

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPKINLY safely and effectively. See full prescribing information for EPKINLY.

EPKINLY® (epcoritamab-hysp) injection, for subcutaneous use
Initial U.S. Approval: 2023

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

See full prescribing information for complete boxed warning.

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity. (2.1, 2.2, 2.6, 5.1)

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity. (2.1, 2.2, 2.6, 5.2)

-----RECENT MAJOR CHANGES-----	
Indications and Usage (1.2)	6/2024
Dosage and Administration (2.1, 2.2, 2.3, 2.7, 2.8, 2.9, 2.10)	6/2024
Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	6/2024

-----INDICATIONS AND USAGE-----

EPKINLY is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of:

Diffuse Large B-cell Lymphoma and High-grade B-cell Lymphoma

- adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. (1.1)

Follicular Lymphoma

- adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. (1.2)

These indications are approved under accelerated approval based on response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

- DOSAGE AND ADMINISTRATION-----
- For subcutaneous injection only. (2.2)
 - Recommended Dosage: (2.2)

DLBCL and High-grade B-cell Lymphoma

Cycle of treatment ^a	Day of treatment	Dose of EPKINLY	
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	First full dose	48 mg
	22		48 mg
Cycles 2 and 3	1, 8, 15 and 22		48 mg
Cycles 4 to 9	1 and 15		48 mg
Cycle 10 and beyond	1		48 mg

^a Cycle = 28 days

Follicular Lymphoma

Cycle of treatment ^a	Day of treatment	Dose of EPKINLY	
Cycle 1	1	Step-up dose 1	0.16 mg
	8	Step-up dose 2	0.8 mg
	15	Step-up dose 3	3 mg
	22	First full dose	48 mg
Cycles 2 and 3	1, 8, 15 and 22		48 mg
Cycles 4 to 9	1 and 15		48 mg
Cycle 10 and beyond	1		48 mg

^a Cycle = 28 days

- Monitor all patients for signs and symptoms of CRS and ICANS. (2.1)
- Patients with DLBCL or high-grade B-cell lymphoma should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg. (2.1)
- Administer premedications, post-medications, and prophylaxis as recommended. (2.4, 2.5)
- Dosages of EPKINLY 0.16 mg and 0.8 mg require dilution prior to administration. (2.7, 2.8)
- See Full Prescribing Information for instructions on preparation and administration. (2.7, 2.8, 2.9, 2.10)

- DOSAGE FORMS AND STRENGTHS-----
- Injection: 4 mg/0.8 mL in a single-dose vial. (3)
 - Injection: 48 mg/0.8 mL in a single-dose vial. (3)

-----CONTRAINDICATIONS-----

None. (4)

- WARNINGS AND PRECAUTIONS-----
- Infections: Can cause serious or fatal infections. Monitor patients for signs or symptoms of infection, including opportunistic infections, and treat appropriately. (5.3)
 - Cytopenias: Monitor complete blood cell counts during treatment. (5.4)
 - Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.5, 8.1, 8.3)

-----ADVERSE REACTIONS-----

LBCL: The most common (≥ 20%) adverse reactions are cytokine release syndrome, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets. (6.1)

FL: The most common (≥ 20%) adverse reactions are injection site reactions, cytokine release syndrome, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, pyrexia, cough, and headache. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genmab US, Inc. at 1-855-4GENMAB (1-855-443-6622) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2024

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FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity [see *Dosage and Administration* (2.1, 2.2, 2.6) and *Warnings and Precautions* (5.1)].

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity [see *Dosage and Administration* (2.1, 2.2, 2.6) and *Warnings and Precautions* (5.2)].

1 INDICATIONS AND USAGE

1.1 DLBCL and High-grade B-cell Lymphoma

EPKINLY is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and durability of response [see *Clinical Studies* (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Follicular Lymphoma

EPKINLY is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and durability of response [see *Clinical Studies* (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- Certain doses of EPKINLY require **dilution** prior to administration. There are 2 available methods to prepare **diluted** EPKINLY:

