1. NAME OF THE MEDICINAL PRODUCT

BLINCYTO 38.5 micrograms powder for concentrate and solution for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 38.5 micrograms blinatumomab.

Reconstitution with water for injections results in a final blinatumomab concentration of 12.5 micrograms/mL.

Blinatumomab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate and solution for solution for infusion.

BLINCYTO powder (powder for concentrate): White to off-white powder.

Solution (stabilizer): Colorless-to-slightly yellow, clear solution with a pH of 7.0.

4. CLINICAL PARTICULARS

Prescriber guide
This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

Patient safety information materials: BLINCYTO Patient Alert Card and BLINCYTO Guide for Patients and Caregivers
This product is marketed with patient safety information materials (patient card and patient guide). Please explain to the patient the implications of this treatment including the need for compliance. Please also explain the signs of important adverse reactions and instruct the patient when to seek medical care.

4.1 Therapeutic indications

BLINCYTO is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

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

BLINCYTO is indicated as monotherapy for the treatment of pediatric patients aged 1 year or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

BLINCYTO is indicated as monotherapy for the treatment of pediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy (see section 4.2).

Limitations of use:
After failure of two previous treatments and with no CNS involvement.

4.2 Posology and method of administration

Treatment should be initiated under the direction of and supervised by physicians experienced in the treatment of hematological malignancies. Patients treated with BLINCYTO should be given the Educational Brochure for Patients and Caregivers and the Patient Card.

For the treatment of relapsed or refractory B-cell precursor ALL, hospitalization is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.

For the treatment of Philadelphia chromosome-negative MRD positive B-cell precursor ALL, hospitalization is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of subsequent cycles.

For pediatric patients with high-risk first relapsed B-cell precursor ALL, hospitalization is recommended at a minimum for the first 3 days of the cycle.

In patients with a history or presence of clinically relevant central nervous system (CNS) pathology (see section 4.4), hospitalization is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalization is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to BLINCYTO in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events have been observed.

For all subsequent cycle starts and reinitiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

Posology

Relapsed or refractory B-cell precursor ALL

Patients with relapsed or refractory B-cell precursor ALL, may receive 2 cycles of treatment. A single cycle of treatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14-day (2 weeks) treatment-free interval.

Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO consolidation treatment, based on an individual benefits-risks assessment.

Recommended daily dose is by body weight (see table 1). Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient’s body surface area (BSA).

Table 1. BLINCYTO recommended dosage for relapsed or refractory B-cell precursor ALL

Body weight	**Cycle 1**			**Subsequent cycles**	
	Days 1-7	**Days 8-28**	**Days 29-42**	**Days 1-28**	**Days 29-42**
Greater than or equal to 45 kg *(fixed-dose)*	9 mcg/day via continuous infusion	28 mcg/day via continuous infusion	14-day treatment-free interval	28 mcg/day via continuous infusion	14-day treatment-free interval
Less than 45 kg *(BSA-based dose)*	5 mcg/m^2/day via continuous infusion *(not to exceed 9 mcg/day)*	15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*		15 mcg/m^2/day via continuous infusion *(not to exceed 28 mcg/day)*	

High-risk first relapsed B-cell precursor ALL

Pediatric patients with high-risk first relapsed B-cell precursor ALL may receive 1 cycle of BLINCYTO treatment after induction and 2 blocks of consolidation chemotherapy. A single cycle of treatment is 28 days (4 weeks) of continuous infusion. See table 2 for the recommended daily dose by body weight for pediatric patients.

Table 2. BLINCYTO recommended dosage for pediatric patients with high-risk first relapsed B-cell precursor ALL post-induction chemotherapy

One consolidation cycle	**Body weight greater than or equal to 45 kg *(fixed-dose)***	**Body weight less than 45 kg *(BSA-based dose)***
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*

Premedication and additional medication recommendations

In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

In pediatric patients, dexamethasone 10 mg/m^2 (not to exceed 20 mg) should be administered orally or intravenously 6 to 12 hours prior to the start of BLINCYTO (cycle 1, day 1). This should be followed by dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes prior to the start of BLINCYTO (cycle 1, day 1).

Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle.

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.

Pre-phase treatment for patients with high tumor burden

For patients with ≥ 50% leukemic blasts in bone marrow or > 15,000/microliter peripheral blood leukemic blast counts treat with dexamethasone (not to exceed 24 mg/day).

MRD positive B-cell precursor ALL

When considering the use of BLINCYTO as a treatment for Philadelphia chromosome-negative MRD positive B-cell precursor ALL, quantifiable MRD should be confirmed in a validated assay with minimum sensitivity of 10^{-4} (see section 5.1). Clinical testing of MRD, regardless of the choice of technique, should be performed by a qualified laboratory familiar with the technique, following well established technical guidelines.

Patients may receive 1 cycle of induction treatment followed by up to 3 additional cycles of BLINCYTO consolidation treatment. A single cycle of treatment of BLINCYTO induction or consolidation is 28 days (4 weeks) of continuous intravenous infusion followed by a 14-day (2 weeks) treatment-free interval (total 42 days). The majority of patients who respond to blinatumomab achieve a response after 1 cycle (see section 5.1). Therefore, the potential benefit and risks associated with continued therapy in patients who do not show hematological and/or clinical improvement after 1 treatment cycle should be assessed by the treating physician.

Recommended dose (for patients at least 45 kg in weight):

Treatment cycle(s)	
Induction Cycle 1	
Days 1-28	**Days 29-42**
28 mcg/day	14-day treatment-free interval
Consolidation Cycles 2-4	
Days 1-28	**Days 29-42**
28 mcg/day	14-day treatment-free interval

Premedication and additional medication recommendations

Prednisone 100 mg intravenously or equivalent (e.g. dexamethasone 16 mg) should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle.

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.

Dose adjustments

For patients with relapsed or refractory B-cell precursor ALL and patients with Philadelphia chromosome-negative MRD positive B-cell precursor ALL receiving BLINCYTO, consideration to discontinue BLINCYTO temporarily or permanently as appropriate should be made in the case of the following severe (grade 3) or life-threatening (grade 4) toxicities (see section 4.4): cytokine release syndrome, tumor lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities.

If the interruption of treatment after an adverse reaction is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse reaction is longer than 7 days, start a new cycle. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently, except if described differently in the table below.

Toxicity	Grade*	Action for patients greater than or equal to 45 kg	Action for patients less than 45 kg
Cytokine release syndrome, Tumor lysis syndrome	Grade 3	Interrupt BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Interrupt BLINCYTO until resolved, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue BLINCYTO permanently.	Discontinue BLINCYTO permanently.
Neurological toxicity	Convulsion	Discontinue BLINCYTO permanently if more than one convulsion occurs.	Discontinue BLINCYTO permanently if more than one convulsion occurs.
	Grade 3	Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with a 24 mg dose of dexamethasone. Then reduce dexamethasone step-wise over 4 days. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.	Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Discontinue BLINCYTO permanently.	Discontinue BLINCYTO permanently.
Elevated liver enzymes	Grade 3	If clinically relevant, interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	If clinically relevant, interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Consider discontinuing BLINCYTO permanently.	Consider discontinuing BLINCYTO permanently.
Other clinically relevant (as determined by treating physician) adverse reactions	Grade 3	Interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur.
	Grade 4	Consider discontinuing BLINCYTO permanently.	Consider discontinuing BLINCYTO permanently.

* Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3 is severe, and grade 4 is life-threatening.

Special populations

Elderly

No dose adjustment is necessary in elderly patients (≥ 65 years of age), see section 5.1. There is limited experience with BLINCYTO in patients ≥ 75 years of age.

Renal impairment

Based on pharmacokinetic analyzes, dose adjustment is not necessary in patients with mild to moderate renal dysfunction (see section 5.2). The safety and efficacy of BLINCYTO have not been studied in patients with severe renal impairment.

Hepatic impairment

Based on pharmacokinetic analyzes, no effect of baseline liver function on blinatumomab exposure is expected and adjustment of the initial dose is not necessary (see section 5.2). The safety and efficacy of BLINCYTO have not been studied in patients with severe hepatic impairment.

Pediatric population

The safety and efficacy of BLINCYTO in children < 1 year of age have not yet been established. There are no data for children < 7 months of age. Currently available data in children are described in sections 4.8 and 5.1.

Method of administration

BLINCYTO is for intravenous use.

For instructions on the handling and preparation of the medicinal product before administration, see section 6.6.

Administer BLINCYTO as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours. The pump should be programmable, lockable, non-elastomeric, and have an alarm.

The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the intravenous tubing and to ensure that the patient will receive the full dose of BLINCYTO.

Infuse prepared BLINCYTO final infusion solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:

- Infusion rate of 10 mL/h for a duration of 24 hours
- Infusion rate of 5 mL/h for a duration of 48 hours
- Infusion rate of 3.3 mL/h for a duration of 72 hours
- Infusion rate of 2.5 mL/h for a duration of 96 hours

Administer prepared BLINCYTO final infusion solution using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micrometer in-line filter.

Important note: Do not flush the BLINCYTO infusion line, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, BLINCYTO should be infused through a dedicated lumen.

The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient. The target therapeutic dose of BLINCYTO delivered does not change.

Change of infusion bag

The infusion bag must be changed at least every 96 hours by a healthcare professional for sterility reasons.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Neurologic events including ICANS

Neurologic events including events with a fatal outcome have been observed. Grade 3 (CTCAE version 4.0) or higher (severe or life-threatening) neurologic events including ICANS following initiation of blinatumomab administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Among patients that experienced a neurologic event, the median time to the first event was within the first two weeks of treatment and the majority of events resolved after treatment interruption and infrequently led to BLINCYTO treatment discontinuation.

Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion.

Patients with a medical history of neurologic signs and symptoms (such as dizziness, hypoesthesia, hyporeflexia, tremor, dysesthesia, paresthesia and memory impairment) demonstrated a higher rate of neurologic events (such as tremor, dizziness, confusional state, encephalopathy and ataxia). Among these patients, the median time to the first neurologic event was within the first cycle of treatment.

BLINCYTO is indicated:
- as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.
- as monotherapy for the treatment of adults with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- as monotherapy for the treatment of pediatric patients aged 1 year or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.
- as monotherapy for the treatment of pediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy.

with no CNS involvement.

