

PACKAGE INSERT

BLINCYTO® (blinatumomab) for injection 35 mcg/vial

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO and treat with corticosteroids as recommended [*see Dosage and Administration (2.4), Warnings and Precautions (5.1)*].
- Neurological toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended [*see Dosage and Administration (2.4), Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 MRD-positive B-cell Precursor ALL

BLINCYTO is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults.

1.2 Relapsed or Refractory B-cell Precursor ALL

BLINCYTO is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients.

1.3 B-cell precursor ALL in the Consolidation Phase

BLINCYTO can be used for pediatric and adult patients with Philadelphia chromosome-negative and CD19-positive B-cell precursor ALL (acute lymphoblastic leukemia) in the consolidation phase [*see Dosage and Administration and Clinical Studies*].

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of 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 weighing 45 kg or more receive a fixed-dose.

Table 1. Recommended BLINCYTO Dose and Schedule for the Treatment of MRD-positive B-cell Precursor ALL

Cycle	Patient Weighing 45 kg or More (Fixed-dose)
<u>Induction Cycle 1</u>	
Days 1-28	28 mcg/day
Days 29-42	14-day treatment-free interval
<u>Consolidation Cycles 2-4</u>	
Days 1-28	28 mcg/day
Days 29-42	14-day treatment-free interval

- Hospitalization 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 hospitalization is recommended.
- Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.
- Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL
 - For adult patients, premedicate 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 administration of BLINCYTO:
 - See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours, or 96 hours.

2.2 Treatment of 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 weighing 45 kg or more receive a fixed-dose and for patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 2. Recommended BLINCYTO Dose and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL

Cycle	Patients Weighing 45 kg or More (Fixed-dose)	Patients Weighing Less than 45 kg (BSA-based dose)
<u>Induction Cycle 1</u>		
Days 1-7	9 mcg/day	5 mcg/m ² /day (not to exceed 9 mcg/day)
Days 8-28	28 mcg/day	15 mcg/m ² /day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
<u>Induction Cycle 2</u>		
Days 1-28	28 mcg/day	15 mcg/m ² /day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
<u>Consolidation Cycles 3-5</u>		
Days 1-28	28 mcg/day	15 mcg/m ² /day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
<u>Continued Therapy Cycles 6-9</u>		
Days 1-28	28 mcg/day	15 mcg/m ² /day (not to exceed 28 mcg/day)
Days 29-84	56-day treatment-free interval	56-day treatment-free interval

- Hospitalization 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 hospitalization is recommended.
- Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.
- Premedicate with dexamethasone
 - For adult patients, premedicate with 20 mg of 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, premedicate with 5 mg/m² 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.

- For administration of BLINCYTO:
 - See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours or 96 hours.

2.3 Treatment of B-cell Precursor ALL in the Consolidation Phase

- Hospitalization 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 reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.
- BLINCYTO is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-week) treatment-free interval. Patients may receive up to 4 cycles of BLINCYTO consolidation treatment.
- See Table 3 for the recommended daily dose by patient weight. Patients weighing greater than or equal to 45 kg receive a fixed-dose, and for patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 3. Recommended Dosage for B-cell Precursor ALL in the Consolidation Phase

Cycle(s) 1-4	Patients Weighing 45 kg or More (Fixed-dose)	Patients Weighing Less than 45 kg (BSA-based dose)
Days 1-28	28 mcg/day	15 mcg/m ² /day (not to exceed 28 mcg/day)
Days 29-42	14-day treatment-free interval	14-day treatment-free interval

- Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.
- Premedicate with dexamethasone
 - For adults patients, premedicate with dexamethasone 20 mg intravenously within 1 hour prior to the first dose of BLINCYTO of each cycle.
 - For pediatric patients, premedicate with 5 mg/m² 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.
- For administration of BLINCYTO:
 - See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours or 96 hours

2.4 Dosage Modifications for Adverse Reactions

If the interruption 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.

Table 4. Dosage Modifications for Adverse Reactions

Adverse Reaction	Grade*	Patients Weighing 45 kg or more	Patients Weighing Less Than 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 mcg/day and escalate to 28 mcg/day after 7 days if the adverse reaction does not recur.	• Interrupt BLINCYTO • Administer dexamethasone 5 mg/m² (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 mcg/m²/day, and escalate to 15 mcg/m²/day after 7 days if the adverse reaction does not recur.
	Grade 4	Discontinue BLINCYTO permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Toxicity	Seizure	Discontinue BLINCYTO permanently if more than one seizure occurs.	
	Grade 2 ICANS	Interrupt BLINCYTO until ICANS resolves. Administer corticosteroids and manage according to current practice guidelines. When ICANS is resolved, restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the adverse reaction does not recur.	Interrupt BLINCYTO until ICANS resolves. Administer corticosteroids and manage according to current practice guidelines. When ICANS is resolved, restart BLINCYTO at 5 mcg/m²/day. Escalate to 15 mcg/m²/day after 7 days if the adverse reaction does not recur.
	Grade 3 Neurologic Events including ICANS	Withhold 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 adverse reaction does not recur. If the adverse reaction occurred at 9 mcg/day, or if the adverse reaction 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 mcg/m²/day. Escalate to 15 mcg/m²/day after 7 days if the adverse reaction does not recur. If the adverse reaction occurred at 5 mcg/m²/day, or if the adverse reaction takes more than 7 days to resolve, discontinue BLINCYTO permanently.
		If ICANS, administer corticosteroids and manage according to current practice guidelines.	
	Grade 4	Discontinue BLINCYTO permanently.	

Adverse Reaction	Grade*	Patients Weighing 45 kg or more	Patients Weighing Less Than 45 kg
	Neurologic Events including ICANS	If ICANS, administer corticosteroids and manage according to current practice guidelines.	
Other Clinically Relevant Adverse Reactions	Grade 3 (Excluding Infections)	Withhold 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 adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Withhold 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 adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider discontinuing BLINCYTO permanently.	

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

2.5 Preparation and Administration of BLINCYTO

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 underdose and overdose) [see Warnings and Precautions (5.10)].

BLINCYTO can be infused over 24 hours, 48 hours, 72 hours or 96 hours. The choice between these options for the infusion duration should be made by the treating healthcare provider considering the frequency of the infusion bag changes and the weight of the patient.

For preparation, reconstitution, and administration of BLINCYTO:

- See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours or 96 hours using 0.9% Sodium Chloride Injection, USP.

The preparation steps differ based on the infusion duration. Follow the steps specific to the infusion duration you are preparing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.5.1 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.

2.5.2 Package Content

One package BLINCYTO includes one vial of BLINCYTO and one 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 intravenous bags and intravenous tubing.
- More than one vial of BLINCYTO may be needed to prepare the recommended doses.

2.5.3 Incompatibility Information

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

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

2.6 Preparation and Administration of BLINCYTO as a 24-Hour, 48-Hour, 72-Hour or 96-Hour Infusion

Reconstitute BLINCYTO with preservative-free Sterile Water for Injection, USP. 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 Injection, USP.

2.6.1 Reconstitution of BLINCYTO for 24-Hour, 48-Hour, 72-Hour or 96-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, USP** by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder. The resulting concentration per BLINCYTO vial is 12.5 mcg/mL.
 - Do not reconstitute BLINCYTO vials 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, prior to preparing the intravenous bag and prior to administration.** The resulting solution should be clear to slightly opalescent, colorless to slightly yellow.

