PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

BLINCYTO® 38,5 µg of lyophilised powder for reconstitution and solution for infusion.

2. QUALITATIVE AND QUATITATIVE COMPOSITION

Each single-use vial contains 38,5 µg preservative-free blinatumomab.

After reconstitution with 3 ml of preservative-free sterile Water for Injection, the resulting total volume of reconstituted solution is 3 ml and each ml contains 12.5 µg blinatumomab.

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- One BLINCYTO® 38,5 µg single-dose vial containing a sterile, preservative-free, white to off-white lyophilised powder
- One IV Solution Stabilizer 10 ml single-dose glass vial containing a sterile, preservative-free, colourless to slightly yellow, clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

MRD-positive B-cell precursor ALL

BLINCYTO® is indicated for the treatment of B-cell precursor acute lymphoblastic leukaemia (ALL) in first or second complete remission (CR) with minimal residual disease (MRD) greater than or equal to 0,1 % in adults and children.

Relapsed or refractory B-cell precursor ALL

BLINCYTO® is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL) in adults and children.

4.2. Posology and Method of Administration

Treatment should be initiated under the direction of and supervision of physicians experienced in the treatment of haematological malignancies.

Posology

MRD-positive B-cell Precursor ALL

- A treatment course consists of 1 cycle of BLINCYTO® for induction followed by up to 3 additional cycles for consolidation.
- A single cycle of treatment of BLINCYTO® induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- See Table 1 for the recommended dose by patient weight and schedule. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 1: Recommended BLINCYTO® Dosage and Schedule for the Treatment of MRD-positive B-cell precursor ALL

Cycle	**Patient Weight Greater Than or Equal to 45 kg *(Fixed-dose)***	**Patient Weight Less Than 45 kg *(BSA-based dose)***
Induction Cycle 1		
Days 1 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29 - 42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 2 - 4		
Days 1 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29 - 42	14-day treatment-free interval	14-day treatment-free interval

- Hospitalisation is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiations (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.
- Pre-medicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL
    - For adult patients, pre-medicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO® in each cycle.

- For pediatric patients, pre-medicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO® in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

Relapsed or Refractory B-cell Precursor ALL

- A treatment course consists of up to 2 cycles of BLINCYTO® for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy.
- A single cycle of treatment of BLINCYTO® induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A single cycle of treatment of BLINCYTO® continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days).
- See Table 2 for the recommended dose by patient weight and schedule. 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 2. Recommended BLINCYTO® Dosage and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL

Cycle	**Patient Weight Greater Than or Equal to 45 kg *(Fixed-dose)***	**Patient Weight Less Than 45 kg *(BSA-based dose)***
Induction Cycle 1		
Days 1 - 7	9 µg/day	5 µg/m^2/day *(not to exceed 9 µg/day)*
Days 8 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29 - 42	14-day treatment-free interval	14-day treatment-free interval
Induction Cycle 2		
Days 1 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29 - 42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 3 - 5		
Days 1 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*

Days 29 - 42	14-day treatment-free interval	14-day treatment free interval
Continued Therapy Cycles 6 - 9		
Days 1 - 28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29 - 84	56-day treatment-free interval	56-day treatment-free interval

- Hospitalisation is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.
- Pre-medicate with dexamethasone
  - For adult patients, pre-medicate with 20 mg dexamethasone 1 hour prior to the first dose of BLINCYTO® of each cycle, prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours.
  - For pediatric patients, pre-medicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO® in the first cycle, prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

Special Populations

Elderly

Of the total number of patients with ALL treated in clinical studies of BLINCYTO® approximately 12 % were 65 and over, while 2 % were 75 and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of serious infections and neurological toxicities, including cognitive disorder, encephalopathy, and confusion.

Renal Impairment

Based on pharmacokinetic analyses, 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 analyses, 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.

Paediatric Population

The safety and efficacy of BLINCYTO® have been established in paediatric patients with relapsed or refractory B-cell precursor ALL. Use of BLINCYTO® is supported by a single-arm trial in paediatric patients with relapsed or refractory B-cell precursor ALL. This study included paediatric patients in the following age groups: 10 infants (1 month up to less than 2 years), 40 children (2 years up to less than 12 years), and 20 adolescents (12 years to less than 18 years). No differences in efficacy were observed between the different age subgroups. The efficacy has also been established based on extrapolation from adequate and well-controlled studies in adults with MRD-positive B-cell precursor ALL.

In general, the adverse reactions in BLINCYTO®-treated paediatric patients were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL, see section 4.8. Adverse reactions that were observed more frequently (> 10 % difference) in the paediatric population compared to the adult population were pyrexia (80 % vs. 61 %), hypertension (26 % vs. 8 %), anaemia (41 % vs 24 %), infusion-related reaction (49 % vs. 34 %), thrombocytopenia (34 % vs 21 %), leukopenia (24 % vs.11 %), and weight increased (17 % vs. 6 %).

In paediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalaemia (50 %) compared to other paediatric age cohorts (15 - 20 %) or adults (17 %).

The steady-state concentrations of blinatumomab were comparable in adult and paediatric patients at the equivalent dose levels based on BSA-based regimens.

Dose adjustments

If the interruption after an adverse event 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 event is longer than 7 days, start a new cycle.