There is limited experience in patients with a history or presence of clinically relevant CNS pathology (e.g. epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome and psychosis) as they were excluded from clinical studies. There is a possibility of a higher risk of neurologic events in this population. The potential benefits of treatment should be carefully weighed against the risk of neurologic events and heightened caution should be exercised when administering BLINCYTO to these patients.

There is limited experience with blinatumomab in patients with documented active ALL in the CNS or cerebrospinal fluid (CSF). However, patients have been treated with blinatumomab in clinical studies after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy). Therefore, once the CSF is cleared, treatment with BLINCYTO may be initiated.

Patients with Down syndrome may have a higher risk of seizures with BLINCYTO therapy; consider seizure prophylaxis prior to initiation of BLINCYTO for these patients.

It is recommended that a neurological examination be performed in patients prior to starting BLINCYTO therapy and that patients be clinically monitored for signs and symptoms of neurologic events including ICANS (e.g. writing test which could be part of a comprehensive neurological assessment). Management of these signs and symptoms to resolution may require either temporary interruption or permanent discontinuation of BLINCYTO and/or treatment with corticosteroids (see section 4.2). In the event of a seizure, secondary prophylaxis with appropriate anticonvulsant medicinal products (e.g. levetiracetam) is recommended.

Infections

In patients receiving blinatumomab, serious infections, including sepsis, pneumonia, bacteremia, opportunistic infections and catheter site infections have been observed, some of which were life-threatening or fatal. Adult patients with Eastern Cooperative Oncology Group (ECOG) performance status at baseline of 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. There is limited experience with BLINCYTO in patients with an active uncontrolled infection.

Patients receiving BLINCYTO should be clinically monitored for signs and symptoms of infection and treated appropriately. Management of infections may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Cytokine release syndrome and infusion reactions

Cytokine release syndrome (CRS) which may be life-threatening or fatal (grade ≥ 4) has been reported in patients receiving BLINCYTO (see section 4.8).

Serious adverse reactions that may be signs and symptoms of CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; uncommonly, these events led to BLINCYTO discontinuation. The median time to onset of a CRS event was 2 days. Patients should be closely monitored for signs or symptoms of these events.

Disseminated intravascular coagulation (DIC) and capillary leak syndrome (CLS, e.g. hypotension, hypoalbuminemia, edema and hemoconcentration) have been commonly associated with CRS (see section 4.8). Patients experiencing capillary leak syndrome should be managed promptly.

Hemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS.

Infusion reactions may be clinically indistinguishable from manifestations of CRS (see section 4.8). The infusion reactions were generally rapid, occurring within 48 hours after initiating infusion. However, some patients reported delayed onset of infusion reactions or in later cycles. Patients should be observed closely for infusion reactions, especially during the initiation of the first and second

treatment cycles and treated appropriately. Anti-pyretic use (e.g. paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle. To mitigate the risk of CRS, it is important to initiate BLINCYTO (cycle 1, days 1-7) at the recommended starting dose in section 4.2.

Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Tumor lysis syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal (grade ≥ 4) has been observed in patients receiving BLINCYTO.

Appropriate prophylactic measures including aggressive hydration and anti-hyperuricemic therapy (such as allopurinol or rasburicase) should be used for the prevention and treatment of TLS during BLINCYTO treatment, especially in patients with higher leukocytosis or a high tumor burden. Patients should be closely monitored for signs or symptoms of TLS, including renal function and fluid balance in the first 48 hours after the first infusion. In clinical studies, patients with moderate renal impairment showed an increased incidence of TLS compared with patients with mild renal impairment or normal renal function. Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Neutropenia and febrile neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) should be monitored routinely during BLINCYTO infusion, especially during the first 9 days of the first cycle, and treated appropriately.

Elevated liver enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of treatment initiation and did not require interruption or discontinuation of BLINCYTO (see section 4.8).

Monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment especially during the first 48 hours of the first 2 cycles should be performed. Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Pancreatitis

Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO in clinical studies and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

Patients should be closely monitored for signs and symptoms of pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Leukoencephalopathy including progressive multifocal leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and anti-leukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

Due to the potential for progressive multifocal leukoencephalopathy (PML), patients should be monitored for signs and symptoms. In case of suspicious events consider consultation with a neurologist, brain MRI and examination of cerebral spinal fluid (CSF), see section 4.8.

CD19-negative relapse

CD19-negative B-cell precursor ALL has been reported in relapsed patients receiving BLINCYTO. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.

Lineage switch from ALL to acute myeloid leukemia (AML)

Lineage switch from ALL to AML has been rarely reported in relapsed patients receiving BLINCYTO, including those with no immunophenotypic and/or cytogenetic abnormalities at initial diagnosis. All relapsed patients should be monitored for presence of AML.

Immunizations

The safety of immunization with live viral vaccines during or following BLINCYTO therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until recovery of B-lymphocytes to normal ranges following last treatment cycle.

Due to the potential depletion of B-cells in newborns following exposure to blinatumomab during pregnancy, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered (see section 4.6).

Contraception

Women of childbearing potential have to use effective contraception during and for at least 48 hours, after treatment with BLINCYTO (see section 4.6).

Medication errors

Medication errors have been observed with BLINCYTO treatment. It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimize medication errors (including underdose and overdose) (see section 4.2).

Excipients with known effect

This medicinal product contains less than 1 mmol (23 mg) sodium over a 24 hour infusion, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Results from an *in vitro* test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities.

Initiation of BLINCYTO treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential have to use effective contraception during and for at least 48 hours after treatment with blinatumomab (see section 4.4).

Pregnancy

Reproductive toxicity studies have not been conducted with blinatumomab. In an embryo-fetal developmental toxicity study conducted in mice, the murine surrogate molecule crossed the placenta and did not induce embryotoxicity, or teratogenicity (see section 5.3). The expected depletions of B- and T-cells were observed in the pregnant mice but hematological effects were not assessed in fetuses.

There are no data from the use of blinatumomab in pregnant women.

Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

In case of exposure during pregnancy, depletion of B-cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered (see section 4.4).

Breast-feeding

It is unknown whether blinatumomab or metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contraindicated during and for at least 48 hours after treatment with blinatumomab.

Fertility

No studies have been conducted to evaluate the effects of blinatumomab on fertility. No adverse effects on male or female mouse reproductive organs in 13-week toxicity studies with the murine surrogate molecule (see section 5.3).

4.7 Effects on ability to drive and use machines

Blinatumomab has major influence on the ability to drive and use machines. Confusion and disorientation, coordination and balance disorders, risk of seizures and disturbances in consciousness can occur (see section 4.4). Due to the potential for neurologic events, patients receiving blinatumomab should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentially dangerous machinery while blinatumomab is being administered. Patients must be advised that they may experience neurologic events.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions described in this section were identified in clinical studies of patients with B-cell precursor ALL (N = 1,045).

The most serious adverse reactions that may occur during blinatumomab treatment include: infections (22.6%), neurologic events (12.2%), neutropenia/febrile neutropenia (9.1%), cytokine release syndrome (2.7%), and tumor lysis syndrome (0.8%).

The most common adverse reactions were: pyrexia (70.8%), infections - pathogen unspecified (41.4%), infusion-related reactions (33.4%), headache (32.7%), nausea (23.9%), anemia (23.3%), thrombocytopenia (21.6%), edema (21.4%), neutropenia (20.8%), febrile neutropenia (20.4%), diarrhea (19.7%), vomiting (19.0%), rash (18.0%), hepatic enzyme increased (17.2%), cough (15.0%), bacterial infectious disorders (14.1%), tremor (14.1%), cytokine release syndrome (13.8%), leukopenia (13.8%), constipation (13.5%), decreased immunoglobulins (13.4%), viral infectious disorders (13.3%), hypotension (13.0%), back pain (12.5%), chills (11.7%), abdominal pain (10.6%), tachycardia (10.6%), insomnia (10.4%), pain in extremity (10.1%), and fungal infectious disorders (9.6%).

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in clinical studies of patients with B-cell precursor ALL (N = 1,045). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Infections and infestations	Bacterial infections[a, b] Viral infections[a, b] Infections - pathogen unspecified[a, b]	Sepsis Pneumonia Fungal infections[a, b]	
Blood and lymphatic system disorders	Febrile neutropenia Anemia[1] Neutropenia[2] Thrombocytopenia[3] Leukopenia[4]	Leukocytosis[5] Lymphopenia[6]	Lymphadenopathy Histiocytosis hematophagic
Immune system disorders	Cytokine release syndrome[a]	Hypersensitivity	Cytokine storm
Metabolism and nutrition disorders		Tumor lysis syndrome	
Psychiatric disorders[a]	Insomnia[18]	Confusional state[18] Disorientation[18]	
Nervous system disorders[a]	Headache[18] Tremor[18]	Encephalopathy[18] Aphasia[18] Paresthesia[18] Seizure[18] Cognitive disorder[18] Memory impairment Dizziness[18] Somnolence[18] Hypoesthesia[18] Cranial nerve disorder[b] Ataxia[18] Immune effector cell-associated neurotoxicity syndrome (ICANS)	Speech disorder[18]
Cardiac disorders	Tachycardia[7]		
Vascular disorders	Hypotension[8] Hypertension[9]	Flushing	Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnea Productive cough Respiratory failure Wheezing	Dyspnea exertional Acute respiratory failure

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Gastrointestinal disorders	Nausea Diarrhea Vomiting Constipation Abdominal pain		Pancreatitis[a]
Hepatobiliary disorders		Hyperbilirubinemia[a, 10]	
Skin and subcutaneous tissue disorders	Rash[11]		
Musculoskeletal and connective tissue disorders	Back pain Pain in extremity	Bone pain	
General disorders and administration site conditions	Pyrexia[12] Chills Edema[13]	Chest pain[14] Pain	
Investigations	Hepatic enzyme increased[a, 15] Decreased immunoglobulins[16]	Weight increased Blood alkaline phosphatase increased	
Injury, poisoning and procedural complications	Infusion-related reactions[17]		

[a] Additional information is provided in "Description of selected adverse reactions".
[b] MedDRA high level group terms (MedDRA version 23.0).