- Empty sterile vial method as described in subsection 2.7 [see [Dosage and Administration \(2.7\)](#)], or
- Sterile syringe method as described in subsection 2.8 [see [Dosage and Administration \(2.8\)](#)].
- Preparation of 3 mg and 48 mg EPKINLY doses do not require dilution. For preparation, refer to subsection 2.9 [see [Dosage and Administration \(2.9\)](#)].
- Administer EPKINLY to well-hydrated patients.
- Premedicate before each dose in Cycle 1 [see [Dosage and Administration \(2.4\)](#)].
- EPKINLY should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [see [Warnings and Precautions \(5.1, 5.2\)](#)].
- Administer EPKINLY subcutaneously according to the step-up dosage schedule in Table 1 for patients with DLBCL or high-grade B-cell Lymphoma, or Table 2 for patients with FL to reduce the incidence and severity of CRS.
- Due to the risk of CRS and ICANS, monitor all patients for signs and symptoms [see [Dosage and Administration \(2.6\)](#)].
 - For Patients with DLBCL or High-grade B-cell Lymphoma:
Patients should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg [see [Dosage and Administration \(2.2\)](#) and [Warnings and Precautions \(5.1, 5.2\)](#)].

2.2 Recommended Dosage

EPKINLY is for subcutaneous injection only.

Administer EPKINLY in 28-day cycles until disease progression or unacceptable toxicity.

Table 1: EPKINLY 2-step up Dosage Schedule for Patients with DLBCL or High-grade B-cell Lymphoma

Indication	Cycle of treatment ^a	Day of treatment	Dose of EPKINLY	
DLBCL or High-grade B-cell Lymphoma	Cycle 1	1	Step-up dose 1	0.16 mg
		8	Step-up dose 2	0.8 mg
		15	First full dose	48 mg
		22	48 mg	
	Cycles 2 and 3	1, 8, 15 and 22	48 mg	

	Cycles 4 to 9	1 and 15	48 mg
	Cycle 10 and beyond	1	48 mg

^a Cycle = 28 days

Table 2: EPKINLY 3-step up Dosage Schedule for Patients with FL

Indication	Cycle of treatment ^a	Day of treatment	Dose of EPKINLY	
Follicular Lymphoma	Cycle 1	1	Step-up dose 1	0.16 mg
		8	Step-up dose 2	0.8 mg
		15	Step-up dose 3	3 mg
		22	First full dose	48 mg
	Cycles 2 and 3	1, 8, 15 and 22	48 mg	
	Cycles 4 to 9	1 and 15	48 mg	
	Cycle 10 and beyond	1	48 mg	

^a Cycle = 28 days

2.3 Restarting EPKINLY after Dosage Delay

If a dose of EPKINLY is delayed, restart therapy based on the recommendations made in Table 3 for patients with DLBCL or high-grade B-cell lymphoma, or Table 4 for patients with FL [*see Dosage and Administration (2.2)*].

Table 3: Recommendations for Restarting Therapy with EPKINLY After Dosage Delay for Patients with DLBCL or High-grade B-cell Lymphoma

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s) ^a
0.16 mg (e.g., on Cycle 1 Day 1)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
0.8 mg (e.g., on Cycle 1 Day 8)	14 days or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
48 mg (e.g., on Cycle 1 Day 15 onwards)	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)^a
^a Administer pretreatment medication prior to EPKINLY dose and monitor patients accordingly [<i>see Dosage and Administration (2.4, 2.6)</i>].		

Table 4: Recommendations for Restarting Therapy with EPKINLY After Dosage Delay for Patients with FL

Last Dose Administered	Time Since the Last Dose Administered	Action for Next Dose(s)^a
0.16 mg (e.g., on Cycle 1 Day 1)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
0.8 mg (e.g., on Cycle 1 Day 8)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
3 mg (e.g., on Cycle 1 Day 15)	14 days or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
48 mg (e.g., on Cycle 1 Day 22 onwards)	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
^a Administer pretreatment medication prior to EPKINLY dose and monitor patients accordingly [<i>see Dosage and Administration (2.4, 2.6)</i>].		

2.4 Recommended Pre- and Post-Administration Medications

Administer pre- and post-administration medications as outlined in Table 5 to reduce the risk of CRS [*see Warnings and Precautions (5.1)*].

