAE that led to blinatumomab interruption in ≥ 3 subjects were CRS (4.1%; 11/267), pyrexia (3.0%, 8/267), neutropenia (1.9%, 5/267), device-related infection (1.5%; 4/267), as well as seizure, somnolence, tremor and confusional state (1.1%, 3/267 each).

SAE leading to treatment interruption were reported in 3.7% (4/109) of subjects receiving SOC chemotherapy and 19.5% (52/267) of subjects receiving blinatumomab. In SOC arm, serious febrile neutropenia (n=2) was the only SAE leading to SOC chemotherapy interruption in more than 1 subjects. In blinatumomab arm, SAE leading to blinatumomab interruption in ≥ 2 subjects were CRS (2.2%; 6/267), pyrexia (1.1%; 3/267) as well as encephalopathy, Bacterial infection, Bacterial sepsis, Escherichia infection and Pneumonia (0.7%, 2/267 each).

AE leading to treatment discontinuation

TEAE leading to treatment discontinuation regardless of relationship were reported in 8.3% (9/109) of subjects receiving SOC chemotherapy and 12.4% (33/267) of subjects receiving blinatumomab. Two highest rates of TEAE leading to blinatumomab discontinuation were in Infections and Infestations (3.4%, 9/267) and Nervous system disorders (3.0%, 8/267).

SAE leading to discontinuation were reported in 6.4% (7/109) in SOC chemotherapy arm. They were reported in 10.5% (28/267) for blinatumomab principally due to Infections and Infestations (3.0%, 8/267) and Nervous system disorders (1.9%, 5/267).

Discussion on clinical safety

TEAE were collected from the first dose of study treatment until 30 days after the last dose or the safety follow-up visit. In this open label study, the causal relationship (ie, related, unrelated) between an AE and study treatments was based on investigator's judgment.

As of the data cutoff date of 4 January 2016, 108/109 subjects (99.1%) in the SOC chemotherapy treatment arm and 263/267 subjects (98.5%) in the blinatumomab treatment arm had experienced at least 1 TEAE. Patients receiving blinatumomab experienced more SAE (45.0% in SOC arm vs 61.8% in blinatumomab arm), events that led to treatment interruption and discontinuation (5.5% and 3.7% in SOC arm, vs 32.2% and 12.4% in blinatumomab arm respectively) than in SOC chemotherapy arm. TEAE of grade ≥ 3 in severity, life-threatening and fatal AE were similar between treatment arms. Fatal TEAE were reported for 19 subjects (17.4%) in the SOC chemotherapy arm and 51 subjects (19.1%) in blinatumomab arm.

In the SOC chemotherapy arm, the TEAE with the highest subject incidence were pyrexia (45.0%; 49/109), anemia (42.2%; 46/109), nausea (42.2%; 46/109) and febrile neutropenia (39.4%, 43/109).

In the blinatumomab arm, the TEAE with the highest subject incidence were pyrexia (59.6%; 159/267), headache (28.8%; 77/267), anemia (25.8%; 69/267) and febrile neutropenia (24.0%, 64/267).

Of common all-causality TEAE, following events were reported more often (≥5% difference) for blinatumomab compared to SOC chemotherapy: pyrexia (59.6% vs 45.0%), cough (14.6% vs 5.5%), CRS (14.2% vs 0), tremor (9.7% vs 0.0%), upper respiratory tract infection (7.1% vs 0.9%).

Events of special interest for blinatumomab included central neuropsychiatric events due to direct neurotoxicities (neurologic events), CRS, infections, elevated liver enzymes, infusion reactions considering duration, TLS, 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]).Compared to SOC chemotherapy arm, subjects receiving blinatumomab experienced higher incidence of central neuropsychiatric events (49.5% vs 61.0%), CRS (0.0% vs 16.1%), infusion reaction (8.3% vs 34.1%), medical errors (0.0% vs 4.5%), TLS (0.9% vs 3.7%), decreased immunoglobulin (1.8% vs 9.7%).and progressive multifocal leukoencephalopathy (0.0% vs (n=2) 0.7%). Infections, elevated liver enzyme, embolic/thrombotic events and cytopenia were more frequent in SOC chemotherapy arm then in blinatumomab.

All these events are already included in the current SmPC. These EOI are also included in the RMP and subjects to additional risk minimization measures in the post-marketing setting, including educational materials for physicians, nurses and patients.

Based on the safety data from Study 00103311, no new ADRs have been identified and the safety and tolerability of blinatumomab remains favorable in the approved indication. The SmPC section 4.4 has been updated to include further information on the neurologic events and section 4.8 has been updated with the pooled safety data.

In addition to investigating the long-term effects of HSCT in the target population and to collect as complete survival data as possible for the Phase 3 study 00103311 (Tower), the CHMP also considered that the ongoing studies in first line B-ALL and B-precursor paediatric ALL are of great interest to assess the B/R of blinatumomab and its real place in related to HSCT in the management of childhood ALL (COG-AALL1331) and the direct benefit (OS) of chemotherapy combined with blinatumomab among MRD-positive subjects following front-line therapy (ECOG-E1910).

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 22 November 2017 to provide advice on the following question:

After treatment with Blincyto, HSCT (which is normally the only potentially curative option) appears as negatively impacting outcomes (OS and RFS). Please discuss the target population for Blincyto, in particular if you foresee that the target population would be limited to patients never eligible to HSCT? If so, would you consider that this population is possible to define prospectively, before treatment?