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. The terms contributing to the relevant adverse reaction are indicated below:
[1] Anemia includes anemia and hemoglobin decreased.
[2] Neutropenia includes neutropenia and neutrophil count decreased.
[3] Thrombocytopenia includes platelet count decreased and thrombocytopenia.
[4] Leukopenia includes leukopenia and white blood cell count decreased.
[5] Leukocytosis includes leukocytosis and white blood cell count increased.
[6] Lymphopenia includes lymphocyte count decreased and lymphopenia.
[7] Tachycardia includes sinus tachycardia, supraventricular tachycardia, tachycardia, atrial tachycardia and ventricular tachycardia.
[8] Hypotension includes blood pressure decreased and hypotension.
[9] Hypertension includes blood pressure increased and hypertension.
[10] Hyperbilirubinemia includes blood bilirubin increased and hyperbilirubinemia.
[11] Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, catheter site rash, rash pustular, genital rash, rash papular and rash vesicular.
[12] Pyrexia includes body temperature increased and pyrexia.
[13] Edema includes bone marrow edema, periorbital edema, eyelid edema, eye edema, lip edema, face edema, localized edema, generalized edema, edema, edema peripheral, infusion site edema, edematous kidney, scrotal edema, edema genital, pulmonary edema, laryngeal edema, angioedema, circumoral edema and lymphedema.
[14] Chest pain includes chest discomfort, chest pain, musculoskeletal chest pain and non-cardiac chest pain.
[15] Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hepatic enzyme increased, liver function test increased and transaminases increased.
[16] Decreased immunoglobulins includes blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, globulins decreased, hypogammaglobulinemia, hypoglobulinemia and immunoglobulins decreased.
[17] 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, rash, tachypnea, swelling face, face edema and rash erythematous.
[18] Events may represent ICANS.

Description of selected adverse reactions

Neurologic events including ICANS

In the randomized phase III clinical study (N = 267) and the single-arm phase II clinical study (N = 189) in patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL treated with BLINCYTO, 66.0% of patients experienced one or more neurologic adverse reactions (including psychiatric disorders), primarily involving the CNS. Serious and grade ≥ 3 neurologic adverse reactions were observed in 11.6% and 12.1% of patients respectively, of which the most common serious adverse reactions were encephalopathy, tremor, aphasia, and confusional state. The majority of neurologic events (80.5%) were clinically reversible and resolved following interruption of BLINCYTO. The median time to the first event was within the first 2 weeks of treatment. One case of fatal encephalopathy has been reported in an earlier phase II clinical single-arm study.

Neurologic events were reported for 62.2% of adult patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL (N = 45). Serious and grade ≥ 3 neurologic events were reported at 13.3% each in adult patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL.

Neurologic events were reported for 71.5% of adult patients with MRD positive B-cell precursor ALL (N = 137), 22.6% of patients experienced serious events. Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 16.1% and 2.2% of adult patients with MRD positive B-cell precursor ALL.

ICANS, including Grade 3 and higher ICANS, were reported in clinical trials and with post-marketing experience. The most frequent clinical manifestations of ICANS were confusional state, aphasia, disorientation, altered state of consciousness, dysarthria, encephalopathy, seizure, mental status changes, somnolence and dysgraphia.

The observed time to onset of ICANS ranged from 0 to 299 days with the majority of ICANS occurring within the first three weeks.

For clinical management of neurologic events, see section 4.4.

Infections

Life-threatening or fatal (grade ≥ 4) viral, bacterial and fungal infections have been reported in patients treated with BLINCYTO. In addition, reactivations of virus infection (e.g. Polyoma (BK)) have been observed in the phase II clinical study in adults with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. Patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL with ECOG performance status at baseline of 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. For clinical management of infections, see section 4.4.

Cytokine release syndrome (CRS)

In the randomized phase III clinical study (N = 267) and the single-arm phase II clinical study (N = 189) in patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL treated with BLINCYTO, 14.7% of patients experienced CRS. Serious CRS reactions were reported in 2.4% of patients with a median time to onset of 2 days.

Cytokine release syndrome was reported in 8.9% of adult patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL (N = 45), 2.2% of patients experienced serious events. No grade ≥ 3 or ≥ 4 events were reported.

Cytokine release syndrome was reported in 2.9% of adult patients with MRD positive B-cell precursor ALL (N = 137). Grade 3 and serious events were reported for 1.5% each of adult patients with MRD positive B-cell precursor ALL; no grade ≥ 4 events were reported.

Capillary leak syndrome was observed in 1 patient in the phase II clinical study in adult patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL and in 1 patient in the phase II clinical study in adult patients with MRD positive B-cell precursor ALL. Capillary leak syndrome was not observed in adult patients in the phase II clinical study in patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL.

For clinical management of CRS, see section 4.4.

Elevated liver enzymes

In the randomized phase III clinical study (N = 267) and the single-arm phase II clinical study (N = 189) in patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL treated with BLINCYTO, 22.4% of patients reported elevated liver enzymes and associated signs/symptoms. Serious and grade ≥ 3 adverse reactions (such as ALT increased, AST increased, and blood bilirubin increased) were observed in 1.5% and 13.6% of patients respectively. The median time to onset to the first event was 4 days from the start of BLINCYTO treatment initiation.

Elevated liver enzyme events were reported for 17.8% of adult patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL (N = 45), 2.2% of patients experienced serious events. Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 13.3% and 6.7% of adult patients with Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL.

Elevated liver enzyme events were reported for 12.4% of adult patients with MRD positive B-cell precursor ALL (N = 137). Grade ≥ 3 and grade ≥ 4 events, respectively, were reported for 8.0% and 4.4% of adult patients with MRD positive B-cell precursor ALL.

The duration of hepatic adverse reactions has generally been brief and with rapid resolution, often when continuing uninterrupted treatment with BLINCYTO.

For clinical management of elevated liver enzymes, see section 4.4.

Pancreatitis

Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO in the clinical studies and the post-marketing settings. The median time to onset was 7.5 days. For clinical management of pancreatitis, see section 4.4.

Leukoencephalopathy including progressive multifocal leukoencephalopathy

Leukoencephalopathy has been reported. Patients with brain MRI/CT findings consistent with leukoencephalopathy experienced concurrent serious adverse reactions including confusional state, tremor, cognitive disorder, encephalopathy, and convulsion. Although there is a potential for the development of progressive multifocal leukoencephalopathy (PML), no confirmed case of PML has been reported in the clinical studies.

Pediatric population

BLINCYTO has been evaluated in pediatric patients with relapsed or refractory B-cell precursor ALL in a phase I/II, single-arm dose escalation/evaluation study (MT103-205), in which 70 pediatric patients, aged 7 months to 17 years, were treated with the recommended dosage regimen.

The most frequently reported serious adverse reactions were pyrexia (11.4%), febrile neutropenia (11.4%), cytokine release syndrome (5.7%), sepsis (4.3%), device-related infection (4.3%), overdose (4.3%), convulsion (2.9%), respiratory failure (2.9%), hypoxia (2.9%), pneumonia (2.9%), and multi-organ failure (2.9%).

The adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients. Adverse reactions that were observed more frequently (≥ 10% difference) in the pediatric population compared to the adult population were anemia, thrombocytopenia, leukopenia, pyrexia, infusion-related reactions, weight increase, and hypertension.

The type and frequency of adverse reactions were similar across different pediatric subgroups (gender, age and geographic region).

At a dose higher than the recommended dose in study MT103-205, a case of fatal cardiac failure occurred in the setting of life-threatening cytokine release syndrome (CRS) and tumor lysis syndrome (TLS), see section 4.4.

BLINCYTO has also been evaluated in pediatric patients with high-risk first relapsed B-cell precursor ALL in a randomized, controlled, open-label phase III study (20120215), in which 54 patients, aged 1 to 18 years, were treated with the recommended dosage regimen for high-risk first relapsed B-cell precursor ALL. The safety profile of BLINCYTO in study 20120215 is consistent with that of the studied pediatric relapsed or refractory B-cell precursor ALL population.

Other special populations

There is limited experience with BLINCYTO in patients ≥ 75 years of age. Generally, safety was similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with BLINCYTO. However, elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy and confusion.

Elderly patients with MRD positive ALL treated with BLINCYTO may have an increased risk of hypogammaglobulinemia compared to younger patients. It is recommended that immunoglobulin levels are monitored in elderly patients during treatment with BLINCYTO.

The safety of BLINCYTO has not been studied in patients with severe renal impairment.

Immunogenicity

In clinical studies of adult ALL patients treated with BLINCYTO, less than 3% tested positive for anti-blinatumomab antibodies. Six of those patients had anti-blinatumomab antibodies with *in vitro* neutralizing activity. No anti-blinatumomab antibodies were detected in clinical studies of pediatric patients with relapsed or refractory ALL treated with blinatumomab.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, the local representative of the Marketing Authorization Holder (Medison email: pv@Medison.co.il) should be contacted to discuss antibody testing.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Reinitiation of BLINCYTO at the correct therapeutic dose should be considered when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion (see section 4.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX07.

Mechanism of action

Blinatumomab is a bispecific T-cell engager molecule that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. The anti-tumor activity of blinatumomab immunotherapy is not dependent on T-cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumor cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, and results in elimination of CD19+ cells.

Pharmacodynamic effects

Consistent immune-pharmacodynamic responses were observed in patients studied. During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, rapid peripheral B-cell depletion, and transient cytokine elevation.

Peripheral T-cell redistribution (i.e. T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of blinatumomab infusion or dose escalation. T-cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. Increase of T-cell counts above baseline (T-cell expansion) was observed in few patients.

Peripheral B-cell counts decreased rapidly to an undetectable level during treatment at doses ≥ 5 mcg/m^2/day or ≥ 9 mcg/day in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week treatment-free period between treatment cycles. Incomplete depletion of B-cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few non-responders at higher doses.

Peripheral lymphocytes were not measured in pediatric subjects.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α and IFN-γ were measured and, IL-6, IL-10 and IFN-γ were most elevated. Transient elevation of cytokines was observed in the first 2 days following start of blinatumomab infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

Clinical efficacy and safety

Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL

A total of 456 patients aged ≥ 18 years of age with relapsed or refractory B-cell precursor ALL were exposed to BLINCYTO during the phase II and phase III clinical studies described below.