Table 5: EPKINLY Pre- and Post-Administration Medications

Cycle	Patients requiring medication	Medication	Administration
Cycle 1	All patients	<ul style="list-style-type: none"> Dexamethasone^a (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent 	<ul style="list-style-type: none"> 30-120 minutes prior to each weekly administration of EPKINLY And for three consecutive days following each weekly administration of EPKINLY in Cycle 1
		<ul style="list-style-type: none"> Diphenhydramine (50 mg oral or intravenous) or equivalent Acetaminophen (650 mg to 1,000 mg oral) 	<ul style="list-style-type: none"> 30-120 minutes prior to each weekly administration of EPKINLY
Cycle 2+	Patients who experienced Grade 2 or 3 ^b CRS with previous dose	<ul style="list-style-type: none"> Dexamethasone^a (15 mg oral or intravenous) or Prednisolone (100 mg oral or intravenous) or equivalent 	<ul style="list-style-type: none"> 30-120 minutes prior to next administration of EPKINLY after a Grade 2 or 3^b CRS event And for three consecutive days following the next administration of EPKINLY until EPKINLY is given without subsequent CRS of Grade 2 or higher
^a Dexamethasone is the preferred corticosteroid when available. ^b Patients will be permanently discontinued from EPKINLY after Grade 4 CRS.			

2.5 Recommended Prophylaxis

Pneumocystis jirovecii pneumonia (PJP)

Provide PJP prophylaxis prior to starting treatment with EPKINLY.

Herpes virus

Consider initiating prophylaxis against herpes virus prior to starting EPKINLY to prevent herpes zoster reactivation.

2.6 Dosage Modifications and Management of Adverse Reactions

See Tables 6 and 7 for recommended actions for adverse reactions of CRS and ICANS, respectively. See Table 8 for recommended actions for other adverse reactions following administration of EPKINLY.

Cytokine Release Syndrome (CRS)

Identify CRS based on clinical presentation [see [Warnings and Precautions \(5.1\)](#)]. Evaluate for and treat other causes of fever, hypotension, and hypoxia.

If CRS is suspected, withhold EPKINLY until CRS resolves. Manage according to the recommendations in Table 6 and consider further management per current practice guidelines. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS.

Table 6: Recommendations for Management of Cytokine Release Syndrome

Grade ^a	Presenting Symptoms	Actions
Grade 1	Temperature $\geq 100.4^{\circ}\text{F}$ (38°C) ^b	<ul style="list-style-type: none">Withhold EPKINLY and manage per current practice guidelines.Ensure CRS symptoms are resolved prior to next dose of EPKINLY.^c
Grade 2	Temperature $\geq 100.4^{\circ}\text{F}$ (38°C) ^b with: Hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen ^e by nasal cannula or blow-by.	<ul style="list-style-type: none">Withhold EPKINLY and manage per current practice guidelines.Ensure CRS symptoms are resolved prior to next dose of EPKINLY.^cAdminister premedication^d prior to next dose of EPKINLY.For the next dose of EPKINLY, monitor more frequently and consider hospitalization.
Grade 3	Temperature $\geq 100.4^{\circ}\text{F}$ (38°C) ^b with: Hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen ^e by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	<ul style="list-style-type: none">Withhold EPKINLY and manage per current practice guidelines, which may include intensive care.Ensure CRS symptoms are resolved prior to the next dose of EPKINLY.^cAdminister premedication^d prior to next dose of EPKINLY.Hospitalize for the next dose of EPKINLY.
		Recurrent Grade 3 CRS <ul style="list-style-type: none">Permanently discontinue EPKINLY.Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
Grade 4	Temperature $\geq 100.4^{\circ}\text{F}$ (38°C) ^b with:	<ul style="list-style-type: none">Permanently discontinue EPKINLY.

Grade ^a	Presenting Symptoms	Actions
	Hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation).	<ul style="list-style-type: none"> Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
<p>^a Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.</p> <p>^b Premedication may mask fever, therefore if clinical presentation is consistent with CRS, follow these management guidelines.</p> <p>^c Refer to Table 3 or Table 4 for information on restarting EPKINLY after dosage delays [see Dosage and Administration (2.3)].</p> <p>^d If Grade 2 or 3 CRS occurs with the second full dose (48 mg) or beyond, administer CRS pre- and post-administration medications with each subsequent dose until a EPKINLY dose is given without subsequent CRS of Grade 2 or higher. Refer to Table 5 for additional information on pre- and post-administration medications.</p> <p>^e Low-flow oxygen defined as oxygen delivered at < 6L/minute; high-flow oxygen defined as oxygen delivered at ≥ 6 L/minute.</p>		

Immune Effector Cell-Associated Neurological Toxicity Syndrome (ICANS)

Monitor patients for signs and symptoms of ICANS [see [Warnings and Precautions \(5.2\)](#)]. At the first sign of ICANS, withhold EPKINLY and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for ICANS [see [Warnings and Precautions \(5.2\)](#)]. Manage ICANS according to the recommendations in Table 7 and consider further management per current practice guidelines.