Dose Modification for Toxicity:

Toxicity	**Grade***	**Patients ≥ 45 kg**	**Patients < 45 kg**
Cytokine Release Syndrome (CRS)	Grade 3	• Interrupt BLINCYTO® • Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days, and taper thereafter over 4 days. • When CRS is resolved, restart BLINCYTO® at 9 µg/day, and escalate to 28 µg/day after 7 days if the toxicity does not recur.	• Interrupt BLINCYTO® • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours intravenously or orally for up to 3 days, and taper thereafter over 4 days. • When CRS is resolved, restart BLINCYTO® at 5 µg/m^2/day, and escalate to 15 µg/m2/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue BLINCYTO® permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Events	Seizure	Discontinue BLINCYTO® permanently if more than one seizure.	
	Grade 3	Withhold BLINCYTO® until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO® at 9 µg/day. Escalate to 28 µg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 µg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO® permanently.	Withhold BLINCYTO® until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO® at 5 µg/m^2/day. Escalate to 15 µg/m^2/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 µg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO® permanently.
	Grade 4	Discontinue BLINCYTO® permanently.	

Toxicity	Grade*	Patients ≥ 45 kg	Patients < 45 kg
Other Clinically Relevant Adverse Reactions	Grade 3 (Excluding Infections)	Withhold BLINCYTO® until no more than Grade 1 (mild), then restart BLINCYTO® at 9 µg/day. Escalate to 28 µg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Withhold BLINCYTO® until no more Grade 1 (mild), then restart BLINCYTO® at 5 µg/m^2/day. Escalate to 15 µg/m^2/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider discontinuing BLINCYTO® permanently.	
* Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 is severe, and Grade 4 is life-threatening.			

Method of Administration

Important note: Do not flush the BLINCYTO® infusion line or intravenous catheter, 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.

For instructions on the handling and preparation of the medicinal product before administration, see section 6.6. It is very important that the instructions for preparation (including admixing) and administration provided in this section and section 6.6 are strictly followed to minimize medication errors.

BLINCYTO® solution for infusion is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a 24 to 48 hours.

The BLINCYTO® solution for infusion must be administered using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0,2 µm in-line filter.

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 BLINCYTO® 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

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

Change of infusion bag

The infusion bag must be changed determined by the treating physician for sterility reasons.

4.3. Contraindications

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

4.4. Special Warnings and Precautions for Use

Cytokine release syndrome and infusion reactions

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. The median time to onset of CRS was 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO®, CRS was reported in 15 % of patients with relapsed or refractory ALL and in 7 % of patients with MRD-positive ALL.

Monitor patients for signs or symptoms of these events. Advise outpatients on BLINCYTO® to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt BLINCYTO® until CRS resolves. Discontinue BLINCYTO® permanently if life-threatening CRS occurs.

Administer corticosteroids for severe or life-threatening CRS (see section 4.2).

Neurological events

In patients with ALL receiving BLINCYTO® in clinical studies, neurological toxicities have occurred in approximately 65 % of patients. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO® treatment and the majority of events resolved. The most common (10 %) manifestations of neurological toxicity were headache, and tremor; the neurological toxicity profile varied by age group [see Use in Specific Populations (8,4, 8,5)]. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO® administration occurred in approximately 13 % of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders.

The majority of neurologic events resolved following interruption of BLINCYTO®, but some resulted in treatment discontinuation.

There is limited experience with BLINCYTO® in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical studies.

Monitor patients receiving BLINCYTO® for signs and symptoms of neurological toxicities. Advise outpatients on BLINCYTO® to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue BLINCYTO® as recommended (see section 4.2).

Infections

In patients with ALL receiving BLINCYTO® in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25 % of patients, some of which were life-threatening or fatal. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO®.

Monitor patients for signs and symptoms of infection and treat appropriately (see section 4.2).

Tumour lysis syndrome

Tumour lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO®. Appropriate prophylactic measures, including pre-treatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO® treatment. Monitor for signs or symptoms of TLS. 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 and treated appropriately. Interrupt BLINCYTO® if prolonged neutropenia occurs.

Elevated liver enzymes

Treatment with BLINCYTO® was associated with transient elevations in liver enzymes. In patients with ALL receiving BLINCYTO® in clinical studies, the median time to onset of elevated liver enzymes was 3 days.

The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7 % of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1 % of patients.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO® treatment. Interrupt BLINCYTO® if the transaminases rise to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal (see section 4.2).

Pancreatitis

Fatal pancreatitis has been reported in patients receiving BLINCYTO® in combination with dexamethasone in clinical studies and the post-marketing setting.

Patients should be closely monitored for signs and symptoms of pancreatitis.

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO® (see section 4.2).

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.

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).

Preparation and Administration Errors

Preparation and administration errors have occurred with BLINCYTO® treatment.

Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including under-dosing and overdosing), see section 6.6.

CD19-Negative Relapse

Relapse of CD19-negative B-precursor ALL has been reported in patients receiving Blincyto in clinical trials and the post-marketing setting. Blincyto is not recommended in patients with CD19-negative disease including those who have relapsed with CD19-negative disease after prior anti-CD19 therapy. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.

Lineage switch from ALL to acute myeloid leukaemia (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.

4.5. Interaction with other Medicines 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.

Immunization

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 range following the last cycle of BLINCYTO®.

4.6. Fertility, Pregnancy and Lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential should use contraception during and for at least 48 hours after treatment with BLINCYTO® (see section 4.4).