The safety and efficacy of BLINCYTO compared to standard of care (SOC) chemotherapy were evaluated in a randomized, open-label, multicenter, phase III study (TOWER). Eligible patients were ≥ 18 years of age and ECOG status ≤ 2 with relapsed or refractory B-cell precursor ALL (had > 5% blasts in the bone marrow and either relapse at any time after allogeneic HSCT, untreated first relapse with first remission duration < 12 months, or refractory to last therapy).

Patients were randomized 2:1 to receive BLINCYTO or 1 of 4 prespecified, investigator-selected, SOC backbone chemotherapy regimens. Randomization was stratified by age (< 35 years versus ≥ 35 years of age), prior salvage therapy (yes versus no), and prior allogeneic HSCT (yes versus no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see table 3).

Table 3. Demographics and baseline characteristics in phase III study (TOWER)

Characteristic	BLINCYTO (N = 271)	SOC chemotherapy (N = 134)
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)
Mean, years (SD)	40.8 (17.1)	41.1 (17.3)
≥ 65 Years, n (%)	33 (12.2)	15 (11.2)
Prior salvage therapy	164 (60.5)	80 (59.7)
0	114 (42.1)	65 (48.5)
1	91 (33.6)	43 (32.1)
≥ 2	66 (24.3)	26 (19.4)
Prior alloHSCT	94 (34.7)	46 (34.3)
ECOG status - n (%)		
0	96 (35.4)	52 (38.8)
1	134 (49.4)	61 (45.5)
2	41 (15.1)	20 (14.9)
Refractory status - n (%)		
Primary refractory	46 (17.0)	27 (20.1)
Refractory to salvage therapy	87 (32.1)	34 (25.4)
Maximum of central/local bone marrow blasts - n (%)		
≥ 50%	201 (74.2)	104 (77.6)

alloHSCT = allogeneic hematopoietic stem cell transplantation
SOC = standard of care

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse reactions. Of the 267 patients who received BLINCYTO, the mean number of completed treatment cycles was 2.0; of the 109 patients who received SOC chemotherapy, the mean number of treatment cycles was 1.3.

The primary endpoint was overall survival (OS). 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 BLINCYTO arm. The hazard ratio (95% CI) was 0.71 (0.55, 0.93) between treatment arms favoring BLINCYTO,

indicated a 29% reduction in hazard rate in the BLINCYTO arm (p-value = 0.012 (stratified log-rank test)), see figure 1. Consistency in OS results was shown in subgroups by stratification factors.

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 BLINCYTO group and 3.9 months (95% CI: 2.8, 4.9) in the SOC group (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 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. Efficacy results from other key endpoints in the study are summarized in table 4.

Figure 1. Kaplan-Meier curve of overall survival

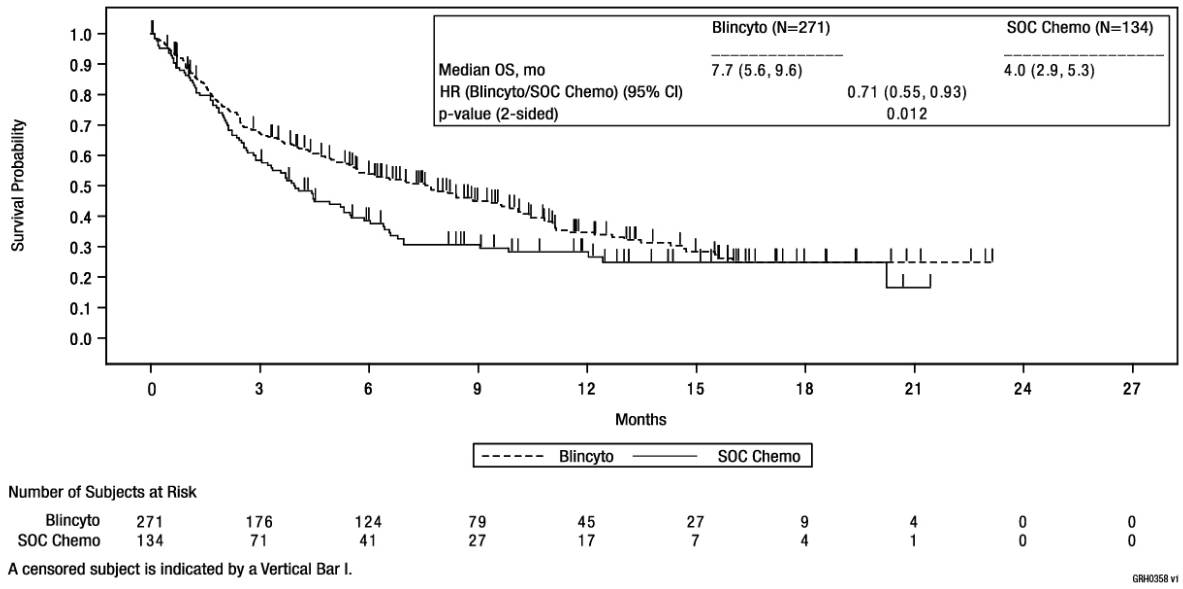


Table 4. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (TOWER)

	BLINCYTO (N = 271)	**SOC chemotherapy (N = 134)**
Complete remission (CR)		
CR[a]/CRh*[b]/CRi[c], n (%) [95% CI]	119 (43.9) (37.9, 50.0)	33 (24.6) (17.6, 32.8)
Treatment difference [95% CI]	19.3 (9.9, 28.7)	
p-value	< 0.001	
CR, n (%) [95% CI]	91 (33.6) (28.0, 39.5)	21 (15.7) (10.0, 23.0)
Treatment difference [95% CI]	17.9 (9.6, 26.2)	
p-value	< 0.001	
Event-free survival[d]		
6-month estimate % [95% CI]	30.7 (25.0, 36.5)	12.5 (7.2, 19.2)
18-months estimate % [95% CI]	9.5 (5.1, 15.6)	7.9 (3.7, 14.2)
HR [95% CI]	0.55 (0.43, 0.71)	
Duration of hematological response- Median time to event [95% CI]		
CR	8.3 (5.7, 10.7)	7.8 (2.2, 19.0)
CR/CRh*/CRi	7.3 (5.8, 9.9)	4.6 (1.8, 19.0)
MRD[e] response for CR/CRh*/CRi		
MRD evaluable patients (%) [95% CI][f]	74/97 (76.3) (66.6, 84.3)	16/33 (48.5) (30.8, 66.5)
Duration of MRD response-	4.5 months (3.6, 9.0)	3.8 months (1.9, 19.0)

	BLINCYTO (N = 271)	SOC chemotherapy (N = 134)
Median time to event [95% CI]		
Postbaseline alloHSCT - n (%)		
Overall subjects	65 (24)	32 (23.9)
Hematological responders (CR/CRh*/CRi)	50 (42.0)	18 (54.5)
Time to alloHSCT among all transplanted patients Median time to event (Interquartile range)	3.7 months (3.0, 5.3) (N = 65)	3.1 months (2.6, 4.3) (N = 32)
Time to alloHSCT among CR/CRh*/CRi responders Median time to event [95% CI] (KM estimate)	11.3 months (5.2, NE) (N = 119)	3.6 months (2.3, 7.2) (N = 33)
100 day mortality after alloHSCT		
n/N (%), [95% CI]	4/38, 12.4% (4.8, 29.9)	0/12, 0.0% (0.0, NE)

[a] CR was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).
[b] CRh* (complete remission with partial hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
[c] CRi (complete remission with incomplete hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microliter or ANC > 1,000/microliter).
[d] EFS time was calculated from the time of randomization until the date of disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever is earlier. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation are considered treatment failures and assigned an EFS duration of 1 day.
[e] MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4}.
[f] Patients who achieved CR/CRh*/CRi and had an evaluable post baseline MRD assessment.

Health related quality of life

In this open-label study, Health related quality of life (HRQoL) reported by patients were measured using the European Organization 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-points 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. Because the health related quality of life results are based on a post-hoc sensitivity analysis, the results should be interpreted with caution.

BLINCYTO was also evaluated in an open-label, multicenter, single-arm phase II study of 189 patients (MT103-211). Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage, or relapsed or refractory after first salvage therapy, or relapsed within 12 months of allogeneic HSCT, and had ≥ 10% blasts in bone marrow).

Premedication, BLINCYTO dose per treatment cycle and route of administration were identical to those in the phase III study. Patients were premedicated with a mandatory cerebrospinal fluid prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines within 1 week prior to start of BLINCYTO treatment. BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in the case of adverse reactions. The treated population included 189 patients who received at least 1 infusion of BLINCYTO; the mean number of cycles per patient was 1.6. Patients who responded to BLINCYTO but later relapsed

had the option to be retreated with BLINCYTO. Among treated patients, the median age was 39 years (range: 18 to 79 years, including 25 patients ≥ 65 years of age), 64 of 189 (33.9%) had undergone HSCT prior to receiving BLINCYTO and 32 of 189 (16.9%) had received more than 2 prior salvage therapies.

The primary endpoint was the complete remission/complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with BLINCYTO. Eighty-one of 189 (42.9%) patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (64 of 81) occurring within 1 cycle of treatment. In the elderly population (≥ 65 years of age) 11 of 25 patients (44.0%) achieved CR/CRh* within the first 2 treatment cycles (see section 4.8 for safety in elderly). Four patients achieved CR during consolidation cycles, resulting in a cumulative CR rate of 35.4% (67/189; 95% CI: 28.6% - 42.7%). Thirty-two of 189 (17%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO (see table 5).