Table 7: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome

Grade ^a	Presenting Symptoms ^b	Actions
Grade 1	ICE score 7-9 ^c , Or depressed level of consciousness ^d : awakens spontaneously.	<ul style="list-style-type: none"> Withhold EPKINLY until ICANS resolves.^e Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
Grade 2	ICE score 3-6 ^c , Or depressed level of consciousness ^d : awakens to voice.	<ul style="list-style-type: none"> Withhold EPKINLY until ICANS resolves.^e Administer dexamethasone^f 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

Grade ^a	Presenting Symptoms ^b	Actions
		<ul style="list-style-type: none"> • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
Grade 3	<p>ICE score 0-2^c,</p> <p>Or depressed level of consciousness^d: awakens only to tactile stimulus,</p> <p>Or seizures,^d either:</p> <ul style="list-style-type: none"> • Any clinical seizure, focal or generalized, that resolves rapidly, or • Non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, <p>Or raised intracranial pressure: focal/local edema on neuroimaging.^d</p> 	<p>First Occurrence of Grade 3 ICANS</p> <ul style="list-style-type: none"> • Withhold EPKINLY until ICANS resolves.^e • Administer dexamethasone^f 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. <p>Recurrent Grade 3 ICANS</p> <ul style="list-style-type: none"> • Permanently discontinue EPKINLY • Administer dexamethasone^f 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
Grade 4	<p>ICE score 0^c,</p> <p>Or depressed level of consciousness^d: either:</p> <ul style="list-style-type: none"> • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma 	<ul style="list-style-type: none"> • Permanently discontinue EPKINLY. • Administer dexamethasone^f 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

Grade ^a	Presenting Symptoms ^b	Actions
	<p>Or seizures,^d either:</p> <ul style="list-style-type: none"> Life-threatening prolonged seizure (> 5 minutes), or Repetitive clinical or electrical seizures without return to baseline in between, <p>Or motor findings^d:</p> <ul style="list-style-type: none"> Deep focal motor weakness, such as hemiparesis or paraparesis, <p>or raised intracranial pressure/cerebral edema,^d with signs/symptoms such as:</p> <ul style="list-style-type: none"> Diffuse cerebral edema on neuroimaging, or Decerebrate or decorticate posturing, or Cranial nerve VI palsy, or Papilledema, or Cushing's triad. 	<ul style="list-style-type: none"> Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.
<p>^a Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.</p> <p>^b Management is determined by the most severe event, not attributable to any other cause.</p> <p>^c If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.</p> <p>^d Not attributable to any other cause.</p> <p>^e See Table 3 or Table 4 for recommendations on restarting EPKINLY after dosage delays [see Dosage and Administration (2.3)].</p> <p>^f All references to dexamethasone administration are dexamethasone or equivalent.</p>		

Table 8: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reaction ¹	Severity ¹	Action
Infections [see Warnings and Precautions (5.3)]	Grades 1-4	<ul style="list-style-type: none"> Withhold EPKINLY in patients with active infection, until the infection resolves.² For Grade 4, consider permanent discontinuation of EPKINLY.

Adverse Reaction ¹	Severity ¹	Action
Neutropenia [see Warnings and Precautions (5.4)]	Absolute neutrophil count less than $0.5 \times 10^9/\text{L}$	<ul style="list-style-type: none"> Withhold EPKINLY until absolute neutrophil count is $0.5 \times 10^9/\text{L}$ or higher.²
Thrombocytopenia [see Warnings and Precautions (5.4)]	Platelet count less than $50 \times 10^9/\text{L}$	<ul style="list-style-type: none"> Withhold EPKINLY until platelet count is $50 \times 10^9/\text{L}$ or higher.²
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3 or higher	<ul style="list-style-type: none"> Withhold EPKINLY until the toxicity resolves to Grade 1 or baseline.²
¹ Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. ² See Table 3 or Table 4 for recommendations on restarting EPKINLY after dosage delays [see Dosage and Administration (2.3)].		

2.7 Preparation of Diluted EPKINLY using the Vial Method

Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require **dilution** prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to improper dose. This section describes preparation of diluted EPKINLY using empty sterile vial method. For preparation using sterile syringe method, see subsection 2.8 [see [Dosage and Administration \(2.8\)](#)].

EPKINLY is prepared and administered by a healthcare provider as a subcutaneous injection. The administration of EPKINLY takes place over the course of 28-day cycles, following the step-up dosage schedule in Section 2.2.