Pregnancy

Based on its mechanism of action, BLINCYTO® may cause fetal harm including B-cell lymphocytopenia when administered to a pregnant woman. There are no data on the use of BLINCYTO® in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 - 4 % and 15 - 20 %, respectively.

Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis.
The surrogate molecule crossed the placental barrier and did not cause 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.

Due to the potential for depletion of B lymphocytes in infants following exposure to BLINCYTO® during pregnancy, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination (see section 4.4). Live virus vaccines can be administered when the B lymphocytes are within the normal range.

Breastfeeding

There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BLINCYTO®, including B-cell lymphocytopenia, advise patients not to breastfeed during and for at least 48 hours after treatment with BLINCYTO®.

Fertility

No studies have been conducted to evaluate the effects of BLINCYTO® on fertility.
There were no 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

Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while
BLINCYTO® is being administered. Patients should be advised that they may experience neurological events

4.8. Undesirable Effects

Summary of safety profile

MRD-positive B-cell Precursor ALL

The safety of BLINCYTO® in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies in which 137 patients were treated with BLINCYTO®. The median age of the study population was 45 years (range: 18 to 77 years).

The most common adverse reactions (≥ 20 %) were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61 %

of patients. The most common serious adverse reactions (≥ 2 %) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection. Adverse reactions of Grade 3 or higher were reported in 64 % of patients. Discontinuation of therapy due to adverse reactions occurred in 17 % of patients; neurologic events were the most frequently reported reasons for discontinuation. There were 2 fatal adverse events that occurred within 30 days of the end of BLINCYTO® treatment (atypical pneumonia and subdural hemorrhage).

Relapsed or Refractory B-cell Precursor ALL

The safety data described below reflect exposure to BLINCYTO® in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO® (n = 267) or standard of care (SOC) chemotherapy (n = 109). The median age of BLINCYTO®-treated patients was 37 years (range: 18 to 80 years), 60 % were male, 84 % were White, 7 % Asian, 2 % were Black or African American, 2 % were American Indian or Alaska Native, and 5 % were Multiple/Other.

The most common adverse reactions (≥ 20 %) in the BLINCYTO® arm were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62 % of patients. The most common serious adverse reactions (≥ 2 %) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia. Adverse reactions of Grade 3 or higher were reported in 87 % of patients. Discontinuation of therapy due to adverse reactions occurred in 12 % of patients treated with BLINCYTO®; neurologic events and infections were the most frequently reported reasons for discontinuation of treatment due to an adverse reaction. Fatal adverse events occurred in 16 % of patients. The majority of the fatal events were infections.

<u>Tabulated summary of adverse reactions</u>

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 the phase III clinical study. Within each system organ class, adverse reactions are:

MeDRA 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 Fungal infections Viral infections Infections – pathogen unspecified		
Blood and lymphatic system disorders	Anaemia[1] Febrile neutropenia Thrombocytopenia[2] Neutropenia[3]	Leukopenia[4] Leucocytosis[5] Lymphadenopathy Lymphopenia[6] Haematophagic histiocytosis	
Immune system disorders	Cytokine release syndrome	Hypersensitivity	Cytokine storm
Metabolism and nutrition disorders		Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Confusional state Disorientation	
Nervous system disorders	Headache	Tremor Dizziness Somnolence Paraesthesia Hypoesthesia Memory impairment Seizures Aphasia Cognitive disorder Encephalopathy	Speech disorder
Cardiac disorders	Tachycardia[7]		

Vascular disorders	Hypotension[17]	Hypertension[18] Flushing	
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnea[15] Productive cough	
Hepatobiliary disorders		Hyperbilirubinemia[11]	
Skin and subcutaneous tissue disorders	Rash[16]		
Musculoskeletal and connective tissue disorders	Back pain Bone pain	Pain in extremities	
General disorders and administration site conditions	Pyrexia[8] Edema[9]	Chills Chest pain[10] Pain	
Investigations	Hepatic enzyme increased[13]	Decreased immunoglobulins[14] Increased weight Increased blood alkaline phosphatase	
Injury, poisoning and procedural complications	Infusion-related reactions[12]	Overdose Accidental overdose	

1. Anaemia includes anaemia and decreased haemoglobin
2. Thrombocytopenia includes decreased platelet count and thrombocytopenia
3. Neutropenia includes neutropenia and decreased neutrophil count
4. Leukopenia includes leukopenia and decreased white blood cell count
5. Leucocytosis includes leucocytosis and increased white blood cell count
6. Lymphopenia includes decreased lymphocyte count and lymphopenia
7. Tachycardia includes sinus tachycardia, supraventricular tachycardia, and tachycardia
8. Pyrexia includes increased body temperature and pyrexia
9. Oedema includes face oedema, generalized oedema, oedema, and oedema peripheral
10. Chest pain includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain

[11] Hyperbilirubinemia includes increased blood bilirubin and hyperbilirubinemia

[12] 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 the event lasted ≤ 2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous

[13] Hepatic enzyme increased includes increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyl transferase, hepatic enzyme increased, and increased transaminases

[14] Decreased immunoglobulins includes decreased blood immunoglobulin G, decreased globulins, hypogammaglobulinemia, hypoglobulinaemia, and decreased immunoglobulins

[15] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, and wheezing

[16] Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, and rash pruritic

[17] Hypotension includes decreased blood pressure and hypotension

[18] Hypertension includes increased blood pressure and hypertension

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of BLINCYTO®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal pancreatitis, has been reported in patients receiving BLINCYTO® in combination with dexamethasone, see section 4.4.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO® has been evaluated using either an electrochemiluminescence detection technology (ECL) or an enzyme-linked immunosorbent assay (ELISA) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In clinical studies, less than 2 % of patients treated with BLINCYTO® tested positive for binding anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, 7 out of 9 (78 %) had *in vitro* neutralizing activity.
Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO®.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology,

sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

4.9. Overdose

Overdoses have been observed, including one adult patient who received 133-fold the recommended therapeutic dose of BLINCYTO® delivered over a short duration.