Table 5. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (MT103-211)

	n (%) n = 189	**95% CI**
Complete remission (CR)[1]/Complete remission with partial hematological recovery (CRh*)[2]	81 (42.9%)	[35.7% – 50.2%]
CR	63 (33.3%)	[26.7% – 40.5%]
CRh*	18 (9.5%)	[5.7% – 14.6%]
Blast free hypoplastic or aplastic bone marrow[3]	17 (9.0%)	[5.3% – 14.0%]
Partial remission[4]	5 (2.6%)	[0.9% – 6.1%]
Relapse[5]-free survival (RFS) for CR/CRh*	5.9 months	[4.8 to 8.3 months]
Overall survival	6.1 months	[4.2 to 7.5 months]

[1] CR was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).
[2] CRh* was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
[3] Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts ≤ 5%, no evidence of disease, insufficient recovery of peripheral blood counts: platelets ≤ 50,000/microliter and/or ANC ≤ 500/microliter.
[4] Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.
[5] Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

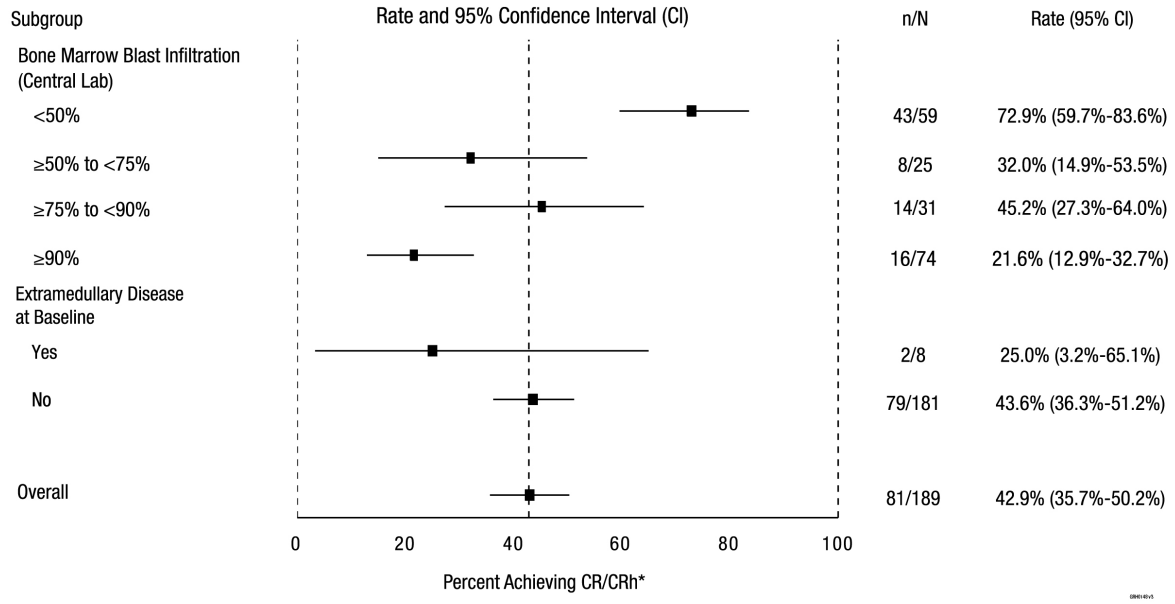
In a prespecified exploratory analysis, 60 of 73 MRD evaluable patients with CR/CRh* (82.2%) also had a MRD response (defined as MRD by PCR < 1×10^{-4}).

Patients with prior allogeneic HSCT had similar response rates to those without prior HSCT, older patients had similar response rates to younger patients, and no substantial difference was observed in remission rates based on the number of lines of prior salvage treatment.

In patients with non-CNS/non-testes extramedullary disease (defined as at least 1 lesion ≥ 1.5 cm) at screening (N = 8/189) clinical response rates (25% [95% CI: 3.2 - 65.1]) were lower compared with patients with no evidence of extramedullary disease (N = 181, 43.6% [95% CI: 36.3 - 51.2]) (see figure 2).

Patients with the highest tumor burden as measured by the percentage of bone marrow blast cells at baseline (≥ 90%) still had a clinically meaningful response with a CR/CRh* rate of 21.6% (95% CI: 12.9 - 32.7) (see figure 2). Patients with low tumor burden (< 50%) responded best to BLINCYTO treatment with CR/CRh* rate of 72.9% (95% CI: 59.7 – 83.6).

Figure 2. Forest plot of CR/CRh* rate during the first 2 cycles for study MT103-211 (primary analysis set)



n = number of patients who achieved CR or CRh* in the first 2 cycles of treatment in the specified subgroup.
N = total number of patients in the specified subgroup.

There is limited data in patients with late first relapse of B-cell precursor ALL defined as a relapse occurring more than 12 months after first remission or more than 12 months after HSCT in the first remission. In clinical phase II studies, 88.9% (8/9) of patients with late first relapse as defined in the individual studies achieved CR/CRh* within the first 2 treatment cycles with 62.5% (6/9) achieving MRD response and 37.5% (3/9) undergoing allogeneic HSCT after treatment with BLINCYTO. The median overall survival (OS) was 17.7 months (95% CI: 3.1 – not estimable).

In the randomized, open-label, multicenter, phase III study (TOWER), 70% (7/10) of post-transplant patients in late first relapse treated with BLINCYTO compared to 20% (1/5) treated with SOC chemotherapy achieved CR/CRh* within the first 2 treatment cycles. Fifty percent (5/10) compared to 0% (0/5) achieved MRD response and 20% (2/10) compared to 40% (2/5) underwent allogeneic HSCT after treatment. The median OS was 15.6 months (95% CI: 5.5 – not estimable) for the BLINCYTO group and 5.3 months (95% CI: 1.1 – not estimable) for the SOC chemotherapy group.

Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL in adult patients

The safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm phase II study (ALCANTARA). Eligible patients were ≥ 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL: relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI); OR intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate.

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse reactions. The treated population included 45 patients who received at least one infusion of BLINCYTO; the mean number of treatment cycles was 2.2 (see table 6 for patient demographics and baseline characteristics).

Table 6. Demographics and baseline characteristics in phase II study (ALCANTARA)

Characteristic	BLINCYTO (N = 45)
Age	
Median, years (min, max)	55 (23, 78)
Mean, years (SD)	52.8 (15)
≥ 65 Years and < 75 years, n (%)	10 (22.2)
≥ 75 Years, n (%)	2 (4.4)
Males, n (%)	24 (53.3)
Race, n (%)	
Asian	1 (2.2)
Black (or African American)	3 (6.7)
Other	2 (4.4)
White	39 (86.7)
Disease History, n (%)	
Prior TKI treatment[a]	
1	7 (15.6)
2	21 (46.7)
≥ 3	17 (37.8)
Prior salvage therapy	31 (61.9)
Prior alloHSCT[b]	20 (44.4)
Bone marrow blasts[c], n (%)	
≥ 50% to < 75%	6 (13.3)
≥ 75%	28 (62.2)

[a] Number of patients that failed ponatinib = 23 (51.1%)
[b] alloHSCT = allogeneic hematopoietic stem cell transplantation
[c] centrally assessed

The primary endpoint was the CR/CRh* rate within 2 cycles of treatment with BLINCYTO. Sixteen out of 45 (35.6%) patients achieved CR/CRh* within the first 2 treatment cycles. Of the 16 patients with CR/CRh* in the first 2 cycles, 12 of 14 (85.7%) patients with a CR and 2 of 2 (100%) patients with a CRh* also achieved an MRD complete response (see table 7).

Two patients achieved CR during subsequent cycles, resulting in a cumulative CR rate of 35.6% (16 out of 45; 95% CI: 21.9 – 51.2). Five out of 16 (31.3%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO.

Table 7. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) (ALCANTARA)

	N = 45
Complete remission (CR)[a]/Complete remission with partial hematological recovery (CRh*)[b], n (%) [95% CI]	16 (35.6) [21.9, 51.2]
CR	14 (31.1) [18.2, 46.6]
CRh*	2 (4.4) [0.5, 15.1]
CRi[c] (without CRh*), n (%) [95% CI]	2 (4.4) [0.5, 15.1]
Blast free hypoplastic or aplastic bone marrow (without CRi)[d], n (%) [95% CI]	3 (6.7) [1.4, 18.3]
Partial remission[e], n (%) [95% CI]	2 (4.4) [0.5, 15.1]
Complete MRD response[f], n (%) [95% CI]	18 (40.0) [25.7, 55.7]
Median Relapse[g]-free survival (RFS) for CR/CRh* [95% CI]	6.7 months [4.4 to NE[h]]
Median Overall survival [95% CI]	7.1 months [5.6 to NE[h]]

[a] CR was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

[b] CRh* was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
[c] CRi (complete remission with incomplete hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microliter or ANC > 1,000/microliter).
[d] Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts ≤ 5%, no evidence of disease, insufficient recovery of peripheral counts: platelets ≤ 50,000/microliter and/or ANC ≤ 500/microliter.
[e] Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.
[f] Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}.
[g] Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.
[h] NE = not estimable.

Patients with the higher tumor burden as measured by the percentage of bone marrow blast cells at baseline (≥ 50%) still had a clinically meaningful response with a CR/CRh* rate of 26.5% (95% CI: 12.9 – 44.4). Patients with low tumor burden (< 50%) responded best to BLINCYTO treatment with CR/CRh* rate of 63.6% (95% CI: 30.8 – 89.1). For patients with high peripheral white blood cell counts (≥ 3.0×10^9/L), response rate was 27.3% (95% CI: 10.7 – 50.2) while percentage of response for those with a lower white blood cell count (< 3.0×10^9/L) was 43.5% (95% CI: 23.2 – 65.5).

Treatment effects in evaluable subgroups (e.g. mutation status, number of prior TKIs, prior HSCT status, and relapse without prior HSCT) were in general consistent with the results in the overall population. Patients with T315I mutation, other mutations, or additional cytogenetic abnormalities responded with a similar rate as compared to those that did not have these mutations or abnormalities.

MRD positive B-cell precursor ALL

The safety and efficacy of BLINCYTO in adult patients with MRD positive B-cell precursor ALL were evaluated in an open-label, multicenter, single-arm phase II study (BLAST). Eligible patients were ≥ 18 years of age with no prior HSCT, had received at least 3 blocks of standard ALL induction therapy, were in complete hematologic remission (defined as < 5% blasts in bone marrow, absolute neutrophil count ≥ 1,000/microliters, platelets ≥ 50,000/microliters, and hemoglobin level ≥ 9 g/dL) and had molecular failure or molecular relapse (defined as MRD ≥ 10^{-3}), see table 8. MRD status at screening was determined from bone marrow aspirations using flow cytometry or polymerase chain reaction (PCR) at a minimum sensitivity of 10^{-4} based on local site evaluations. A central laboratory subsequently confirmed MRD levels by PCR. Final interpretation of MRD results followed EuroMRD Consortium guidelines.