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

Use aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

0.16 mg Dose Preparation Instructions (2 dilutions required) – Empty Sterile Vial Method

Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial
 - a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
 - b. Allow the vial to come to room temperature for no more than 1 hour.
 - c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform first dilution
 - a. Label an appropriately sized empty vial as “**Dilution A.**”
 - b. Transfer **0.8 mL of EPKINLY** into the **Dilution A** vial.

<ul style="list-style-type: none"> c. Transfer 4.2 mL of 0.9% Sodium Chloride Injection into the Dilution A vial. The initially diluted solution contains 0.8 mg/mL of EPKINLY. d. Gently swirl the Dilution A vial for 30 to 45 seconds.
3. Perform second dilution <ul style="list-style-type: none"> a. Label an appropriately sized empty vial as “Dilution B.” b. Transfer 2 mL of solution from the Dilution A vial into the Dilution B vial. The Dilution A vial is no longer needed. c. Transfer 8 mL of 0.9% Sodium Chloride Injection into the Dilution B vial to make a final concentration of 0.16 mg/mL. d. Gently swirl the Dilution B vial for 30 to 45 seconds.
4. Withdraw dose <ul style="list-style-type: none"> a. Withdraw 1 mL of the diluted EPKINLY from the Dilution B vial into a syringe.
5. Label syringe <ul style="list-style-type: none"> a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

0.8 mg Dose Preparation Instructions (**1 dilution required**) – Empty Sterile Vial Method

Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial <ul style="list-style-type: none"> a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator. b. Allow the vial to come to room temperature for no more than 1 hour. c. Gently swirl the EPKINLY vial. <p>DO NOT invert, vortex, or vigorously shake the vial.</p>
2. Perform dilution <ul style="list-style-type: none"> a. Label an appropriately sized empty vial as “Dilution A”. b. Transfer 0.8 mL of EPKINLY into the Dilution A vial. c. Transfer 4.2 mL of 0.9% Sodium Chloride Injection into the Dilution A vial to make a final concentration of 0.8 mg/mL. d. Gently swirl the Dilution A vial for 30 to 45 seconds.
3. Withdraw dose <ul style="list-style-type: none"> a. Withdraw 1 mL of the diluted EPKINLY from the Dilution A vial into a syringe.
4. Label syringe <ul style="list-style-type: none"> a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.8 Preparation of Diluted EPKINLY using the Syringe Method

Read this entire section carefully before preparation of EPKINLY. Certain doses of EPKINLY require **dilution** prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to improper dose.

EPKINLY is prepared and administered by a healthcare provider as a subcutaneous injection. The administration of EPKINLY takes place over the course of 28-day cycles, following the step-up dosage schedule in Section 2.2.

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

Use aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

0.16 mg Dose Preparation Instructions (2 dilutions required) – Sterile Syringe Method

Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial

- Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- Allow the vial to come to room temperature for no more than 1 hour.
- Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform first dilution

- Label an appropriately sized syringe as “**Dilution A.**”
- Withdraw **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** syringe. Include approximately 0.2 mL air in the syringe.
- In a new syringe labeled as “**Syringe 1**”, withdraw **0.8 mL of EPKINLY**.
- Connect the two syringes and push the **0.8 mL of EPKINLY** into the **Dilution A** syringe. The initially diluted solution contains 0.8 mg/mL of EPKINLY
- Gently mix by inverting the connected syringes 180 degrees 5 times.
- Disconnect the syringes and discard **Syringe 1**.

3. Perform second dilution

- Label an appropriately sized syringe as “**Dilution B.**”
- Withdraw **8 mL of 0.9% Sodium Chloride Injection** into the **Dilution B** syringe. Include approximately 0.2 mL air in the syringe.
- Label another appropriately sized syringe as “**Syringe 2.**”
- Connect **Syringe 2** to the **Dilution A** syringe and transfer **2 mL of solution** into **Syringe 2**. The **Dilution A** syringe is no longer needed.
- Connect **Syringe 2** to the **Dilution B** syringe and push the **2 mL of solution** into the **Dilution B** syringe to make a final concentration of 0.16 mg/mL.

f. Gently mix by inverting the connected syringes 180 degrees 5 times.
g. Disconnect the syringes and discard Syringe 2 .
4. Withdraw dose
a. Connect and transfer 1 mL of the diluted EPKINLY from the Dilution B syringe into a new syringe. The Dilution B syringe is no longer needed
5. Label syringe
a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