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

2.6.2 Preparation of BLINCYTO Infusion for 24-Hour, 48-Hour, 72-Hour or 96-Hour Infusion Bag

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Tables 5 and 6 to prepare the BLINCYTO infusion bag.**

- Table 5 for patients weighing 45 kg or more
 - Table 6 for patients weighing less than 45 kg
1. Aseptically **add 270 mL 0.9% Sodium Chloride Injection, USP** to the empty intravenous bag.
 2. Aseptically **transfer 5.5 mL IV Solution Stabilizer** to the intravenous bag containing 0.9% Sodium Chloride Injection, USP. 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 Injection, USP and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
 - Refer to Table 5 for patients weighing 45 kg or more for the specific volume of reconstituted BLINCYTO.
 - Refer Table 6 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. Remove air from the intravenous bag. This is particularly important for use with an ambulatory infusion pump.
 5. 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.
 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 *Storage Requirements (2.6)*].

Table 5. For Patients Weighing 45 kg or More

Infusion Duration	Dose	Reconstituted BLINCYTO	
		Volume	Vials
24 hours	9 mcg/day	0.83 mL	1
	28 mcg/day	2.6 mL	1
48 hours	9 mcg/day	1.7 mL	1
	28 mcg/day	5.2 mL	2
72 hours	9 mcg/day	2.5 mL	1
	28 mcg/day	8 mL	3
96 hours	9 mcg/day	3.3 mL	2
	28 mcg/day	10.7 mL	4

Table 6. For Patients Weighing Less Than 45 kg

Infusion Duration	Dose	BSA (m ²)	Reconstituted BLINCYTO	
			Volume	Vials
24 hours	5 mcg/m ² /day	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
		0.35 – 0.39	0.17 mL	1
		0.3 – 0.34	0.15 mL	1
		0.25 – 0.29	0.12 mL	1
		0.2 – 0.24	0.1 mL	1
24 hours	15 mcg/m ² /day	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

Infusion Duration	Dose	BSA (m ²)	Reconstituted BLINCYTO	
			Volume	Vials
		0.35 – 0.39	0.51 mL	1
		0.3 – 0.34	0.44 mL	1
		0.25 – 0.29	0.37 mL	1
		0.2 – 0.24	0.3 mL	1
48 hours	5 mcg/m ² /day	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
		0.35 – 0.39	0.34 mL	1
		0.3 – 0.34	0.29 mL	1
		0.25 – 0.29	0.25 mL	1
		0.2 – 0.24	0.20 mL	1
48 hours	15 mcg/m ² /day	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

Infusion Duration	Dose	BSA (m ²)	Reconstituted BLINCYTO	
			Volume	Vials
		0.6 – 0.69	1.7 mL	1
		0.5 – 0.59	1.4 mL	1
		0.4 – 0.49	1.2 mL	1
		0.35 – 0.39	1 mL	1
		0.3 – 0.34	0.88 mL	1
		0.25 – 0.29	0.75 mL	1
		0.2 – 0.24	0.61 mL	1
72 hours	5 mcg/m ² /day	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
		0.35 – 0.39	0.51 mL	1
		0.3 – 0.34	0.45 mL	1
		0.25 – 0.29	0.37 mL	1
		0.2 – 0.24	0.31 mL	1
72 hours	15 mcg/m ² /day	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

Infusion Duration	Dose	BSA (m ²)	Reconstituted BLINCYTO			
			Volume	Vials		
		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		
		0.35 – 0.39	1.6 mL	1		
		0.3 – 0.34	1.3 mL	1		
		0.25 – 0.29	1.1 mL	1		
		0.2 – 0.24	0.92 mL	1		
		96 hours	5 mcg/m ² /day	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		
0.35 – 0.39	0.68 mL			1		
0.3 – 0.34	0.59 mL			1		
0.25 – 0.29	0.50 mL			1		
0.2 – 0.24	0.40 mL			1		
96 hours	15 mcg/m ² /day	1.5 – 1.59	8.4 mL	3		
		1.4 – 1.49	7.9 mL	3		

Infusion Duration	Dose	BSA (m ²)	Reconstituted BLINCYTO	
			Volume	Vials
		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
		0.35 – 0.39	2.1 mL	1
		0.3 – 0.34	1.8 mL	1
		0.25 – 0.29	1.5 mL	1
		0.2 – 0.24	1.2 mL	1

2.6.3 Administration of BLINCYTO for 24-Hour, 48-Hour, 72-Hour or 96-Hour infusion Bag

- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. 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.
- Administer prepared BLINCYTO final infusion solution using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- 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/hour for a duration of 24 hours, OR
 - Infusion rate of 5 mL/hour for a duration of 48 hours, OR
 - Infusion rate of 3.3 mL/hour for a duration of 72 hours, OR
 - Infusion rate of 2.5 mL/hour for a duration of 96 hours
- **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, infuse BLINCYTO through a dedicated lumen. Before flushing the catheter system, residual amounts of BLINCYTO must be aspirated from the catheter system to avoid bolus administration.**
- At the end of the infusion, discard any unused BLINCYTO solution in the intravenous bag and intravenous tubing in accordance with local requirements.

2.7 Storage of Reconstituted BLINCYTO

The information in Table 7 indicates the storage time for the reconstituted BLINCYTO vial and prepared infusion bag.

Table 7. Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag

	Maximum Storage Time	
	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Reconstituted BLINCYTO Vial	4 hours	24 hours
Prepared BLINCYTO Infusion Bag	96 hours*	10 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.

3 DOSAGE FORMS AND STRENGTHS

For injection: 35 mcg of white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

BLINCYTO is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

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 lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS). Evaluation for HLH/MAS should be considered when CRS is atypical or prolonged, or when features of macrophage activation are present. 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, in 7% of patients with MRD-positive ALL, and in 16% of patients receiving BLINCYTO cycles in the consolidation phase of therapy [see *Adverse Reactions* (6.1)].

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 *Dosage and Administration* (2.4)].

5.2 Neurological Toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome

BLINCYTO can cause serious or life-threatening neurologic toxicity, including ICANS [see *Adverse Reactions* 6.1].

The incidence of neurologic toxicities in clinical trials was approximately 65% [see *Adverse Reactions* (6.1)]. Among patients that experienced a neurologic toxicity, the median time to the first event was within the first 2 weeks of BLINCYTO treatment. The most common ($\geq 10\%$) 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 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 toxicities resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

The incidence of signs and symptoms consistent with ICANS in clinical trials was 7.5%. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

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. 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.

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities, including ICANS. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Management of neurologic toxicity may require interruption or discontinuation of BLINCYTO as recommended and/or treatment with corticosteroids [see *Dosage and Administration* (2.4)].

5.3 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 [see *Adverse Reactions* (6.1)]. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO [see *Adverse Reactions* (6.1)]. Appropriate prophylactic measures, including pretreatment 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 *Dosage and Administration* (2.4)].

5.5 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO [see *Adverse Reactions* (6.1)]. Monitor laboratory parameters (including, but not

limited to, white blood cell count and absolute neutrophil count) during BLINCYTO infusion. Interrupt BLINCYTO if prolonged neutropenia occurs.

5.6 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures and ICANS, patients receiving BLINCYTO are at risk for loss of consciousness [see *Warnings and Precautions* (5.2)]. 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.

5.7 Elevated Liver Enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes [see *Adverse Reactions* (6.1)]. 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.

5.8 Pancreatitis

Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone in clinical studies and the postmarketing setting [see *Adverse Reactions* (6.3)].

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO and dexamethasone [see *Dosage and Administration* (2.4)].