The SAG experts concluded that for relapsed/refractory disease, the target population corresponds to the population treated in the prospective, randomized, phase 3 trial (TOWER) including patients with Ph-negative B-cell precursor ALL refractory to primary induction therapy or to salvage with intensive combination chemotherapy, first relapse with the first remission lasting less than 12 months, second or greater relapse, or relapse at any time after allogeneic stem-cell transplantation. Longer follow-up should be requested post-approval to confirm in secondary (exploratory) analyses the long term efficacy and assess if a long-term benefit can be established or if the effect on OS is mainly transient. It is acknowledged that due to cross-over, treatment switching and other uncontrolled events the effect currently observed may be diluted in the long-term, but this can be explored using statistical techniques.

Conclusion on clinical safety

Overall, based on the safety data from Study 00103311, no new ADRs have been identified and the safety and tolerability of blinatumomab remains favorable in the approved indication. The SmPC section 4.4 has been updated to include further information on the neurologic events and section 4.8 has been updated with the pooled safety data.

To further characterize the safety in the subgroup of patients undergoing HSCT after blinatumumab, the CHMP requested the MAH to evaluate the safety of patients post-HSCT in registries as well as prospectively in a study comparing blinatumumab vs SOC chemotherapy and in ongoing studies in childhood ALL (see RMP).

4.3. Risk Management Plan

Safety concerns

Table 49 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)
Missing information	Use in pregnancy and breastfeeding
	Use in pediatric and adolescent patients
	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

Pharmacovigilance plan

Table 50 Table of On-Going and Planned Additional PhV 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 leukemia (ALL) Category 3	• To evaluate CNS symptoms and explore potential predictive factors for CNS events associated with blinatumomab	Neurologic events	Ongoing	Final CSR: June 2018
Study MT103-205: A phase 1/2, single-arm, dose finding/efficacy study in patients < 18 years with B precursor ALL in second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments; > 25% blasts in bone marrow Category 3	• To determine the recommended phase 2 dose of blinatumomab • To assess the efficacy of blinatumomab	Pediatric patients	Ongoing	Primary CSR: 15 December 2015
Study 00103311 (TOWER): A phase 3, randomized, open-label study investigating the efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ALL) Category 3	Primary • To evaluate the effect of blinatumomab on OS when compared to standard of care chemotherapy	All important identified risks, selected important potential risks, and missing information of long-term safety and efficacy	Ongoing	Primary analysis report: Q1 2017

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
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	Pediatric patients	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 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	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

	practice			
Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
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 2018
Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Study 20170610: Overall survival and incidence of transplant-related adverse events in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients after allogeneic stem cell transplant: Induction with blinatumomab treatment versus induction with chemotherapy Category 3	Primary objective: • To generate data on HSCT for patients with ALL, such as the type of HSCT, source of HSC, donor-type, preparative regimen, functional status, and ALL disease characteristics.	Long-term safety and efficacy	Planned	Final Protocol: Q2 2019 Interim CSR: Q2 2022 Final CSR: Q2 2025

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

Table 51 Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Neurologic events	SmPC section: 4.2 4.4, 4.7, 4.8, PIL: Section 2, Section 4	Educational materials for physicians, nurses, and patients (including caregivers) (Annex 10).
Infections	SmPC section: 4.4, 4.8, PIL:Section 2, Section 3, Section 4.	None
Cytokine release syndrome	SmPC section: 4.2, 4.4, 4.5, 4.8, 5.1, Section 5.3, PIL: Section 4,	None
Infusion reactions	SmPC section: 4.4, 4.8. PIL: Section 2, Section 3.	None
Tumor lysis syndrome	SmPC section: 4.2, 4.4, 4.8. PIL: Section 2, Section 4,	None
Capillary leak syndrome	SmPC section: 4.4, 4.8. PIL: Section 4.	None
Elevated liver enzymes	SmPC section: 4.2, 4.4, 4.8. 5.2. PIL: Section 2, Section 4.	None
Medication errors	SmPC section: 4.4, 4.9, 6.6.	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 10).
Febrile neutropenia and neutropenia	SmPC section: 4.4, 4.8. PIL: Section 2, Section 4.	None
Decreased immunoglobulin	SmPC section: 4.8. PIL: Section 4.	None
Pancreatitis	SmPC section: 4.4, 4.8. PL: Section 2, Section 4.	A DHPC was distributed to communicate the changes to the prescribing information.
Important Potential Risk		
Off-label use	SmPC section:4.1, 5.1.	None
Leukoencephalopathy (including PML)	SmPC section: 4.4, 4.8. PIL: Section 4.	None
Thromboembolic events (including disseminated intravascular coagulation)	SmPC section: Section 4.4.	None
Immunogenicity	SmPC section: Section 4.8.	None
Worsening of hepatic impairment in patients with hepatic impairment	SmPC section: 4.2, 5.2.	None
Use in patients with active or a history of high risk CNS pathology including patients with untreated ALL in CNS	SmPC section: 4.2, 4.4.	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)	SmPC section: 4.4, 4.6.	None
Missing information		

Use in pregnancy and breastfeeding	SmPC section: 4.3, 4.4, 4.6. PIL: Section 2.	None
Use in pediatric and adolescent patients	SmPC section: 4.2, 4.8, 5.1, 5.2, PIL: Section 2.	None
Use in elderly	SmPC section: 4.2, 4.4 4.8, 5.1.	None
Use in patients with renal impairments	SmPC section: 4.2, 4.4 4.8, 5.2.	None
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	SmPC section: 4.4.	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	SmPC section: 4.6.	None
Long-term safety and efficacy	No risk minimization activities are proposed.	None

Conclusion

Risk Management Plan version 7.1 is considered acceptable.