0.8 mg Dose Preparation Instructions (1 dilution required) – Sterile Syringe Method

Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial
a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
b. Allow the vial to come to room temperature for no more than 1 hour.
c. Gently swirl the EPKINLY vial.
DO NOT invert, vortex, or vigorously shake the vial.
2. Perform first dilution
a. Label an appropriately sized syringe as “ Dilution A. ”
b. Withdraw 4.2 mL of 0.9% Sodium Chloride Injection into the Dilution A syringe. Include approximately 0.2 mL air in the syringe.
c. In a new syringe labeled as “ Syringe 1 ”, withdraw 0.8 mL of EPKINLY .
d. Connect the two syringes and push the 0.8 mL of EPKINLY into the Dilution A syringe to make a final concentration of 0.8 mg/mL.
e. Gently mix by inverting the connected syringes 180 degrees 5 times.
f. Disconnect the syringes and discard Syringe 1 .
3. Withdraw dose
a. Connect a new syringe to the Dilution A syringe and transfer 1 mL of the diluted EPKINLY into the new syringe. The Dilution A syringe is no longer needed.
4. Label syringe
a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.9 Preparation of 3 mg and 48 mg EPKINLY Doses

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

Use aseptic technique to prepare EPKINLY.

3 mg Dose Preparation Instructions (No dilution required)

EPKINLY 3 mg dose is required for patients with FL only [see [Dosage and Administration \(2.2\)](#)].

1. Prepare EPKINLY vial
a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
b. Allow the vial to come to room temperature for no more than 1 hour.
c. Gently swirl the EPKINLY vial.
DO NOT invert, vortex, or vigorously shake the vial.
2. Withdraw dose
a. Withdraw 0.6 mL of EPKINLY into a syringe.
3. Label syringe
a. Label the syringe with the dose strength (3 mg) and the time of day.

Discard the vial containing unused EPKINLY.

48 mg Dose Preparation Instructions (No dilution required)

EPKINLY 48 mg/0.8 mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

1. Prepare EPKINLY vial
a. Retrieve one 48 mg/0.8 mL EPKINLY vial from the refrigerator.
b. Allow the vial to come to room temperature for no more than 1 hour.
c. Gently swirl the EPKINLY vial.
DO NOT invert, vortex, or vigorously shake the vial.
2. Withdraw dose
a. Withdraw 0.8 mL of EPKINLY into a syringe.
3. Label syringe
a. Label the syringe with the dose strength (48 mg) and the time of day.

Discard the vial containing unused EPKINLY.

2.10 Storage and Administration

Storage of EPKINLY Solution in the Syringe

Use EPKINLY solution in the syringe immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to

25°C (68°F to 77°F) for up to 12 hours. The total storage time from the start of dose preparation to administration should not exceed 24 hours. Protect from direct sunlight. Discard unused EPKINLY solution beyond the allowable storage time.

Administration of EPKINLY

To minimize injection pain, allow EPKINLY solution to equilibrate to room temperature for no more than 1 hour before administration. Inject the required volume of EPKINLY into the subcutaneous tissue of the lower part of the abdomen (preferred injection site) or the thigh.

Change of injection site from the left or right side or vice versa is recommended, especially during the weekly administrations (Cycles 1 to 3). Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard, or not intact.

3 DOSAGE FORMS AND STRENGTHS

EPKINLY is a clear to slightly opalescent, colorless to slightly yellow solution for subcutaneous injection:

- Injection: 4 mg/0.8 mL in a single-dose vial
- Injection: 48 mg/0.8 mL in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

EPKINLY can cause CRS, including serious or life-threatening reactions [*see Adverse Reactions (6.1)*].

Relapsed or Refractory Large B-cell Lymphoma (LBCL)

CRS occurred in 51% of patients with LBCL receiving EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL, with Grade 1 CRS occurring in 37%, Grade 2 in 17%, and Grade 3 in 2.5% of patients. Recurrent CRS occurred in 16% of patients. Of all the CRS events, most (92%) occurred during Cycle 1. In Cycle 1, 9% of CRS events occurred after the 0.16 mg dose on Cycle 1 Day 1, 16% after the 0.8 mg dose on Cycle 1 Day 8, 61% after the 48 mg dose on Cycle 1 Day 15, and 6% after the 48 mg dose on Cycle 1 Day 22. The median time to onset of CRS from the most recent administered EPKINLY dose across all doses was 24 hours (range: 0 to 10 days). The median time to onset after the first full 48 mg dose was 21 hours (range: 0 to 7 days). CRS resolved in 98% of patients and the median duration of CRS events was 2 days (range: 1 to 27 days). Patients with DLBCL or high-grade B-cell lymphoma should be

hospitalized for 24 hours following administration of the first full 48 mg dose [See *Dosage and Administration* (2.1, 2.2)].