In the dose evaluation phase of the Phase 1/2 study in paediatric and adolescent patients with relapsed or refractory B-cell precursor ALL, one patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) at a 30 µg/m^2/day (higher than the maximum tolerated/recommended) dose, see sections 4.4 and 4.8.

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, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care, see section 4.4. Consider re-initiation of BLINCYTO® at the correct therapeutic dose 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

A26 Cytotoxic agents

Mechanism of action

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds 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.

Blinatumomab mediates the formation of a synapse between the T-cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

Pharmacodynamic effects

During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, reduction in peripheral B cells, 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 BLINCYTO® 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 patients. Increase of T-cell counts above baseline (T-cell expansion) was observed in few patients

Peripheral B-cell counts decreased to less than or equal to 10 cells/µl during the first treatment cycle at doses ≥ 5 µg/m^2/day or ≥ 9 µg/day in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO®- free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0,5 µg/m^2/day and 1,5 µg/m^2/day and in a few patients at higher doses.

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 elevated. The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO® 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

MRD-positive B-cell Precursor ALL

BLAST Study

The efficacy of BLINCYTO® was evaluated in an open-label, multicenter, single-arm study (BLAST Study) [NCT01207388] that included patients who were ≥ 18 years of age, had received at least 3 chemotherapy blocks of standard ALL therapy, were in hematologic CR (defined as < 5 % blasts in bone marrow, absolute neutrophil count > 1 Gi/l, platelets > 100 Gi/l) and had MRD at a level of ≥ 0,1 % using an assay with a minimum sensitivity of 0,01 %. BLINCYTO® was administered at a constant dose of 15 µg/m^2/day (equivalent to the recommended dosage of 28 µg/day) intravenously for all treatment cycles. Patients received up to 4 cycles of treatment.
Dose adjustment was possible in case of adverse events.

The treated population included 86 patients in first or second hematologic CR (CR1 or CR2). The demographics and baseline characteristics are shown in Table 3. The median number of treatment cycles was 2 (range: 1 to 4). Following treatment with BLINCYTO®, 45 out of 61 (73,8 %) patients in CR1 and 14 out of 25 (56,0 %) patients in CR2 underwent allogeneic hematopoietic stem cell transplantation (HSCT) in continuous hematologic CR.

Table 3: Demographics and Baseline Characteristics in BLAST Study

Characteristic	**BLINCYTO®** **(N = 86)**
Age	
Median, years (min, max)	43 (18,76)
≥ 65 years, n (%)	10 (12)
Males, n (%)	50 (58)
Race, n (%)	
Asian	1 (1)
Other (mixed)	0 (0)
White	76 (88)
Unknown	9 (11)

Characteristic	BLINCYTO® (N = 86)
Philadelphia chromosome disease status, n (%)	
Positive	1 (1)
Negative	85 (99)
Relapse history, n (%)	
Patients in 1st CR	61 (71)
Patients in 2nd CR	25 (29)
MRD level at baseline*, n (%)	
≥ 10 %	7 (8)
≥ 1 % and < 10 %	34 (40)
≥ 0,1 % and < 1 %	45 (52)

* Assessed centrally using an assay with minimum sensitivity of 0.01 %

Efficacy was based on achievement of undetectable MRD within one cycle of BLINCYTO® treatment and hematological relapse-free survival (RFS). The assay used to assess MRD response had a sensitivity of 0,01 % for 6 patients and.≤ 0,005 % for 80 patients. Overall, undetectable MRD was achieved by 70 patients (81,4 %: 95 % CI: 71,6 %, 89,0 %). The median hematological RFS was 22,3 months.

Table 4 shows the MRD response and hematological RFS by remission number.

Table 4. Efficacy Results in Patients ≥ 18 Years of Age with MRD-positive B-cell Precursor ALL (BLAST Study)

	Patients in CR1 (n=61)	Patients in CR2 (n=25)
Complete MRD response[1], n (%), [95 % CI]	52 (85,2) [73,8, 93,0]	18 (72.0) [50,6, 87,9]
Median hematological relapse-free survival[2] in months (range)	35,2 (0,4, 53,5)	12,3 (0,7, 42,3)

1. Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 0,01%

2.	Relapse was defined as either hematological or extramedullary relapse, secondary leukemia, or death due to any cause; Includes time after transplantation; Kaplan Meier estimate

Undetectable MRD was achieved by 65 of 80 patients (81,3 %: 95 % CI: 71,0 %, 89,1 %) with an assay sensitivity of at least 0,005 %. The estimated median hematological RFS among the 80 patients using the higher sensitivity assay was 24,2 months (95 % CI: 17,9, NE).

Relapsed/Refractory B-cell Precursor ALL

TOWER Study

The efficacy of BLINCYTO® was compared to standard of care (SOC) chemotherapy in a randomized, open-label, multicentre study (TOWER Study) [NCT02013167].