5.9 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 antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

5.10 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 underdose and overdose) [see *Dosage and Administration* (2.4)].

5.11 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 immune recovery following last cycle of BLINCYTO.

5.12 Embryo-Fetal Toxicity

Based on its mechanism of action, BLINCYTO may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO and for 48 hours after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome [see *Warnings and Precautions* (5.1)]
- Neurological Toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome [see *Warnings and Precautions* (5.2)]
- Infections [see *Warnings and Precautions* (5.3)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.4)]
- Neutropenia and Febrile Neutropenia [see *Warnings and Precautions* (5.5)]
- Effects on Ability to Drive and Use Machines [see *Warnings and Precautions* (5.6)]
- Elevated Liver Enzymes [see *Warnings and Precautions* (5.7)]
- Pancreatitis [see *Warnings and Precautions* (5.8)]
- Leukoencephalopathy [see *Warnings and Precautions* (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BLINCYTO in patients with MRD-positive B-cell precursor ALL (n = 137), relapsed or refractory B-cell precursor ALL (n = 267), and Philadelphia chromosome-negative B-cell precursor ALL in consolidation (n = 165) was evaluated in clinical studies. The most common adverse reactions ($\geq 20\%$) to BLINCYTO in this pooled population were pyrexia, infusion-related reactions, headache, infection, musculoskeletal pain, neutropenia, nausea, anemia, thrombocytopenia, and diarrhea.

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 ($\geq 20\%$) 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 ($\geq 2\%$) 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 reactions that occurred within 30 days of the end of BLINCYTO treatment (atypical pneumonia and subdural hemorrhage).

Table 8 summarizes the adverse reactions occurring at a $\geq 10\%$ incidence for any grade or $\geq 5\%$ incidence for Grade 3 or higher.

Table 8. Adverse Reactions Occurring at $\geq 10\%$ Incidence for Any Grade or $\geq 5\%$ Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL

Adverse Reaction	BLINCYTO (N = 137)	
	Any Grade* n (%)	Grade ≥ 3 * n (%)
<i>Blood and lymphatic system disorders</i>		
Neutropenia ¹	21 (15)	21 (15)
Leukopenia ²	19 (14)	13 (9)
Thrombocytopenia ³	14 (10)	8 (6)
<i>Cardiac disorders</i>		
Arrhythmia ⁴	17 (12)	3 (2)
<i>General disorders and administration site conditions</i>		
Pyrexia ⁵	125 (91)	9 (7)
Chills	39 (28)	0 (0)
<i>Infections and infestations</i>		
Infections - pathogen unspecified	53 (39)	11 (8)
<i>Injury, poisoning and procedural complications</i>		
Infusion-related reaction ⁶	105 (77)	7 (5)
<i>Investigations</i>		
Decreased immunoglobulins ⁷	25 (18)	7 (5)
Weight increased	14 (10)	1 (< 1)
Hypertransaminasemia ⁸	13 (9)	9 (7)
<i>Musculoskeletal and connective tissue disorders</i>		
Back pain	16 (12)	1 (< 1)
<i>Nervous system disorders</i>		
Headache ⁹	54 (39)	5 (4)
Tremor ^{9,10}	43 (31)	6 (4)
Aphasia ⁹	16 (12)	1 (< 1)
Dizziness ⁹	14 (10)	1 (< 1)
Encephalopathy ^{9,11}	14 (10)	6 (4)
<i>Psychiatric disorders</i>		
Insomnia ^{9,12}	24 (18)	1 (< 1)
<i>Respiratory, thoracic and mediastinal disorders</i>		
Cough	18 (13)	0 (0)
<i>Skin and subcutaneous tissue disorders</i>		
Rash ¹³	22 (16)	1 (< 1)
<i>Vascular disorders</i>		
Hypotension	19 (14)	1 (< 1)

* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

¹ Neutropenia includes febrile neutropenia, neutropenia, and neutrophil count decreased.

² Leukopenia includes leukopenia and white blood cell count decreased.

³ Thrombocytopenia includes platelet count decreased and thrombocytopenia.

⁴ Arrhythmia includes bradycardia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, tachycardia and ventricular extrasystoles.

⁵ Pyrexia includes body temperature increased and pyrexia.

⁶ Infusion-related reaction 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: cytokine release syndrome, eye swelling, hypertension, hypotension, myalgia, periorbital edema, pruritus generalized, pyrexia, and rash.
- 7 Decreased immunoglobulins includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, hypoglobulinemia, and immunoglobulins decreased.
- 8 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased.
- 9 May represent ICANS.
- 10 Tremor includes essential tremor, intention tremor, and tremor.
- 11 Encephalopathy includes cognitive disorder, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, leukoencephalopathy, memory impairment, somnolence, and toxic encephalopathy.
- 12 Insomnia includes initial insomnia, insomnia, and terminal insomnia.
- 13 Rash includes dermatitis contact, eczema, erythema, rash, and rash maculo-papular.

Additional adverse reactions in patients with MRD-positive ALL that did not meet the threshold criteria for inclusion in Table 8 were:

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: edema peripheral, pain, and chest pain (includes chest pain and musculoskeletal chest pain)

Hepatobiliary disorders: blood bilirubin increased

Immune system disorders: hypersensitivity and cytokine release syndrome

Infections and infestations: viral infectious disorders, bacterial infectious disorders, and fungal infectious disorders

Injury, poisoning and procedural complications: medication error and overdose (includes overdose and accidental overdose)

Investigations: blood alkaline phosphatase increased

Musculoskeletal and connective tissue disorders: pain in extremity and bone pain

Nervous system disorders: seizure (includes seizure and generalized tonic-clonic seizure), speech disorder, and hypoesthesia

Psychiatric disorders: confusional state, disorientation, and depression

Respiratory, thoracic and mediastinal disorders: dyspnea and productive cough

Vascular disorders: hypertension (includes blood pressure increased and hypertension), flushing (includes flushing and hot flush), and capillary leak syndrome

Relapsed or Refractory B-cell Precursor ALL

The safety of BLINCYTO was evaluated 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 ($\geq 20\%$) 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 ($\geq 2\%$) 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.

The adverse reactions occurring at a $\geq 10\%$ incidence for any grade or $\geq 5\%$ incidence for Grade 3 or higher in the BLINCYTO-treated patients in first cycle of therapy are summarized in Table 9.

Table 9. Adverse Reactions Occurring at $\geq 10\%$ Incidence for Any Grade or $\geq 5\%$ Incidence for Grade 3 or Higher in BLINCYTO-treated Patients in First Cycle of Therapy