Table 8. Demographics and baseline characteristics in MRD study (BLAST)

Characteristic	BLINCYTO (N = 116)
Age	
Median, years (min, max)	45 (18, 76)
Mean, years (SD)	44.6 (16.4)
≥ 65 years, n (%)	15 (12.9)
Males, n (%)	68 (58.6)
Race, n (%)	
Asian	1 (0.9)
Other (mixed)	1 (0.9)
White	102 (87.9)
Unknown	12 (10.3)
Relapse history n (%)	
Patients in 1st CR	75 (64.7)
Patients in 2nd CR	39 (33.6)
Patients in 3rd CR	2 (1.7)

Characteristic	BLINCYTO (N = 116)
MRD level at baseline*, n (%)	
$\geq 10^{-1}$ and < 1	9 (7.8)
$\geq 10^{-2}$ and < 10^{-1}	45 (38.8)
$\geq 10^{-3}$ and < 10^{-2}	52 (44.8)
< 10^{-3}	3 (2.6)
Below lower limit of quantification	5 (4.3)
Unknown	2 (1.7)

* Centrally assessed in an assay with minimum sensitivity of 10^{-4}

BLINCYTO was administered as a continuous intravenous infusion. Patients received BLINCYTO at a constant dose of 15 mcg/m^2/day (equivalent to the recommended dosage of 28 mcg/day) for all treatment cycles. Patients received up to 4 cycles of treatment. Dose adjustment was possible in case of adverse reactions. The treated population included 116 patients who received at least one infusion of BLINCYTO; the mean number of completed treatment cycles was 1.8 (range: 1 to 4).

The primary endpoint was the proportion of patients who achieved a complete MRD response within one cycle of BLINCYTO treatment. Eighty-eight out of 113 (77.9%) evaluable patients achieved a complete MRD response after one cycle of treatment; see table 9. Two subjects achieved a complete MRD response with 1 additional cycle of BLINCYTO. MRD response rates by age and MRD level at baseline subgroups were consistent with the results in the overall population. RFS in patients with Philadelphia chromosome-negative B-cell precursor ALL at 18 months censored at HSCT or post-BLINCYTO chemotherapy was 54% (33%, 70%). RFS at 18 months not censored at HSCT or post-BLINCYTO chemotherapy was 53% (44%, 62%).

Table 9. Efficacy results in patients ≥ 18 years of age with MRD positive B-cell precursor ALL (BLAST)

Complete MRD response[a], n/N (%), [95% CI]	88/113[b] (77.9) [69.1 - 85.1]
≥ 65 years old	12/15 (80.0) [51.9 - 95.7]
Patients in 1st CR	60/73 (82.2) [71.5 - 90.2]
Patients in 2nd CR	27/38 (71.1) [54.1 - 84.6]
Patients in 3rd CR	1/2 (50.0) [1.3 - 98.7]
Duration of complete MRD response [95% CI]	17.3 months [12.6 - 23.3]

[a] Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}.

[b] One hundred thirteen patients (97.4%; 113/116) were included in the primary endpoint full analysis set.

Pediatric population

The safety and efficacy of BLINCYTO compared to standard of care (SOC) consolidation chemotherapy were evaluated in a randomized, controlled, open-label, multicenter study (20120215). Eligible patients were between 28 days and 18 years of age with high-risk first relapsed Philadelphia chromosome-negative B-cell precursor ALL and had < 25% blasts in the bone marrow. High-risk patients were defined as per IntReALL criteria. Patients with clinically relevant CNS pathology requiring treatment (e.g. unstable epilepsy) or evidence of current CNS involvement by ALL were excluded from the study. Patients were enrolled and randomized after induction and 2 blocks of consolidation chemotherapy.

Patients were randomized 1:1 to receive BLINCYTO or a third block of SOC consolidation chemotherapy (High-risk consolidation 3, HC3). Patients in the BLINCYTO arm received one cycle of BLINCYTO as a continuous intravenous infusion at 15 mcg/m^2/day over 4 weeks (maximum daily dose was not to exceed 28 mcg/day). Dose adjustment was possible in case of adverse reactions. Randomization was stratified by age (< 1 year, 1 to 9 years, and > 9 years), bone marrow status determined at the end of the second block of consolidation chemotherapy and MRD status determined

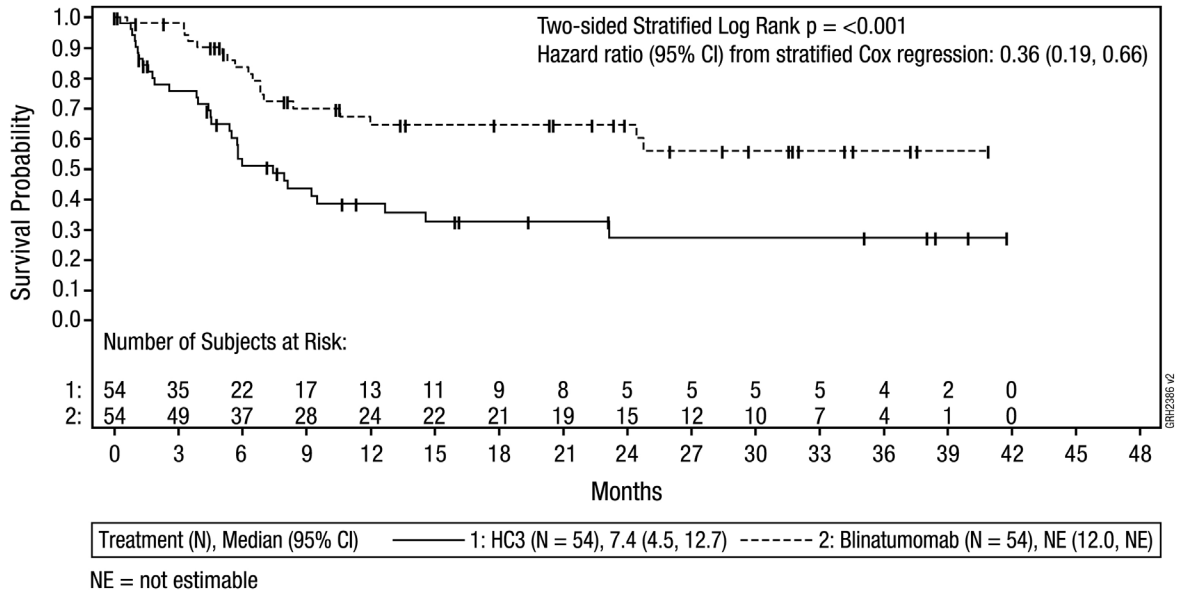
at the end of induction (blasts < 5% with MRD level < 10^{-3}, blasts < 5% with MRD level ≥ 10^{-3}, and blasts ≥ 5% and < 25%). The demographics and baseline characteristics were well-balanced between the two arms (see table 10). No subject had prior HSCT.

Table 10. Demographics and baseline characteristics in study 20120215

Characteristics	BLINCYTO (N = 54)	SOC Chemotherapy (N = 54)
Age, n (%)		
< 1 year	0 (0.0)	0 (0.0)
1 to 9 years	39 (72.2)	38 (70.4)
≥ 10 to 18 years	15 (27.8)	16 (29.6)
Males, n (%)	30 (55.6)	22 (40.7)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	1 (1.9)	3 (5.6)
Black (or African American)	0 (0.0)	3 (5.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Other	3 (5.6)	5 (9.3)
White	50 (92.6)	43 (79.6)
Occurrence and type of any genetic abnormality, n (%)		
No	34 (63.0)	29 (53.7)
Yes	20 (37.0)	25 (46.3)
Hyperdiploidy	6 (11.1)	6 (11.1)
Hypodiploidy	1 (1.9)	0 (0.0)
t(v;11q23)/MLL rearranged	0 (0.0)	4 (7.4)
t(12;21)(p13;q22)/TEL-AML1	2 (3.7)	3 (5.6)
t(1;19)(q23;p13.3)/E2A-PBX1	2 (3.7)	2 (3.7)
t(5;14)(q31;32)/IL3-IGH	0 (0.0)	0 (0.0)
Other	9 (16.7)	10 (18.5)
Extramedullary disease at relapse, n (%)		
No	44 (81.5)	40 (74.1)
Yes	10 (18.5)	14 (25.9)
Cytomorphology, n (%)		
Blasts < 5%	54 (100.0)	51 (94.4)
Blasts ≥ 5% and < 25%	0 (0.0)	2 (3.7)
Blasts ≥ 25%	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	1 (1.9)
MRD PCR value, n (%)		
≥ 10^{-4}	10 (18.5)	13 (24.1)
< 10^{-4}	20 (37.0)	22 (40.7)
Time from first diagnosis to relapse (month), n (%)		
< 18 months	19 (35.2)	22 (40.7)
≥ 18 months and ≤ 30 months	32 (59.3)	28 (51.9)
> 30 months	3 (5.6)	4 (7.4)

The primary endpoint was event-free survival (EFS). The study demonstrated statistically significant improvement in EFS for patients treated with BLINCYTO as compared to SOC consolidation chemotherapy. In patients who received the SOC consolidation chemotherapy, the 36-month Kaplan-Meier estimate of EFS, with a hazard ratio (95% CI) of 0.36 (0.19, 0.66) was 26.9% (95% CI: 13.2%, 42.8%) compared to 55.7% (95% CI: 37.8%, 70.4%) in patients who received BLINCYTO. Treatment effects in subgroups (e.g. age, tumor burden/MRD status, time from first diagnosis to relapse) were in general consistent with the results in the overall population. See figure 3 and table 11 for efficacy results from study 20120215.

Figure 3. Kaplan-Meier curve of event-free survival



CI = confidence interval, HC3 = High-risk consolidation 3, N = number of patients in the analysis set.

Table 11. Efficacy results in pediatric patients with high-risk first relapsed B-cell precursor ALL (20120215)

	BLINCYTO (N = 54)	**SOC Chemotherapy** (N = 54)
Event-free survival[a]		
Events (%)	18 (33.3)	31 (57.4)
Median, months [95% CI]	NE[b] [12.0, NE[b]]	7.4 [4.5, 12.7]
Hazard ratio [95% CI][c]	0.36 [0.19, 0.66]	
p-value[d]	< 0.001	
Overall survival		
Number of deaths (%)	8 (14.8)	16 (29.6)
36-month estimate (%) [95% CI]	81.1 [65.5, 90.2]	55.8 [36.9, 71.0]
Hazard ratio [95% CI][c,d]	0.43 [0.18, 1.01]	
p-value[e,f]	0.047	
MRD response[g]		
Number of MRD response, n_1/n_2[h] (%)	44/49 (89.8)	26/48 (54.2)
[95% CI]	[77.8, 96.6]	[39.2, 68.6]
p-value[f,i]	< 0.001	

Note: Efficacy results from primary analysis (data cut-off of 17 July 2019).