Eligible patients were ≥ 18 years of age with relapsed or refractory B-cell precursor ALL [> 5 % blasts in the bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration < 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT)]. BLINCYTO® was administered at 9 µg/day on Days 1 - 7 and 28 µg/day on Days 8 - 28 for Cycle 1, and 28 µg/day on Days 1 - 28 for Cycles 2 - 5 in 42-day cycles and for Cycles 6 - 9 in 84-day cycles.

Dose adjustment was possible in case of adverse events. SOC chemotherapy included fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (FLAG); high-dose cytarabine arabinoside (HiDAC); high-dose methotrexate- (HDMTX) based combination; or clofarabine/clofarabine-based regimens.

There were 405 patients randomized 2:1 to receive BLINCYTO® or investigator-selected SOC chemotherapy. Randomization was stratified by age (< 35 years vs. ≥ 35 years of age), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see Table 5).

Table 5. Demographics and Baseline Characteristics in TOWER Study

Characteristic	**BLINCYTO® (N = 271)**	**Standard of Care (SOC) Chemotherapy (N = 134)**
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)

< 35 years, n (%)	124 (46)	60 (45)
≥ 35 years, n (%)	147 (54)	74 (55)
≥ 65 years, n (%)	33 (12)	15 (11)
≥ 75 years, n (%)	10 (4)	2 (2)
Males, n (%)	162 (60)	77 (58)
Race, n (%)		
American Indian or Alaska Native	4 (2)	1 (1)
Asian	19 (7)	9 (7)
Black (or African American)	5 (2)	3 (2)
Multiple	2 (1)	0
Native Hawaiian or Other Pacific Islander	1 (0)	1 (1)
Other	12 (4)	8 (6)
White	228 (84)	112 (84)
Prior salvage therapy	171 (63)	70 (52)
Prior alloHSCT[1]	94 (35)	46 (34)
Eastern Cooperative Group Status - n (%)		
0	96 (35)	52 (39)
1	134 (49)	61 (46)
2	41 (15)	20 (15)
Unknown	0	1 (1)
Refractory to salvage treatment - n (%)		
Yes	87 (32)	34 (25)
No	182 (67)	99 (74)
Unknown	2 (1)	1 (1)
Maximum of central/local bone marrow blasts - n (%)		
≤ 5 %	0	0
> 5 to < 10 %	9 (3)	7 (5)
10 to < 50 %	60 (22)	23 (17)
≥ 50 %	201 (74)	104 (78)
Unknown	1 (0)	0

[1] alloHSCT = allogeneic hematopoietic stem cell transplantation

Of the 271 patients randomized to the BLINCYTO® arm, 267 patients received BLINCYTO® treatment. The median number of treatment cycles was two (range: 1 to 9 cycles); 267 (99 %) received Cycles 1 - 2 (induction), 86 (32 %) received Cycles 3 - 5 (consolidation), and 27 (10 %) received Cycles 6 - 9 (continued therapy).

Of the 134 patients on the SOC arm, 25 dropped out prior to start of study treatment, and 109 patients received a median of 1 treatment cycle (range: 1 to 4 cycles).

The determination of efficacy was based on overall survival (OS). The study. demonstrated statistically significant improvement in OS for patients treated with BLINCYTO® as compared to SOC chemotherapy.

See Figure 1 and Table 6 below for efficacy results from the TOWER Study.

Figure 1. Kaplan-Meier Curve of Overall Survival in TOWER Study

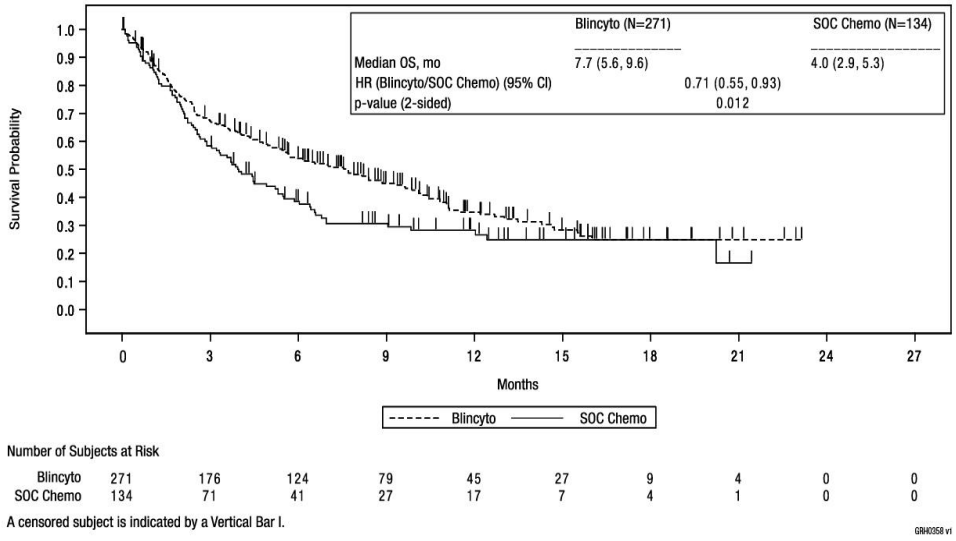


Table 6. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (TOWER Study)