Adverse Reaction	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	Any Grade* n (%)	Grade $\geq 3^*$ n (%)	Any Grade* n (%)	Grade $\geq 3^*$ n (%)
<i>Blood and lymphatic system disorders</i>				
Neutropenia ¹	84 (31)	76 (28)	67 (61)	61 (56)
Anemia ²	68 (25)	52 (19)	45 (41)	37 (34)
Thrombocytopenia ³	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia ⁴	21 (8)	18 (7)	9 (8)	9 (8)
<i>Cardiac disorders</i>				
Arrhythmia ⁵	37 (14)	5 (2)	18 (17)	0 (0)
<i>General disorders and administration site conditions</i>				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema ⁶	48 (18)	3 (1)	20 (18)	1 (1)
<i>Immune system disorders</i>				
Cytokine release syndrome ⁷	37 (14)	8 (3)	0 (0)	0 (0)
<i>Infections and infestations</i>				
Infections - pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)
Fungal infections disorders	27 (10)	13 (5)	15 (14)	9 (8)
<i>Injury, poisoning and procedural complications</i>				
Infusion-related reaction ⁸	79 (30)	9 (3)	9 (8)	1 (1)
<i>Investigations</i>				
Hypertransaminasemia ⁹	40 (15)	22 (8)	13 (12)	7 (6)
<i>Nervous system disorders</i>				
Headache ¹⁰	61 (23)	1 (< 1)	30 (28)	3 (3)
<i>Skin and subcutaneous tissue disorders</i>				
Rash ¹¹	31 (12)	2 (1)	21 (19)	0 (0)
* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. ¹ Neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased. ² Anemia includes anemia and hemoglobin decreased. ³ Thrombocytopenia includes platelet count decreased and thrombocytopenia. ⁴ Leukopenia includes leukopenia and white blood cell count decreased. ⁵ Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia. ⁶ Edema includes face edema, fluid retention, edema, edema peripheral, peripheral swelling, and swelling face. ⁷ Cytokine release syndrome includes cytokine release syndrome and cytokine storm. ⁸ Infusion-related reaction 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				

Adverse Reaction	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	Any Grade* n (%)	Grade ≥ 3* n (%)	Any Grade* n (%)	Grade ≥ 3* n (%)
⁹ syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous. ⁹ Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased. ¹⁰ May represent ICANS. ¹¹ Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, skin exfoliation, and toxic skin eruption.				

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 in first cycle of therapy are shown in Table 10.

Table 10. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-related Maximal Grade 3-4* in First Cycle of Therapy

	BLINCYTO Grade 3 or 4 (%)	SOC Chemotherapy Grade 3 or 4 (%)
Hematology		
Decreased lymphocyte count	80	83
Decreased white blood cell count	53	97
Decreased hemoglobin	29	43
Decreased neutrophil count	57	68
Decreased platelet count	47	85
Chemistry		
Increased ALT	11	11
Increased bilirubin	5	4
Increased AST	8	4

* Includes only patients who had both baseline and at least one laboratory measurement during first cycle of therapy available.

Other important adverse reactions from pooled relapsed or refractory B-cell precursor ALL studies were:

Blood and lymphatic system disorders: lymphadenopathy, hemophagocytic lymphohistiocytosis, and leukocytosis (includes leukocytosis and white blood cell count increased)

General disorders and administration site conditions: chills, chest pain (includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain), pain, body temperature increased, hyperthermia, and systemic inflammatory response syndrome

Hepatobiliary disorders: hyperbilirubinemia (includes blood bilirubin increased and hyperbilirubinemia)

Immune system disorders: hypersensitivity (includes hypersensitivity, anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, and urticaria)

Injury, poisoning and procedural complications: medication error and overdose (includes overdose, medication error, and accidental overdose)

Investigations: weight increased, decreased immunoglobulins (includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia), blood alkaline phosphatase increased, and hypertransaminasemia

Metabolism and nutrition disorders: tumor lysis syndrome

Musculoskeletal and connective tissue disorders: back pain, bone pain, and pain in extremity
Nervous system disorders: tremor (resting tremor, intention tremor, essential tremor, and tremor), altered state of consciousness (includes altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, stupor, and somnolence), dizziness, memory impairment, seizure (includes seizure and atonic seizure), aphasia, cognitive disorder, speech disorder, hypoesthesia, encephalopathy, paresthesia, and cranial nerve disorders (trigeminal neuralgia, trigeminal nerve disorder, sixth nerve paralysis, cranial nerve disorder, facial nerve disorder, and facial paresis)
Psychiatric disorders: insomnia, disorientation, confusional state, and depression (includes depressed mood, depression, suicidal ideation, and completed suicide)
Respiratory, thoracic and mediastinal disorders: dyspnea (includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, respiratory distress, bronchospasm, bronchial hyperreactivity, tachypnea, and wheezing), cough, and productive cough
Vascular disorders: hypotension (includes blood pressure decreased, hypotension, hypovolemic shock, and circulatory collapse), hypertension (includes blood pressure increased, hypertension, and hypertensive crisis), flushing (includes flushing and hot flush), and capillary leak syndrome.

B-cell Precursor ALL in the Consolidation Phase

Study E1910

The safety of a consolidation regimen comprised of multiple cycles of BLINCYTO monotherapy in addition to multiple cycles of chemotherapy (BLINCYTO arm) was evaluated in a randomized trial in adult patients with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL (Study E1910) [NCT02003222] [see *Clinical Studies* (14.3)] which included 111 patients treated in the BLINCYTO arm and 112 patients treated in the chemotherapy alone arm. In the BLINCYTO arm, the median (range) of cycles was 8 (1-8) (4 cycles of BLINCYTO and 4 cycles of chemotherapy). In the chemotherapy alone arm, the median (range) of cycles was 4 (1-4).

Fatal adverse reactions occurred in 2 patients (2%) during BLINCYTO cycles and were due to infection (n = 1) and coagulopathy (n=1). Permanent discontinuation of BLINCYTO due to an adverse reaction occurred in 2% of patients. Dosage interruptions of BLINCYTO due to an adverse reaction occurred in 5% of patients. Dose reductions of BLINCYTO due to an adverse reaction occurred in 28% of patients.

The most common ($\geq 20\%$) adverse reactions during consolidation cycles in the BLINCYTO arm were neutropenia, thrombocytopenia, anemia, leukopenia, headache, infection, nausea, lymphopenia, diarrhea, musculoskeletal pain, and tremor. The adverse reactions occurring at a difference between arms in incidence of $\geq 10\%$ for All Grades or $\geq 5\%$ for Grade 3 or higher are summarized in Table 11.

Table 11. Adverse Reactions with a Difference Between Arms of $\geq 10\%$ for Any Grade or $\geq 5\%$ for Grade 3 or 4 during Consolidation (Study E1910)

Adverse Reaction	Consolidation Consisting of			
	BLINCYTO Cycles + Chemotherapy Cycles (n = 111)		Chemotherapy Cycles Alone (n = 112)	
	All Grades (%) ⁷	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia ¹	82	77	89	89
Thrombocytopenia ¹	75	57	75	71
Anemia	59	29	50	38
Leukopenia ¹	43	41	57	56

Lymphopenia ¹	32	30	25	23
Febrile neutropenia	19	19	25	25
Gastrointestinal disorders				
Nausea ²	32	5	22	4
Diarrhea ¹	29	3	15	3
Immune system disorders				
Cytokine release syndrome ³	16	4	0	0
Infections and infestations				
Infection – pathogen unspecified	35	31	22	21
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ⁴	23	5	5	4
Nervous system disorders				
Headache ⁶	41	5	30	5
Tremor ⁶	23	3	3	0
Aphasia ^{5,6}	10	8	0	0
Vascular disorders				
Hypertension	12	10	5	3

¹ Other related adverse reactions included: ²Nausea: vomiting; ³Cytokine release syndrome: capillary leak syndrome; ⁴Musculoskeletal pain: pain in extremity, back pain, arthralgia, myalgia, neck pain, flank pain, bone pain, non-cardiac chest pain; ⁵Aphasia: dysarthria.

⁶ May represent ICANS.

⁷ Includes the following fatal adverse reaction: infection (n=1).

Study 20120215

The safety of BLINCYTO as the 3rd cycle of the consolidation phase was evaluated in a randomized, open-label study (Study 20120215) following induction and two cycles of consolidation chemotherapy in pediatric and young adult patients with high-risk first-relapsed B-cell precursor ALL [see *Clinical Studies* (14.3)]. The study included 54 patients treated with one cycle of BLINCYTO and 52 patients treated with one cycle of chemotherapy.