[a] EFS time was calculated from the time of randomization until the date of relapse or tumor burden of ≥ 5% and < 25% blasts after having achieved a complete remission (CR), failure to achieve a CR at the end of treatment, secondary malignancy, or death due to any cause, whichever occurs first.

[b] NE = not estimable.

[c] Based on stratified Cox's model.

[d] The updated hazard ratio for OS (data cut-off of 14 September 2020) was 0.33 (95% CI: 0.15 to 0.72).

[e] The p-value was derived using a stratified log-rank test.

[f] Endpoint not formally tested. The p-value was not adjusted for multiplicity.

[g] MRD (minimum residual disease) response was defined as MRD by PCR < 1×10^{-4}.

[h] n_1: number of patients who achieved a MRD response after having a baseline MRD ≥ 10^{-4} or < 10^{-4}; n_2: number of patients assessed.

[i] The p-value was derived using Cochran Mantel Haenszel test.

The safety and efficacy of BLINCYTO were also evaluated in an open-label, multicenter, single-arm study in 93 pediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, in any marrow relapse after allogeneic HSCT, or refractory to other treatments, and also with > 25% blasts in bone marrow) (MT103-205). This was a two-part study, a dose-finding part to determine the appropriate dosing regimen, followed by a single-arm efficacy part using this regimen.

BLINCYTO was administered as a continuous intravenous infusion. In the dose-finding part of the study, doses of up to 30 mcg/m^2/day were evaluated. The recommended dose for the pharmacokinetics (PK) expansion and efficacy parts of the study was determined to be 5 mcg/m^2/day on days 1-7 and 15 mcg/m^2/day on days 8-28 for cycle 1, and 15 mcg/m^2/day on days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse reactions. Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO.

The treated population (in the dose-finding, PK expansion, and efficacy parts) included 70 patients who received at least 1 infusion of BLINCYTO at the recommended dose; the mean number of treatment cycles was 1.5. Among treated patients, the median age was 8 years (range: 7 months to 17 years), 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving BLINCYTO, and 39 out of 70 (55.7%) had refractory disease. Most patients had a high tumor burden (≥ 50% leukemic blasts in bone marrow) at baseline with a median of 75.5% bone marrow blasts.

Twenty out of 70 (28.6%) patients achieved CR/CRh* within the first 2 treatment cycles with 17 out of 20 (85%) occurring within cycle 1 of treatment. Four patients achieved M1 bone marrow but did not meet the peripheral blood count recovery criteria for CR or CRh*. Eleven of the 20 patients (55%) who achieved CR/CRh* received an allogeneic HSCT. The CR/CRh* for patients less than 2 years of age was 40.0% (4/10), for patients 2 to 6 years was 30.0% (6/20); and for patients aged 7 to 17 years was 25.0% (10/40). Three patients < 1 year of age refractory to prior treatment and without prior alloHSCT received one cycle of BLINCYTO at a dose of 5-15 mcg/m^2/day. None of the 3 subjects < 1 year old achieved a CR/CRh*, 1 patient had progressive disease (OS 2.3 months) and 2 were non-responders (OS 1.1 months and 8.7 months, respectively). The type of adverse reactions observed in infants were similar to those observed in the overall pediatric population. See table 12 for the efficacy results.

Table 12. Efficacy results in patients < 18 years of age with relapsed or refractory B-cell precursor ALL (MT103-205)

	N = 70
CR[a]/CRh*[b], n (%) [95% CI]	20 (28.6%) [18.4% – 40.6%]
CR, n (%) [95% CI]	11 (15.7%) [8.1% – 26.4%]
CRh*, n (%) [95% CI]	9 (12.9%) [6.1% – 23.0%]
Complete MRD response for CR/CRh*[c], n1/n2[d] (%) [95% CI]	11/20 (55.0%) [31.5 – 76.9]
CR, n1/n2[d] (%) [95% CI]	6/11 (54.5%) [23.4 – 83.3]
CRh*, n1/n2[d] (%) [95% CI]	5/9 (55.6%) [21.2 – 86.3]
Median relapse[e]-free survival (RFS)[e] for CR/CRh* [95% CI]	6.8 months [2.2 to 12.0 months]
Median overall survival [95% CI]	7.5 months [4.0 to 11.8 months]
100-day mortality after alloHSCT[f]	
n/N (%), [95% CI]	1/6 (16.7%) [2.5% – 72.7%]

[a] CR was defined as M1 marrow (≤ 5% of blasts in the bone marrow), no evidence of circulating blasts or extramedullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter) and no relapse within 28 days.
[b] CRh* was defined as M1 marrow (≤ 5% of blasts in the bone marrow), no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter) and no relapse within 28 days.
[c] Complete MRD response. No detectable signal for leukemic cells either by PCR or flow cytometry.
[d] n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. One CR/CRh* responder with missing MRD data was considered as a MRD-non-responder.

[e] Relapse was defined as hematological relapse (blasts in bone marrow greater than 25% following CR) or an extramedullary relapse.
[f] Only patients with HSCT in CR/CRh* remission (with no anti-leukemia agents used prior to HSCT) are included.

5.2 Pharmacokinetic properties

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9-162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (C_{ss}) was achieved within a day and remained stable over time. The increase in mean C_{ss} values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed or refractory ALL, the mean (SD) C_{ss} was 228 (356) pg/mL and 616 (537) pg/mL, respectively. The pharmacokinetics of blinatumomab in patients with MRD positive B-cell precursor ALL was similar to patients with relapsed or refractory ALL.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 4.35 (2.45) L with the continuous intravenous infusion of blinatumomab.

Biotransformation

The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 3.11 (2.98) L/hour. The mean (SD) half-life was 2.10 (1.41) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Body surface area, gender and age

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that age (7 months to 80 years) and gender do not influence the pharmacokinetics of blinatumomab. Body surface area (0.37 to 2.70 m^2) influences the pharmacokinetics of blinatumomab. However, the influence is negligible in adults and body surface area based dosing is recommended in the pediatric population.

Renal impairment

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

Pharmacokinetic analyzes showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal dysfunction and normal renal function. However high inter-patient variability was discerned (CV% up to 96.8%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected.

Hepatic impairment

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with hepatic impairment. Baseline ALT and AST levels were used to assess the effect of hepatic impairment on the

clearance of blinatumomab. Population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab.

Pediatric population

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m^2/day in pediatric patients with relapsed or refractory B-cell precursor ALL. At the recommended doses of 5 and 15 mcg/m^2/day, the mean (SD) steady state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL) and terminal half-life ($t_{1/2,z}$) were 3.91 (3.36) L/m^2, 1.88 (1.90) L/hr/m^2 and 2.19 (1.53) hours, respectively.

The pharmacokinetics of blinatumomab in patients with high-risk first relapsed B-cell precursor ALL was characterized with an estimated mean (SD) C_{ss} at 15 mcg/m^2/day and CL were 921 (1,010) pg/mL and 0.988 (0.450) L/hr/m^2, respectively; the observed values are not considered to be clinically different from those in patients with relapsed or refractory B-cell precursor ALL. Volume of distribution and half-life could not be estimated.

5.3 Preclinical safety data

Repeat-dose toxicity studies conducted with blinatumomab and the murine surrogate revealed the expected pharmacologic effects (including release of cytokines, decreases in leukocyte counts, depletion of B-cells, decreases in T-cells, decreased cellularity in lymphoid tissues). These changes reversed after cessation of treatment.

Reproductive toxicity studies have not been conducted with blinatumomab. In an embryo-fetal developmental toxicity study performed in mice, the murine surrogate crossed the placenta to a limited extent (fetal-to-maternal serum concentration ratio < 1%) and did not induce embryo-fetal toxicity or teratogenicity. The expected depletions of B- and T-cells were observed in the pregnant mice but hematological effects were not assessed in fetuses. No studies have been conducted to evaluate treatment-related effects on fertility. There were no effects on male or female reproductive organs in toxicity studies with the murine surrogate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Citric acid monohydrate (E330)
Trehalose dihydrate
Lysine hydrochloride
Polysorbate 80
Sodium hydroxide NF (for pH-adjustment)

Solution (stabilizer)

Citric acid monohydrate (E330)
Lysine hydrochloride
Polysorbate 80
Sodium hydroxide NF (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C or 4 hours at room temperature (23°C - 27°C). Keep in the outer carton to protect from light.

From a microbiological point of view, unless the method of reconstituting precludes the risks of microbial contamination, the reconstituted solution should be diluted immediately. If not diluted immediately, in-use storage times and conditions are the responsibility of the user.

Diluted solution (prepared infusion bag)

Chemical and physical in-use stability has been demonstrated for 10 days at 2°C – 8°C or 96 hours at room temperature (23°C – 27°C).

From a microbiological point of view, the prepared infusion bags should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C).
Do not freeze.
Store the vials in the original package in order to protect from light.
After removal from the refrigerator, BLINCYTO may be stored at room temperature (23°C – 27°C) and used within 8 hours.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each BLINCYTO pack contains 1 vial of powder for concentrate for solution for infusion and 1 vial of solution (stabilizer):

- 38.5 micrograms blinatumomab powder in a vial (type I glass) with a stopper (elastomeric rubber), seal (aluminum) and a flip off cap, and
- 10 mL solution in a vial (type I glass) with a stopper (elastomeric rubber), seal (aluminum) and a flip off cap.

6.6 Special precautions for disposal and other handling

Aseptic preparation

Aseptic handling must be ensured when preparing the infusion. Preparation of BLINCYTO should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose).

Other instructions

- BLINCYTO is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- At the end of infusion, any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of the solution for infusion

These supplies are also required, but **not** included in the package:

- Sterile single-use disposable syringes
- 21 - 23 gauge needle(s) (recommended)
- Water for injections
- Infusion bag with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection;
    - To minimize the number of aseptic transfers, use a 250 mL pre-filled infusion bag. **BLINCYTO dose calculations are based on a usual overfill volume of 265 to 275 mL sodium chloride 9 mg/mL (0.9%) solution for injection.**
    - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micrometer in-line filter.
    - Ensure that the tubing is compatible with the infusion pump.