	BLINCYTO® (N = 271)	**SOC Chemotherapy** (N = 134)
Overall Survival		

Number of deaths (%)	164 (61)	87 (65)
Median, months [95 % CI]	7,7 [5,6, 9,6]	4,0 [2,9, 5,3]
Hazard Ratio [95 % CI][1]	0,71 [0,55, 0,93]	
p-value[2]	0,012	
Overall Response		
CR[4]/CRh*[5], n (%) [95 % CI]	115 (42) [37, 49]	27 (20) [14, 28]
Treatment difference [95 % CI]	22 [13, 31]	
p-value[3]	< 0.001	
CR, n (%) [95 % CI]	91 (34) [28, 40]	21 (16) [10, 23]
Treatment difference [95 % CI]	18 [10, 26]	
p-value[3]	< 0,001	
MRD Response[6] for CR/CRh*		
n1/n2 (%)[6] [95 % CI]	73/115 (64) [54, 72]	14/27 (52) [32, 71]

1 Based on stratified Cox's model.

2 The p-value was derived using stratified log rank test.

3 The p-value was derived using Cochran-Mantel-Haenszel test.

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

5 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/µl and ANC > 500/µl).

6 MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10^{-4} (0,01 %).

7 n1: number of patients who achieved MRD response and CR/CRh*; n2: number of patients who achieved CR/CRh* and had a postbaseline assessment.

Study MT103-211

Study MT103-211 [NCT01466179] was an open-label, multicenter, single-arm study.

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 alloHSCT and had ≥ 10 % blasts in bone marrow).

BLINCYTO® was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be 9 µg/day on Days 1 - 7 and 28 µg/day on Days 8 - 28 for Cycle 1, and 28 µg/day on Days 1 - 28 for subsequent cycles. Dose adjustment was possible in case of adverse

events. The treated population included 185 patients who received at least 1 infusion of BLINCYTO®; the median number of treatment cycles was 2 (range: 1 to 5). 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), 63 out of 185 (34,1 %) had undergone HSCT prior to receiving BLINCYTO®, and 32 out of 185 (17,3 %) had received more than 2 prior salvage therapies.

Efficacy was based on the CR rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO®. Table 7 shows the efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39 % (30 out of 77).

Table 7. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell precursor ALL (Study MT103-211)

	N = 185		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	60 (32,4) [25,7 – 39,7]	17 (9,2) [5,4 – 14,3]	77 (41,6) [34,4 – 49,1]
MRD response[3]			
n1/n2 (%)[4] [95 % CI]	48/60 (80,0) [67,7 – 89,2]	10/17 (58,8) [32,9 – 81,6]	58/77 (75,,3) [642 – 84,4]
DOR/RFS[5]			
Median (months) (range)	6,7 (0,46 – 16,5)	5,0 (0,13 – 8,8)	5,9 (0,13 – 16,5)

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

2 CRh* (complete remission with partial hematological recovery) was defined as ≤ 5 % of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/µl and ANC > 500/µl).

3 MRD (minimal residual disease) response was defined as MRD by PCR < 1 x 10^{-4} (0,01 %).

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponder's.

[5] DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5 % following CR) or an extramedullary relapse.

ALCANTARA Study

The efficacy of BLINCYTO® for treatment of Philadelphia chromosome-positive B-cell precursor ALL was evaluated in an open-label, multicenter, single-arm study (ALCANTARA Study) [NCT02000427]. 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 at 9 µg/day on Days 1 - 7 and 28 µg/day on Days 8 - 28 for Cycle 1, and 28 µg/day on Days 1 - 28 for subsequent cycles. Dose adjustment was possible in case of adverse events.

The treated population included 45 patients who received at least one infusion of BLINCYTO®; the median number of treatment cycles was 2 (range: 1 to 5). The demographics and baseline characteristics are shown in Table 8.

Table 8. Demographics and Baseline Characteristics in ALCANTARA Study

Characteristic	**BLINCYTO®** **(N = 45)**
Age	
Median, years (min, max)	55 (23, 78)
≥ 65 years and < 75 years, n (%)	10 (22)
≥ 75 years, n (%)	2 (4)
Males, n (%)	24 (53)
Race, n (%)	
Asian	1 (2)
Black (or African American)	3 (7)
Other	2 (4)
White	39 (87)
Disease History	

Prior TKI treatment[1], n (%)	
1	7 (16)
2	21 (47)
≥ 3	17 (38)
Prior salvage therapy	31 (62)
Prior alloHSCT[2]	20 (44)
Bone marrow blasts[3]	
≥ 50 % to < 75 %	6 (13)
≥ 75 %	28 (62)
[1] Number of patients that failed ponatinib = 23 (51 %) [2] alloHSCT = allogeneic hematopoietic stem cell transplantation [3] centrally assessed	

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO®. Table 9 shows the efficacy results from ALCANTARA Study. Five of the 16 responding (31 %) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO®. There were 10 patients with document T315I mutation; four achieved CR within 2 cycles of treatment with BLINCYTO®.