Serious adverse reactions occurred in 28% of patients who received BLINCYTO. Permanent discontinuation of BLINCYTO due to an adverse reaction occurred in 4% of patients. Adverse reactions that led to discontinuation included nervous system disorder and seizure. Dosage interruptions of BLINCYTO due to an adverse reaction occurred in 11% of patients. Adverse reactions which required dosage interruption in > 2% of patients included nervous system disorder.

The most common ($\geq 20\%$) adverse reactions in the BLINCYTO arm were pyrexia, nausea, headache, rash, hypogammaglobulinemia, and anemia. The adverse reactions occurring at a difference of $\geq 10\%$ incidence for any grade or at a difference of $\geq 5\%$ incidence for Grade 3 or 4 between the BLINCYTO arm and chemotherapy arm are summarized in Table 12.

Table 12. Adverse Reactions with a Difference Between Arms of $\geq 10\%$ for Any Grade or $\geq 5\%$ for Grade 3 or 4 during Consolidation Cycle 3 (Study 20120215)

Adverse Reaction	BLINCYTO (n = 54)		Chemotherapy (n = 52)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Anemia ¹	24	15	46	42

Adverse Reaction	BLINCYTO (n = 54)		Chemotherapy (n = 52)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutropenia ¹	19	17	35	31
Thrombocytopenia ¹	15	15	39	35
Febrile neutropenia	2	2	25	25
Gastrointestinal disorders				
Nausea ²	43	2	31	2
Abdominal pain ¹	13	0	23	2
Stomatitis ³	11	4	60	29
General disorders and administration site conditions				
Pyrexia	76	6	19	0
Hepatobiliary disorders				
Liver function test abnormal ⁴	9	6	27	17
Immune system disorders				
Hypogammaglobulinemia ¹	24	2	12	2
Infections and infestations				
Infection – pathogen unspecified	13	6	29	10
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ⁵	9	0	29	2
Nervous system disorders				
Headache ⁷	37	0	15	0
Skin and subcutaneous disorders				
Rash ¹	22	2	12	0
Vascular disorders				
Hemorrhage ⁶	11	2	23	6

¹ Other related adverse reactions included: ²Nausea: vomiting; ³Stomatitis: mouth ulceration, mucosal inflammation; ⁴Liver function test abnormal: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia; ⁵Musculoskeletal pain: back pain, pain in extremity, bone pain; ⁶Hemorrhage: Epistaxis, petechiae, hemarthrosis, hematoma, hematuria.

⁷ May represent ICANS.

6.2 Postmarketing 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 in patients receiving BLINCYTO in combination with dexamethasone [see *Warnings and Precautions (5.8)*].

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BLINCYTO. Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g.,

cyclosporine). Adjust the dose of the concomitant drug as needed [see *Clinical Pharmacology* (12.2, 12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLINCYTO may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on the use of BLINCYTO in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier (see *Data*).

Blinatumomab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD19 on B-cells and the finding of B-cell depletion in non-pregnant animals, blinatumomab can cause B-cell lymphocytopenia in infants exposed to blinatumomab *in-utero*. Advise pregnant women of the potential risk to a fetus.

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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Due to the potential for B-cell lymphocytopenia in infants following exposure to BLINCYTO *in-utero*, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination [see *Warnings and Precautions* (5.11)].

Data

Animal Data

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.

8.2 Lactation

Risk Summary

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 breastfed infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during treatment with BLINCYTO and for at least 48 hours after the last dose.

8.3 Females and Males of Reproductive Potential

BLINCYTO may cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BLINCYTO treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO and for at least 48 hours after the last dose.

8.4 Pediatric Use

Relapsed or Refractory B-cell Precursor ALL

The safety and efficacy of BLINCYTO have been established in pediatric patients with relapsed or refractory B-cell precursor ALL. Use of BLINCYTO is supported by a single-arm trial in pediatric patients with relapsed or refractory B-cell precursor ALL. This study included pediatric 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 [*see Clinical Studies (14.2)*].

In general, the adverse reactions in BLINCYTO-treated pediatric patients with relapsed or refractory ALL were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL [*see Adverse Reactions (6.1)*]. Adverse reactions that were observed more frequently ($\geq 10\%$ difference) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).

In pediatric patients less than 2 years old (infants) with relapsed or refractory ALL, 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 hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

B-cell Precursor ALL in the Consolidation Phase

The safety and efficacy of BLINCYTO for the treatment of Philadelphia chromosome-negative B-cell precursor ALL in the consolidation phase have been established in pediatric patients. Use of BLINCYTO for this indication is supported by extrapolation from a randomized controlled study in adults (Study E1910, NCT02003222) and evidence from two randomized, controlled studies in pediatric patients (Study 20120215 and Study AALL1331) [*see Adverse Reactions (6.1)*, *Use in Specific Populations (8.4)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.3)*].

8.5 Geriatric Use

There were 158 (7%) patients 65 years and older in clinical studies of BLINCYTO for patients with MRD positive, CD19 positive B-cell precursor ALL in first or second complete remission, relapsed or refractory CD19 positive B-cell precursor ALL, and CD19 positive, Philadelphia-chromosome negative B-cell precursor ALL in the consolidation phase. Of the total number of BLINCYTO-treated patients in these

studies, 123 (8%) were 65 years of age and older and 21 (1%) were 75 years of age or 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 [*see Warnings and Precautions (5.2, 5.3)*].

10 OVERDOSAGE

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 ½ a study in pediatric 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 mcg/m²/day (higher than the maximum tolerated/recommended) dose [*see Warnings and Precautions (5.1) and Adverse Reactions (6)*].

Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended dosage and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of adverse reactions, and provide supportive care [*see Warnings and Precautions (5.10)*]. Consider re-initiation of BLINCYTO at the recommended dosage when all adverse reactions have resolved and no earlier than 12 hours after interruption of the infusion [*see Dosage and Administration (2.1, 2.2 and 2.3)*].

11 DESCRIPTION

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager. Blinatumomab is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each BLINCYTO package contains one vial BLINCYTO and one vial IV Solution Stabilizer.

BLINCYTO (blinatumomab) for injection is supplied in a single-dose vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous use. Each single-dose vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-dose vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-dose vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

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 of 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/microliter during the first treatment cycle at doses ≥ 5 mcg/m²/day or ≥ 9 mcg/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 mcg/m²/day and 1.5 mcg/m²/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.

12.3 Pharmacokinetics

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m²/day (approximately equivalent to 9 to 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 adult patients with MRD positive B-cell precursor ALL and in adult patients with B-cell precursor ALL in the consolidation phase were similar to patients with relapsed or refractory ALL.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 5.27 (4.37) L with continuous intravenous infusion of blinatumomab.

Metabolism

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 3.10 (2.94) L/hour. The mean (SD) half-life was 2.20 (1.34) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Specific populations

There were no clinically meaningful differences in the pharmacokinetics of blinatumomab based on age (0.6 to 80 years of age), sex, race (72% White, 17% Asian, 3% Black, ethnicity or Philadelphia chromosome status or mild (total bilirubin $\leq$ upper limit of normal [ULN] and AST $>$ ULN or total bilirubin $>$ 1 to $1.5 \times$ ULN and any AST) or moderate hepatic impairment (total bilirubin $>$ 1.5 to $3 \times$ ULN and any AST). The effect of other races or severe hepatic impairment (total bilirubin $>$ $3 \times$ ULN, any AST) on the pharmacokinetics of blinatumomab is unknown. Body surface area (0.4 to 2.9 m^2) influences the pharmacokinetics of blinatumomab, supporting BSA-based dosing in patients $< 45 \text{ kg}$.