Reconstitute BLINCYTO with water for injections. Do not reconstitute BLINCYTO vials with the solution (stabilizer).

To prime the intravenous tubing, use only the solution in the bag containing the FINAL prepared BLINCYTO solution for infusion. Do not prime with sodium chloride 9 mg/mL (0.9%) solution for injection.

Reconstitution of BLINCYTO

1. Determine the number of BLINCYTO vials needed for a dose and infusion duration.
2. Using a syringe, reconstitute each vial of BLINCYTO powder for concentrate using 3 mL of water for injections. Direct the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder.
    - **Do <u>not</u> reconstitute BLINCYTO powder for concentrate with the solution (stabilizer).**
    - The addition of water for injections to the powder for concentrate results in a total volume of 3.08 mL for a final BLINCYTO concentration of 12.5 mcg/mL.
3. Gently swirl contents to avoid excess foaming.
    - **Do not shake.**
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to preparing infusion bag. The resulting solution should be clear to slightly opalescent, colorless-to-slightly yellow.
    - **Do not use if the solution is cloudy or has precipitated.**

Preparation of BLINCYTO infusion bag

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in tables 13 and 14 to prepare the BLINCYTO infusion bag**.

- Table 13 for patients weighing greater than or equal to 45 kg
- Table 14 for patients weighing less than 45 kg

1. Use an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection that usually contains a total volume of 265 to 275 mL.
2. To coat the infusion bag, using a syringe, aseptically transfer 5.5 mL of the solution (stabilizer) to the infusion bag. Gently mix the contents of the bag to avoid foaming. Discard the remaining solution (stabilizer).
3. Using a syringe, aseptically transfer the required volume of reconstituted BLINCYTO solution into the infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection and the solution (stabilizer). Gently mix the contents of the bag to avoid foaming.
   - Refer to table 13 for patients weighing greater than or equal to 45 kg for the specific volume of reconstituted BLINCYTO.
   - Refer to table 14 for patients weighing less than 45 kg (dose based on BSA) for the specific volume of reconstituted BLINCYTO.
   - Discard the vial containing any unused BLINCYTO reconstituted solution.
4. Remove air from the infusion bag. This is particularly important for use with an ambulatory infusion pump.
5. Under aseptic conditions, attach the intravenous tubing to the infusion bag with the sterile 0.2 micron in-line filter. Ensure that the intravenous tubing is compatible with the infusion pump.
6. **Prime the intravenous infusion line only with the solution in the bag containing the FINAL prepared BLINCYTO solution for infusion.**
7. Store refrigerated at 2°C – 8°C if not used immediately.

Table 13. For patients weighing greater than or equal to 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabilizer), and reconstituted BLINCYTO to add to infusion bag

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)			250 mL (usual overfill volume of 265 to 275 mL)	
Solution (stabilizer) (fixed volume for 24, 48, 72, and 96-hour infusion durations)			5.5 mL	
Infusion duration	**Dose**	**Infusion rate**	**Reconstituted BLINCYTO**	
			Volume	**Vials**
24 hours	9 mcg/day	10 mL/hour	0.83 mL	1
	28 mcg/day	10 mL/hour	2.6 mL	1
48 hours	9 mcg/day	5 mL/hour	1.7 mL	1
	28 mcg/day	5 mL/hour	5.2 mL	2
72 hours	9 mcg/day	3.3 mL/hour	2.5 mL	1
	28 mcg/day	3.3 mL/hour	8 mL	3
96 hours	9 mcg/day	2.5 mL/hour	3.3 mL	2
	28 mcg/day	2.5 mL/hour	10.7 mL	4

Table 14. For patients weighing less than 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabilizer), and reconstituted BLINCYTO to add to infusion bag

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)	250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabilizer) (fixed volume for 24, 48, 72, and 96-hour infusion durations)	5.5 mL

Infusion duration	**Dose**	**Infusion rate**	**BSA (m^2)***	**Reconstituted BLINCYTO**	
				Volume	**Vials**
24 hours	5 mcg/m^2/day	10 mL/hour	1.5 – 1.59	0.7 mL	1
			1.4 – 1.49	0.66 mL	1
			1.3 – 1.39	0.61 mL	1
			1.2 – 1.29	0.56 mL	1
			1.1 – 1.19	0.52 mL	1
			1 – 1.09	0.47 mL	1
			0.9 – 0.99	0.43 mL	1
			0.8 – 0.89	0.38 mL	1
			0.7 – 0.79	0.33 mL	1
			0.6 – 0.69	0.29 mL	1
			0.5 – 0.59	0.24 mL	1
			0.4 – 0.49	0.2 mL	1
24 hours	15 mcg/m^2/day	10 mL/hour	1.5 – 1.59	2.1 mL	1
			1.4 – 1.49	2 mL	1
			1.3 – 1.39	1.8 mL	1
			1.2 – 1.29	1.7 mL	1
			1.1 – 1.19	1.6 mL	1
			1 – 1.09	1.4 mL	1
			0.9 – 0.99	1.3 mL	1
			0.8 – 0.89	1.1 mL	1
			0.7 – 0.79	1 mL	1
			0.6 – 0.69	0.86 mL	1
			0.5 – 0.59	0.72 mL	1
			0.4 – 0.49	0.59 mL	1

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)	250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabilizer) (fixed volume for 24, 48, 72, and 96-hour infusion durations)	5.5 mL

Infusion duration	**Dose**	**Infusion rate**	**BSA (m^2)***	**Reconstituted BLINCYTO**	
				Volume	**Vials**
48 hours	5 mcg/m^2/day	5 mL/hour	1.5 – 1.59	1.4 mL	1
			1.4 – 1.49	1.3 mL	1
			1.3 – 1.39	1.2 mL	1
			1.2 – 1.29	1.1 mL	1
			1.1 – 1.19	1 mL	1
			1 – 1.09	0.94 mL	1
			0.9 – 0.99	0.85 mL	1
			0.8 – 0.89	0.76 mL	1
			0.7 – 0.79	0.67 mL	1
			0.6 – 0.69	0.57 mL	1
			0.5 – 0.59	0.48 mL	1
			0.4 – 0.49	0.39 mL	1
48 hours	15 mcg/m^2/day	5 mL/hour	1.5 – 1.59	4.2 mL	2
			1.4 – 1.49	3.9 mL	2
			1.3 – 1.39	3.7 mL	2
			1.2 – 1.29	3.4 mL	2
			1.1 – 1.19	3.1 mL	2
			1 – 1.09	2.8 mL	1
			0.9 – 0.99	2.6 mL	1
			0.8 – 0.89	2.3 mL	1
			0.7 – 0.79	2 mL	1
			0.6 – 0.69	1.7 mL	1
			0.5 – 0.59	1.4 mL	1
			0.4 – 0.49	1.2 mL	1

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)	250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabilizer) (fixed volume for 24, 48, 72, and 96-hour infusion durations)	5.5 mL

Infusion duration	**Dose**	**Infusion rate**	**BSA (m^2)***	**Reconstituted BLINCYTO**	
				Volume	**Vials**
72 hours	5 mcg/m^2/day	3.3 mL/hour	1.5 – 1.59	2.1 mL	1
			1.4 – 1.49	2 mL	1
			1.3 – 1.39	1.8 mL	1
			1.2 – 1.29	1.7 mL	1
			1.1 – 1.19	1.6 mL	1
			1 – 1.09	1.4 mL	1
			0.9 – 0.99	1.3 mL	1
			0.8 – 0.89	1.1 mL	1
			0.7 – 0.79	1 mL	1
			0.6 – 0.69	0.86 mL	1
			0.5 – 0.59	0.72 mL	1
			0.4 – 0.49	0.59 mL	1
72 hours	15 mcg/m^2/day	3.3 mL/hour	1.5 – 1.59	6.3 mL	3
			1.4 – 1.49	5.9 mL	3
			1.3 – 1.39	5.5 mL	2
			1.2 – 1.29	5.1 mL	2
			1.1 – 1.19	4.7 mL	2
			1 – 1.09	4.2 mL	2
			0.9 – 0.99	3.8 mL	2
			0.8 – 0.89	3.4 mL	2
			0.7 – 0.79	3 mL	2
			0.6 – 0.69	2.6 mL	1
			0.5 – 0.59	2.2 mL	1
			0.4 – 0.49	1.8 mL	1

Sodium chloride 9 mg/mL (0.9%) solution for injection (starting volume)	250 mL (usual overfill volume of 265 to 275 mL)
Solution (stabilizer) (fixed volume for 24, 48, 72, and 96-hour infusion durations)	5.5 mL

Infusion duration	**Dose**	**Infusion rate**	**BSA (m^2)***	**Reconstituted BLINCYTO**	
				Volume	**Vials**
96 hours	5 mcg/m^2/day	2.5 mL/hour	1.5 – 1.59	2.8 mL	1
			1.4 – 1.49	2.6 mL	1
			1.3 – 1.39	2.4 mL	1
			1.2 – 1.29	2.3 mL	1
			1.1 – 1.19	2.1 mL	1
			1 – 1.09	1.9 mL	1
			0.9 – 0.99	1.7 mL	1
			0.8 – 0.89	1.5 mL	1
			0.7 – 0.79	1.3 mL	1
			0.6 – 0.69	1.2 mL	1
			0.5 – 0.59	0.97 mL	1
			0.4 – 0.49	0.78 mL	1
96 hours	15 mcg/m^2/day	2.5 mL/hour	1.5 – 1.59	8.4 mL	3
			1.4 – 1.49	7.9 mL	3
			1.3 – 1.39	7.3 mL	3
			1.2 – 1.29	6.8 mL	3
			1.1 – 1.19	6.2 mL	3
			1 – 1.09	5.7 mL	3
			0.9 – 0.99	5.1 mL	2
			0.8 – 0.89	4.6 mL	2
			0.7 – 0.79	4 mL	2
			0.6 – 0.69	3.4 mL	2
			0.5 – 0.59	2.9 mL	2
			0.4 – 0.49	2.3 mL	1

BSA = body surface area
*The safety of the administration of BLINCYTO for BSA of less than 0.4 m^2 has not been established.

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