Table 9. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Positive Relapsed or Refractory B-cell Precursor ALL (ALCANTARA Study)

	N = 45		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95 % CI]	14 (31) [18 – 47]	2 (4) [1 – 15]	16 (36) [22 – 51]
MRD response[3]			
n1/n2 (%)[4] [95 % CI]	12/14 (86) [57 – 98]	2/2 (100) [16, 100]	14/16 (88) [62 – 98]
DOR/RFS[5]			
Median (months) (range)	6,7 (3.6 – 12,0)	NE[6] (3,7 - 9,0)	6,7 (3,6 – 12,0)

1	CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100 000/µl and absolute neutrophil counts [ANC] > 1 000/µl).
2	CRh* (complete remission with partial haematological recovery) was defined as ≤ 5 % of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50 000/µl and ANC > 500/µl).
3	MRD (minimal residual disease) response was defined as MRD by PCR < 1 x 10^{-4} (0,01 %).
4	n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponder's.
5	DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5 % following CR) or an extramedullary relapse.
6	NE = not estimable

Study MT103-205

Study MT103-205 [NCT01471782] was an open-label, multicentre, single-arm study in paediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments, and had > 25 % blasts in bone marrow). BLINCYTO® was administered at 5 µg/m^2/day on Days 1 - 7 and 15 µg/m^2/day on Days 8 - 28 for cycle 1, and 15 µg/m^2/day on Days 1 - 28 for subsequent cycles. Dose adjustment was possible in case of adverse events. Patients who responded to BLINCYTO® but later relapsed had the option to be retreated with BLINCYTO®.

Among the 70 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. The median number of treatment cycles was 1 (range: 1 to 5).

Twenty-three out of 70 (32,9 %) patients achieved CR/CRh* within the first 2 treatment cycles with 17 out of 23 (73,9 %) occurring within cycle 1 of treatment.
See Table 10 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh* was 48 % (11 out of 23).

Table 10. Efficacy Results in Patients < 18 Years of Age with Relapsed or Refractory B-cell precursor ALL (Study MT103-205)

	N = 70

	CR[1]	CRh*[2]	CR/CRh*
n (%) [95 % CI]	12 (17,1) [9,2 – 28,0]	11 (15,7) [8,1 – 26,4]	23 (32,9) [22,1 – 45,1]
MRD response[3]			
n1/n2 (%)[4] [95 % CI]	6/12 (50,0) [21,1 – 78,9]	4/11 (36,4) [10,9 – 69,2]	10/23 (43,5) [23,2 – 65,5]
DOR/RFS[5]			
Median (months) (range)	6,0 (0,5 – 12,1)	3,5 (0,5 – 16,4)	6,0 (0,5 – 16,4)

1. CR (complete remission) was defined as ≤ 5 % of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and full recovery of peripheral blood counts (platelets > 100 000/µl and absolute neutrophil counts [ANC] > 1 000/µl).
2. CRh* (complete remission with partial haematological recovery) was defined as ≤ 5 % of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and partial recovery of peripheral blood counts (platelets > 50 000/µl and ANC > 500/µl).
3. MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4} (0,01 %).
4. 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 an MRD-Nonresponder.
5. DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

5.2. Pharmacokinetic Properties

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 µg/m^2/day (approximately equivalent to 9 to 162 µg/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 µg/day and 28 µg/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.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 4,35 (2,45) l with continuous intravenous infusion of blinatumomab.

Biotransformation

The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO® 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.

Characteristics in patients

Body surface area, gender and age

Population pharmacokinetic analyses indicate that age (0,62 to 80 years of age) and gender do not influence the pharmacokinetics of Blinatumomab. Body surface area (0,4 to 2,70 m^2) influences the pharmacokinetics of blinatumomab, however the clinical relevance of this effect is unknown.

Hepatic impairment

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

Renal impairment

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

Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal impairment (CrCL ranging from 30 to 59 ml/min, N = 21) and normal renal function (CrCL more than 90 ml/min, N = 215). However, high interpatient 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. There is no information available in patients with severe renal impairment (CrCL less than 30 ml/min) or patients on hemodialysis.

Drug Interactions

Transient elevation of cytokines may suppress CYP450 enzyme activities, see sections 4.5 and 5.1.

Paediatric

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 µg/m^2/day in pediatric patients. At the recommended doses of 5 and15 µg/m2/day for the treatment of relapsed or refractory B-cell precursor ALL, the mean (SD) steady state concentration (Css) values were 162 (179) and 533(392) pg/ml. 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.

5.3. Preclinical safety data

No studies have been conducted to evaluate the effects of blinatumomab on fertility.

A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.

Carcinogenicity

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder

Citric acid monohydrate

Trehalose dihydrate

Lysine hydrochloride

Polysorbate 80

Sodium hydroxide

IV solution stabiliser

Citric acid monohydrate

Lysine hydrochloride

Polysorbate 80

Sodium hydroxide

Water for injection

6.2. Incompatibilities:

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

BLINCYTO® is incompatible with di-ethylhexylphthalate (DEHP) due to the possibility of particle formation, leading to a cloudy solution.

- Use polyolefin, PVC DEHP-free, or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Use polyolefin, PVC DEHP-free, or EVA IV tubing sets.

6.3. Shelf life:

Unopened vials: 5 years; refrigerated at 2 ˚C to 8 ˚C.

Solution Stabiliser: 5 years; refrigerated at 2 ˚C to 8 ˚C.

After opening:

The information in Table 11 indicates the storage time for the reconstituted BLINCYTO® vial and prepared infusion bag.

Store lyophilised BLINCYTO® and IV Solution Stabilizer vials for a maximum of 8 hours at room temperature in the original carton to protect from light, see sections 6.4 and 6.5.