Pediatric Patients

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to $30 \text{ mcg/m}^2/\text{day}$ in pediatric patients. At the recommended doses of 5 and $15 \text{ mcg/m}^2/\text{day}$ for the treatment of relapsed or refractory B-cell precursor ALL, the mean (SD) steady-state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL respectively. The pharmacokinetics of blinatumomab in pediatric patients with B-cell precursor ALL in the consolidation phase were similar to pediatric patients with relapsed or refractory ALL.

In all pediatric patients with ALL, the estimated mean (SD) volume of distribution (V_z), clearance (CL) and terminal half-life ($t_{1/2,z}$) in Cycle 1 were 4.14 (3.32) L/m^2 , 1.65 (1.62) L/hr/m^2 and 2.14 (1.44) hours, respectively.

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

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 , $N = 49$) and normal renal function (CrCL more than 90 mL/min , $N = 674$). However, high interpatient variability was discerned (CV% up to 98.4%), and clearance values in renal impaired patients were essentially within the range observed in subjects with normal renal function. There is no information available in patients with severe renal impairment (CrCL 15 - 29 mL/min) or patients on hemodialysis.

Drug Interactions

Transient elevation of cytokines may suppress CYP450 enzyme activities [see *Drug Interactions (7)* and *Clinical Pharmacology (12.2)*].

12.6 Immunogenicity

The observed incidence of anti-drug antibody is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibody in the studies described below with the incidence of anti-drug antibodies in other studies, including those of BLINCYTO.

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.

Overall, the totality of clinical evidence supports the finding that anti-blinatumomab antibodies are not suggestive of any clinical impact on the safety or effectiveness of BLINCYTO.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

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.

14 CLINICAL STUDIES

14.1 MRD-positive B-cell Precursor ALL

BLAST Study

The efficacy of BLINCYTO was evaluated in an open-label, multicenter, single-arm study (BLAST Study) that included patients who were ≥ 18 years of age, had received at least 3 chemotherapy blocks of standard ALL therapy, were in hematologic complete remission (defined as $< 5\%$ blasts in bone marrow, absolute neutrophil count $> 1 \text{ Gi/L}$, platelets $> 100 \text{ Gi/L}$) and had MRD at a level of $\geq 0.1\%$ using an assay with a minimum sensitivity of 0.01% . BLINCYTO was administered at a constant dose of $15 \text{ mcg/m}^2/\text{day}$ (equivalent to the recommended dosage of 28 mcg/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 complete remission (CR1 or CR2). The demographics and baseline characteristics are shown in Table 13. 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 in continuous hematologic complete remission.

Table 13. Demographics and Baseline Characteristics in BLAST Study

Characteristics	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)

Philadelphia chromosome disease status, n (%)	
Positive	1 (1)
Negative	85 (99)
Relapse history, n (%)	
Patients in 1 st CR	61 (71)
Patients in 2 nd 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 14 shows the MRD response and hematological RFS by remission number.

Table 14. 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).

14.2 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, multicenter study (TOWER Study). 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 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/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 15).

Table 15. Demographics and Baseline Characteristics in TOWER Study

Characteristics	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 16 below for efficacy results from the TOWER Study.

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

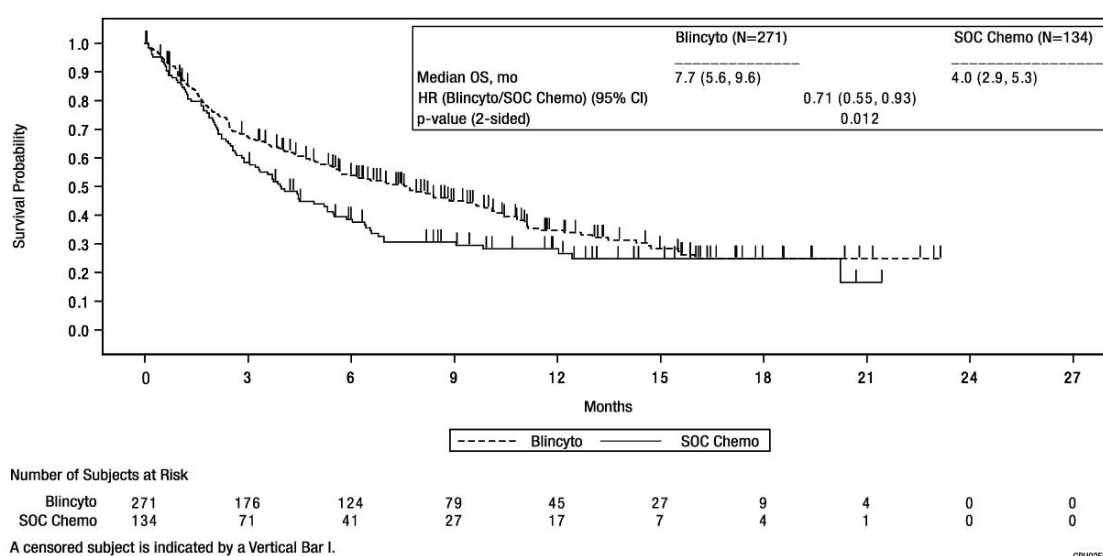


Table 16. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (TOWER Study)

	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 (%) ⁷ [95% CI]	73/115 (64) [54, 72]	14/27 (52) [32, 71]

¹ Based on stratified Cox's model.

	BLINCYTO (N = 271)	SOC Chemotherapy (N = 134)
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- 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 $\leq 5\%$ blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets $> 100,000/\text{microliter}$ and absolute neutrophil counts [ANC] $> 1,000/\text{microliter}$).
- ⁵ CRh* (complete remission with partial hematologic recovery) was defined as $\leq 5\%$ blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets $> 50,000/\text{microliter}$ and ANC $> 500/\text{microliter}$).
- ⁶ MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry $< 1 \times 10^{-4}$ (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 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 $\geq 10\%$ blasts in bone marrow).

BLINCYTO was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/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 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 17 shows the efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39% (30 out of 77).

Table 17. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell precursor ALL (Study MT103-211)

	N = 185		
	CR¹	CRh*²	CR/CRh*
n (%)	60 (32.4)	17 (9.2)	77 (41.6)
[95% CI]	[25.7, 39.7]	[5.4, 14.3]	[34.4, 49.1]
MRD response³			
n1/n2 (%) ⁴	48/60 (80.0)	10/17 (58.8)	58/77 (75.3)
[95% CI]	[67.7, 89.2]	[32.9, 81.6]	[64.2, 84.4]

	N = 185		
	CR¹	CRh*²	CR/CRh*³
DOR/RFS⁵			
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 $\leq 5\%$ of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets $> 100,000/\text{microliter}$ and absolute neutrophil counts [ANC] $> 1,000/\text{microliter}$).

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

³ MRD (minimal residual disease) response was defined as MRD by PCR $< 1 \times 10^{-4}$ (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-nonresponders.

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 hematological 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). 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 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/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 18.

Table 18. Demographics and Baseline Characteristics in ALCANTARA Study

Characteristics	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)

Characteristics	BLINCYTO (N = 45)
≥ 3	17 (38)
Prior salvage therapy	31 (62)
Prior alloHSCT ²	20 (44)
Bone marrow blasts ³	
$\geq 50\%$ to $< 75\%$	6 (13)
$\geq 75\%$	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 19 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 documented T315I mutation; four achieved CR within 2 cycles of treatment with BLINCYTO.