Relapsed or Refractory Follicular Lymphoma (FL)

CRS occurred in 49% (42/86) of patients with FL receiving EPKINLY at the recommended 3-step up dosage schedule in EPCORE NHL-1, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Recurrent CRS occurred in 23% of patients. Of all the CRS events, most (88%) occurred during Cycle 1. In Cycle 1, 14% of CRS events occurred after the 0.16 mg dose on Cycle 1 Day 1, 7% after the 0.8 mg dose on Cycle 1 Day 8, 17% after the 3 mg dose on Cycle 1 Day 15, and 49% after the 48 mg dose on Cycle 1 Day 22. The median time to onset of CRS from the most recent administered EPKINLY dose across all doses was 59 hours (range: 0.1 to 7 days). The median time to onset after the first full 48 mg dose was 61 hours (range: 0.1 to 7 days). CRS resolved in 100% of patients and the median duration of CRS events was 2 days (range: 1 to 14 days).

In both patients with LBCL and FL who experienced CRS, the signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients with LBCL and 4.7% of patients with FL. Concurrent neurological adverse reactions observed in patients with LBCL included headache, confusional state, tremors, dizziness, and ataxia. Concurrent neurological adverse reactions observed in patients with FL included headache and dizziness.

Initiate therapy according to EPKINLY step-up dosage schedule. Administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS following EPKINLY accordingly [see *Dosage and Administration* (2.2, 2.3, 2.4)]. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Withhold or discontinue EPKINLY based on the severity of CRS [see *Dosage and Administration* (2.6)].

Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

5.2 Immune Effector Cell-Associated Neurotoxicity Syndrome

EPKINLY can cause life-threatening and fatal immune effector cell-associated neurotoxicity syndrome (ICANS) [see *Adverse Reactions* (6.1)].

Relapsed or Refractory Large B-cell Lymphoma (LBCL)

ICANS occurred in 6% (10/157) of patients with LBCL receiving EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients. There was one (0.6%) fatal ICANS occurrence. Of the 10 ICANS events, 9 occurred within Cycle 1 of EPKINLY treatment, with a median time to onset of ICANS of 16.5 days (range: 8 to 141 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range:

1 to 13 days). The median duration of ICANS was 4 days (range: 0 to 8 days) with ICANS resolving in 90% of patients with supportive care.

Relapsed or Refractory Follicular Lymphoma (FL)

ICANS occurred in 6% (8/127) of patients with FL receiving EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 3.9% and Grade 2 ICANS in 2.4% of patients. The median time to onset of ICANS was 21.5 days (range: 14-66 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 0.4 to 7 days). The median duration of ICANS was 2 days (range: 1-7 days) with ICANS resolving in 100% of patients.

For patients with LBCL or FL, clinical manifestations of ICANS included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Monitor patients for potential ICANS following EPKINLY. At the first signs or symptoms of ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or discontinue EPKINLY per recommendations and consider further management per current practice guidelines [*see Dosage and Administration (2.6)*].

Patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

5.3 Infections

EPKINLY can cause serious and fatal infections [*see Adverse Reactions (6.1)*].

Serious infections, including opportunistic infections, were reported in 15% of patients with LBCL receiving EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1 and were most commonly due to sepsis (4.5%) and pneumonia (3.2%). Fatal infections occurred in 1.3% of patients and included COVID-19 (1.3%).

Serious infections, including opportunistic infections, were reported in 40% of patients with FL receiving EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1 and were most commonly due to COVID-19 (20%), pneumonia (13%), and urinary tract infections (3%). Fatal infections occurred in 6% of patients and included COVID-19 (5%), pneumonia (0.8%), and sepsis (0.8%).

Monitor patients for signs and symptoms of infection prior to and during treatment with EPKINLY and treat appropriately. Avoid administration of EPKINLY in patients with active infections. Provide PJP prophylaxis prior to initiating treatment with EPKINLY; consider initiating prophylaxis against herpes virus prior to starting EPKINLY [*see Dosage and Administration (2.5)*].