Table 11. Storage Time for Reconstituted BLINCYTO® Vial and Prepared BLINCYTO® Infusion Bag

Maximum Storage Time of Reconstituted BLINCYTO® Vial		**Maximum Storage Time of Prepared BLINCYTO® Infusion Bag**	
Room Temperature 23 °C to 27 °C	Refrigerated 2 °C to 8 °C	Room Temperature 23 °C to 27 °C	Refrigerated 2 °C to 8 °C
4 hours	24 hours	48 hours*	8 days
* Storage time includes infusion time. If the prepared BLINCYTO® infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.			

6.4. Special Precautions for Storage

Unopened vials should be stored refrigerated (store between 2 ˚C and 8 ˚C).

Store in original carton to protect from light.

Do not freeze.

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

6.5. Nature and contents of container

Each BLINCYTO® pack contains: 1 vial of lyophilised powder for reconstitution for infusion and 1 vial of solution stabiliser:

- 38,5 µg blinatumomab sterile, preservative-free, white to off-white lyophilised powder in a vial (type I glass) with a grey stopper (elastomeric rubber), seal (aluminium), a yellow flip off cap and grey skirt (aluminium look) and
- 10 ml sterile, preservative-free, colourless to slightly yellow, clear solution in a vial (type I glass) with a grey stopper (elastomeric rubber), seal (aluminium), a clear flip off cap and red skirt.

6.6. Special precautions for disposal and other handling

Reconstitution and Preparation of Solution for Infusion

It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including under-dosing and overdosing), see section 4.4.

BLINCYTO® can be infused over 24 hours or 48 hours. The choice between these options for the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient.

For preparation, reconstitution, and administration of BLINCYTO®:

- See section 6.6 for infusion over 24 hours or 48 hours.

Aseptic Preparation

Strictly observe aseptic technique when preparing the solution for infusion since BLINCYTO® vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO® according to aseptic standards, including but not limited to:

- Prepare BLINCYTO® in a USP <797> compliant facility.
- Prepare BLINCYTO® in an ISO Class 5 laminar flow hood or better.

- Ensure that the admixing area has appropriate environmental specifications, confirmed by periodic monitoring.
- Ensure that personnel are appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Ensure that personnel wear appropriate protective clothing and gloves.
- Ensure that gloves and surfaces are disinfected.

Package content:

NOTE: 1 package of BLINCYTO® includes 1 vial of BLINCYTO® and 1 vial of IV Solution Stabilizer.

- **Do not use IV Solution Stabilizer for reconstitution of BLINCYTO®.** IV Solution Stabilizer is provided with the BLINCYTO® package and is used to coat the intravenous bag prior to addition of reconstituted BLINCYTO® to prevent adhesion of BLINCYTO® to IV bags and intravenous tubing.
- More than 1 package of BLINCYTO® may be needed to prepare the recommended dose.

Preparation and Administration of Blincyto as 24-Hour or 48-Hour Infusion

Reconstitute Blincyto with preservative-free Sterile Water for Injection. Do not reconstitute Blincyto vials with the IV 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 0.9% Sodium Chloride.

Reconstitution of BLINCYTO® for 24-Hour or 48-Hour Infusion

1. Determine the number of BLINCYTO® vials needed for a dose and infusion duration
2. Reconstitute each BLINCYTO® vial with **3 ml of preservative-free Sterile Water** for Injection, by directing the water along the walls of the BLINCYTO® vial and not directly on the lyophilised powder. The resulting concentration per BLINCYTO® vial is 12,5 µg/ml.
    - Do not reconstitute BLINCYTO® with IV Solution Stabilizer.
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 infusion**. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow.

- Do not use if solution is cloudy or has precipitated.

24-Hour or 48-Hour Infusion of BLINCYTO®

Preparation of BLINCYTO® Infusion Bag for 24- or 48-Hour Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO® infusion bag.

To minimize errors, **use the specific volumes described in Tables 12 & 13 to prepare the BLINCYTO® infusion bag.**

- Table 12 for patients weighing greater than or equal to 45 kg
- Tables 13 for patients weighing less than 45 kg

1. Aseptically **add 270 ml 0,9 % Sodium Chloride** to the empty intravenous bag.
2. Aseptically **transfer 5,5 ml IV Solution Stabilizer** to the intravenous bag containing 0,9 % Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. Aseptically **transfer the required volume of reconstituted BLINCYTO® solution** into the intravenous bag containing 0,9 % Sodium Chloride and IV Solution Stabilizer.
   Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 12 for patients weighing greater than or equal to 45 kg for the specific volume of reconstituted Blincyto®.
   - Refer to Table 13 for patients weighing less than 45 kg (dose based on BSA) for the specific volume of reconstituted Blincyto®.
   - Discard the vial containing unused Blincyto®.
4. Under aseptic conditions, attach the intravenous tubing to the intravenous bag with the sterile 0,2 micron in-line filter.
   - Ensure that the intravenous tubing is compatible with the infusion pump.
5. Remove air from the intravenous bag. This is particularly important for use with an ambulatory infusion pump.
6. **Prime the intravenous tubing only with the solution in the bag containing the FINAL prepared BLINCYTO® solution for infusion**.
7. Store refrigerated at 2 °C to 8 °C if not used immediately, see section 6.3.

Table 12. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to Add to Intravenous Bag

0,9% Sodium Chloride (starting volume)			270 ml	
IV Solution Stabilizer (fixed volume for 24 and 48-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

Table 13. For Patients Weighing Less Than 45 kg: Volumes to Add to Intravenous Bag

0,9% Sodium Chloride (starting volume)				270 ml	
IV Solution Stabilizer (fixed volume for 24, and 48-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
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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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