Table 19. 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 (%)	14 (31)	2 (4)	16 (36)
[95% CI]	[18, 47]	[1, 15]	[22, 51]
MRD response³			
n1/n2 (%) ⁴	12/14 (86)	2/2 (100)	14/16 (88)
[95% CI]	[57, 98]	[16, 100]	[62, 98]
DOR/RFS⁵			
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 $\leq 5\%$ of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets $> 100,000/\text{microliter}$ and absolute neutrophil counts [ANC] $> 1,000/\text{microliter}$).

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

³ MRD (minimal residual disease) response was defined as MRD by PCR $< 1 \times 10^{-4}$ (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-nonresponders.

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 hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

⁶ NE = not estimable.

Study MT103-205

Study MT103-205 was an open-label, multicenter, single-arm study in pediatric 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 mcg/m²/day on Days 1-7 and 15 mcg/m²/day on Days 8-28 for Cycle 1, and 15 mcg/m²/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 20 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh* was 48% (11 out of 23).

Table 20. 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 (%)	12 (17.1)	11 (15.7)	23 (32.9)
[95% CI]	[9.2, 28.0]	[8.1, 26.4]	[22.1, 45.1]
MRD response³			
n1/n2 (%) ⁴	6/12 (50.0)	4/11 (36.4)	10/23 (43.5)
[95% CI]	[21.1, 78.9]	[10.9, 69.2]	[23.2, 65.5]
DOR/RFS⁵			
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 $\leq 5\%$ of blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, and full recovery of peripheral blood counts (platelets $> 100,000/\text{microliter}$ and absolute neutrophil counts [ANC] $> 1,000/\text{microliter}$).

² CRh* (complete remission with partial hematological recovery) was defined as $\leq 5\%$ of blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts (platelets $> 50,000/\text{microliter}$ and ANC $> 500/\text{microliter}$).

³ MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry $< 1 \times 10^{-4}$ (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 a 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 hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

14.3 B-cell precursor ALL in the Consolidation Phase

Study E1910

In Study (E1910 [20129152]), the safety and efficacy of BLINCYTO were evaluated in a Phase 3, randomized, controlled study in adult patients with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL. Eligible patients received induction chemotherapy. After induction, patients in hematologic complete remission (CR) or CR with incomplete peripheral blood count recovery (CRi) continued on study and received intensification chemotherapy. After intensification therapy, 286 patients were randomized or assigned to receive BLINCYTO alternating with chemotherapy (n = 152) or standard of care (SOC) consolidation chemotherapy alone (n = 134). Patients in each arm received the same maintenance chemotherapy. Randomization was stratified by MRD status (MRD negativity defined as $< 1 \times 10^{-4}$), age (< 55 years versus ≥ 55 years), CD20 status, rituximab use, and intent to receive allogeneic stem cell transplant (SCT).

The BLINCYTO arm of the study consisted of 2 cycles of BLINCYTO (each cycle consisted of 28 mcg/day BLINCYTO administered as continuous intravenous infusion for 28 days, with a 14-day treatment-free interval between cycles), followed by 3 cycles of consolidation chemotherapy, another cycle of BLINCYTO (third cycle of BLINCYTO) followed by an additional cycle of consolidation chemotherapy, and then a fourth cycle of BLINCYTO. The SOC arm of the study consisted of 4 cycles of consolidation chemotherapy. Patients in each arm received the same number of cycles and doses of consolidation chemotherapy. Patients who were randomized to the SOC arm could proceed directly to allogeneic SCT or to consolidation chemotherapy. Patients who were randomized or assigned to the BLINCYTO arm received 2 cycles of BLINCYTO, and thereafter could proceed to allogeneic SCT or continue on to receive 2 additional cycles of BLINCYTO.

Baseline demographics and characteristics were generally well-balanced between the 2 treatment arms. For the SOC chemotherapy plus blinatumomab arm and SOC chemotherapy arm, 45.4% and 52.2% of subjects, respectively, were male and 54.6% and 47.8% of subjects, respectively, were female; median age at enrolment was 51 years and 50.5 years, respectively. Overall, 58.7% of subjects were < 55 years of age and 41.3% of subjects were > 55 years of age. Of the subjects who had data on race, 77.0% and 82.15% in the SOC chemotherapy plus blinatumomab arm and SOC chemotherapy arm, respectively, were white, 7.9% and 3.7%, respectively, were black or African American, 2.6% and 1.5%, respectively, were Asian, 1.3% and 0.7%, respectively, were American Indian or Alaska native, and 0.7% and 0.0%, respectively, were native Hawaiian or other Pacific Islander. Of the subjects who provided ethnicity, 82.2% and 82.8%, respectively, were not of Hispanic or Latino ethnicity, and 13.8% and 11.2%, respectively, were Hispanic or Latino. The overall median percentage of bone marrow blasts was 1.0%. Most subjects had an ECOG performance status of 0 (37.1%) or 1 (58.7%).

The primary endpoint was overall survival (OS) in patients who were MRD-negative. Secondary endpoints included relapse-free survival (RFS) in patients who were MRD-negative, OS and RFS in patients who were MRD-positive.

The study demonstrated improvement in OS and RFS. The stratified hazard ratios and Kaplan-Meier estimates for OS and RFS in patients who were MRD-negative or MRD-positive, and all patients combined regardless of MRD status are provided in Table 21.

Table 21. Overall Survival in MRD-negative Patients

	BLINCYTO Arm	SOC Arm
MRD-negative		
Number of patients	112	112
Median follow-up time (years) ^{a,b}	4.5	4.5
Overall Survival		
5-year Kaplan-Meier estimate (%) [95% CI]	82.4 [73.7, 88.4]	62.5 [52.0, 71.3]
Hazard ratio [95% CI] ^c	0.44 [0.25, 0.76]	
p-value	0.003	

Full analysis set includes all randomized or assigned patients who are assessed as MRD-negative or MRD-positive centrally after induction and intensification chemotherapy. CI = Confidence interval. Relapse-free survival (RFS) is calculated from time of randomization or registration until relapse or death due to any cause. Overall survival (OS) is calculated from time of randomization or registration until death due to any cause.

MRD-positive defined as MRD value $\geq 1 \times 10^{-4}$ and MRD-negative defined as MRD value $< 1 \times 10^{-4}$.

^a Years are calculated as days from randomisation date to event/censor date, divided by 365.25.

^b Time to censoring measures follow-up time calculated by reversing the status indicator for censored and events.

^c The hazard ratio estimates are obtained from a stratified Cox regression model. A hazard ratio < 1.0 indicates a lower average death rate and a longer survival for patients in the BLINCYTO arm relative to patients in the SOC arm.

Study 20120215

The safety and efficacy of BLINCYTO compared to “standard of care” (SOC) 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-precursor ALL and had $< 25\%$ blasts in the bone marrow. Patients were enrolled after induction and 2 blocks of consolidation chemotherapy.

Patients were randomized 1:1 to receive BLINCYTO or a third block of SOC chemotherapy. Patients in the BLINCYTO arm received one cycle of BLINCYTO as a continuous intravenous infusion at $15 \text{ mcg/m}^2/\text{day}$ over 4 weeks (maximum daily dose was not to exceed 28 mcg/day). Dose adjustment was possible in case of adverse events. Randomization was stratified by age (1 to 9 years, < 1 year and > 9 years), bone marrow status determined at the end of the second block of chemotherapy and MRD status determined at the end of induction. The demographics and baseline characteristics were well-balanced between the two arms).

Approximately half of the subjects were females (52.3%), and prevalent number of the subjects were white (86.5%). The median (range) age was 5.0 (1, 17) years, and majority of the subjects were in the age group of 1 to 9 years (72.1%). Important baseline disease characteristics, including favourable and unfavourable cytogenetics, time elapsing from diagnosis to relapse, extramedullary disease status at primary diagnosis and at relapse, bone marrow disease burden, MRD assessment by PCR and flow cytometry, and white blood cell counts were similar between the treatment arms.

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 chemotherapy. The overall median follow-up time for EFS was 51.9 months (95% CI: 47.2 to 62.1 months). In patients who received the SOC chemotherapy, the 5-year Kaplan-Meier estimate of EFS was 27.6% (95% CI: 16.2%, 40.3%) compared to 57.8% (95% CI: 42.5% to 70.4%) in patients who received BLINCYTO. The EFS hazard ratio from a stratified Cox proportional hazard model was 0.35 (95% CI: 0.20, 0.61). 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 Table 22 for efficacy results from Study 20120215.

Table 22. Efficacy Results in Pediatric Patients with High-risk First Relapsed B-cell precursor ALL (20120215)

	BLINCYTO (N = 54)	SOC Chemotherapy (N = 57)
Event-free survival^a		
Events, n (%)	21 (38.9)	37 (64.9)
Median, months [95% CI]	NE ^b [24.8, NE ^b]	7.8 [5.8, 13.4]
5-year KM estimate (%) [95% CI] ^a	57.8 [42.5, 70.4]	27.6 [16.2, 40.3]
Hazard ratio [95% CI] ^{b, c}	0.35 [0.20, 0.61]	
p-value ^d	< 0.001	

Note: Efficacy results from final analysis (data cut-off of 21 November 2022).

NE = Not estimable. PCR = Polymerase chain reaction. CI = Confidence interval.

^a Months were calculated as days from randomization date to event/censor date, divided by 30.5.

^b Stratification factors were: age (1 to 9 years vs. other [< 1 year and > 9 years]), and marrow/MRD status (M1 with MRD level $< 10^{-3}$ vs M1 with MRD level $\geq 10^{-3}$ vs M2).

^c The hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicated a lower average event rate and a longer EFS for BLINCYTO relative to SOC chemotherapy.

^d The p-value was derived using a stratified log-rank test.

The median follow-up time for the secondary endpoint OS was 55.2 months for the overall population. The OS hazard ratio from a stratified Cox proportional hazard model was 0.33 (95% CI: 0.16 to 0.66). The median OS was 25.6 months (95% CI: 17.5 months to NE) in the SOC chemotherapy arm and was not reached in the BLINCYTO arm. The Kaplan-Meier estimate of survival at 5 years was 41.4% (95% CI: 26.3% to 55.9%) in the SOC chemotherapy arm and 78.4% (95% CI: 64.2% to 87.4%) in the BLINCYTO consolidation arm.

Study AALL1331

In addition, the safety and efficacy of BLINCYTO were evaluated in a randomized, phase 3 open-label study in pediatric and young adult patients (≥ 1 to < 31 years of age) at first relapse with Philadelphia-negative B-cell acute lymphoblastic leukemia (B-ALL) (AALL1331 [20139021]). Enrolled patients received reinduction chemotherapy, and upon completion, were risk-assessed as either high-risk (HR), intermediate-risk (IR) or low-risk (LR) relapse, or treatment-failure. Risk stratification was based on site of relapse, time to relapse, and end-of-reinduction bone marrow morphology and MRD levels. The primary endpoint was disease-free survival (DFS), the main factors of secondary endpoint were overall survival and tolerability. BLINCYTO was administered by continuous IV infusion at a dose of 15 mcg/m²/day. Each BLINCYTO cycle lasted 5 weeks (28 day continuous IV infusion, followed by a 7-day treatment-free interval).

In the HR/IR group, 103 eligible patients were randomized to receive chemotherapy and 105 eligible patients were randomized to receive 2 cycles of BLINCYTO. The median follow-up time for DFS in the HR/IR group was 5.2 years for the BLINCYTO arm. The 5-year DFS rate was 49.4% (95% CI: 39.5%, 58.5%) in the BLINCYTO arm and 38.5% (95% CI: 29%, 48.0%) in the chemotherapy arm (1 sided $p = 0.064$). The DFS hazard ratio from a stratified Cox proportional hazard model was 0.75 (95% CI: 0.52, 1.09).

In the LR group, 128 eligible patients were randomized to receive chemotherapy alone and 127 eligible patients were randomized to receive 3 cycles BLINCYTO alternating with chemotherapy. The median follow-up time for DFS in the LR group was 4.6 years for the BLINCYTO arm. The 5-year DFS rate was 59.7% (95% CI: 49.6%, 68.4%) in the BLINCYTO arm and 43.2% (95% CI: 33.7%, 52.2%) in the chemotherapy arm (1 sided p = 0.020). The DFS hazard ratio from a stratified Cox proportional hazard model was 0.68 (95% CI: 0.47, 0.99).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each BLINCYTO package contains:

- One BLINCYTO (blinatumomab) for injection 35 mcg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized powder and
- One IV Solution Stabilizer 10 mL single-dose glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. **Do not use the IV Solution Stabilizer to reconstitute BLINCYTO.**

16.2 Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C. Do not freeze.

BLINCYTO and IV Solution Stabilizer vials may be stored for a maximum of 8 hours at room temperature [23°C to 27°C (73°F to 81°F)] in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Cytokine Release Syndrome (CRS)

Advise patients of the risk of CRS and infusion reactions, and to contact their healthcare professional for signs and symptoms associated with CRS or infusion reactions (pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing) [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

Neurological Toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome

Advise patients of the risk of neurological toxicities, including ICANS, and to contact their healthcare professional for signs and symptoms associated with this event (including convulsions, speech disorders, and confusion) [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.1)].

Infections

Advise patients of the risk of infections, and to contact their healthcare professional for signs or symptoms of infection [see *Warnings and Precautions* (5.3) and *Adverse Reactions* (6.1)].

Inform patients of the importance of keeping the skin clean around the intravenous catheter to reduce the risk of infection.

Pancreatitis

Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis which include severe and persistent stomach pain, with or without nausea and vomiting [see *Warnings and Precautions* (5.8) and *Adverse Reactions* (6.3)].

Driving and Engaging in Hazardous Occupations

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, including seizures and ICANS [see *Warnings and Precautions* (5.6)].

Infusion Pump Errors

Inform patients they should not adjust the setting on the infusion pump. Any changes to pump function may result in dosing errors. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant [see *Warnings and Precautions* (5.12) and *Use in Specific Populations* (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO and for at least 48 hours after the last dose [see *Warnings and Precautions* (5.12) and *Use in Specific Populations* (8.3)].

Lactation

Advise women not to breastfeed during treatment with BLINCYTO and for at least 48 hours after the last dose [see *Use in Specific Populations* (8.2)].



BLINCYTO® (blinatumomab)

Product Registration Holder:

Amgen Biopharmaceuticals Malaysia Sdn Bhd
Common Ground, 1 Powerhouse,
Horizon Penthouse, No. 1,
Persiaran Bandar Utama, Bandar Utama,
47800 Petaling Jaya, Selangor, Malaysia.

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