Withhold or consider permanent discontinuation of EPKINLY based on severity [see [Dosage and Administration \(2.6\)](#)].

5.4 Cytopenias

EPKINLY can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia [see [Adverse Reactions \(6.1\)](#)].

Among LBCL patients who received EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1, Grade 3 or 4 decreased neutrophils occurred in 32%, decreased hemoglobin in 12%, and decreased platelets in 12% of patients. Febrile neutropenia occurred in 2.5%. In patients with FL who received EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1, Grade 3 or 4 decreased neutrophils occurred in 30%, decreased hemoglobin in 10%, and decreased platelets in 8% of patients. Febrile neutropenia occurred in 3.1%.

Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY [see [Dosage and Administration \(2.6\)](#)]. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, EPKINLY 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 EPKINLY and for 4 months 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 \(5.1\)](#)].
- Immune Effector Cell-Associated Neurotoxicity Syndrome [see [Warnings and Precautions \(5.2\)](#)].
- Infections [see [Warnings and Precautions \(5.3\)](#)].
- Cytopenias [see [Warnings and Precautions \(5.4\)](#)].

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.

Relapsed or Refractory Large B-cell Lymphoma (LBCL)

EPCORE NHL-1

The safety of EPKINLY was evaluated in EPCORE NHL-1, a single-arm study of patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, high grade B-cell lymphoma, and other B-cell lymphomas [see [Clinical Studies \(14.1\)](#)]. A total of 157 patients with LBCL received EPKINLY via subcutaneous injection until disease progression or unacceptable toxicities according to the following 28-day cycle schedule:

- Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22
- Cycles 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: EPKINLY 48 mg on Days 1 and 15
- Cycles 10 and beyond: EPKINLY 48 mg on Day 1

Of the 157 patients treated, the median age was 64 years (range: 20 to 83), 60% were male, and 97% had an ECOG performance status of 0 or 1. Race was reported in 133 (85%) patients; of these patients, 61% were White, 19% were Asian, and 0.6% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The median number of prior therapies was 3 (range: 2 to 11). The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, an ongoing active infection, and any patients with known impaired T-cell immunity.

The median duration of exposure for patients receiving EPKINLY was 5 cycles (range: 1 to 20 cycles).

Serious adverse reactions occurred in 54% of patients who received EPKINLY. Serious adverse reactions in $\geq 2\%$ of patients included CRS, infections (including sepsis, COVID-19, pneumonia, and upper respiratory tract infections), pleural effusion, febrile neutropenia, fever, and ICANS. Fatal adverse reactions occurred in 3.8% of patients who received EPKINLY, including COVID-19 (1.3%), hepatotoxicity (0.6%), ICANS (0.6%), myocardial infarction (0.6%), and pulmonary embolism (0.6%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 3.8% of patients. Adverse reactions which resulted in permanent discontinuation of EPKINLY included COVID-19, CRS, ICANS, pleural effusion, and fatigue.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 34% of patients who received EPKINLY. Adverse reactions which required dosage interruption in $\geq 3\%$ of patients included CRS, neutropenia, sepsis, and thrombocytopenia.

The most common ($\geq 20\%$) adverse reactions were CRS, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Table 9 summarizes the adverse reactions in EPCORE NHL-1.

Table 9: Adverse Reactions (≥ 10%) in Patients with Relapsed or Refractory LBCL Who Received EPKINLY in EPCORE NHL-1

Adverse Reaction [§]	EPKINLY (N=157)	
	All Grades (%)	Grade 3 or 4 (%)
Immune system disorders		
Cytokine release syndrome [*]	51	2.5 [#]
General disorders and administration site conditions		
Fatigue ^a	29	2.5 [#]
Injection site reactions ^b	27	0
Pyrexia	24	0
Edema ^c	14	1.9 [#]
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^d	28	1.3 [#]
Gastrointestinal disorders		
Abdominal pain ^e	23	1.9 [#]
Diarrhea	20	0
Nausea	20	1.3 [#]
Vomiting	12	0.6 [#]
Skin and subcutaneous disorders		
Rash ^f	15	0.6 [#]
Nervous system disorder		
Headache	13	0.6 [#]
Metabolism and nutrition disorders		
Decreased appetite	12	0.6 [#]
Cardiac disorders		
Cardiac arrhythmias ^g	10	0.6 [#]
[§] Adverse reactions were graded based on CTCAE Version 5.0 [#] Only grade 3 adverse reactions occurred. [*] CRS was graded using ASTCT consensus criteria (Lee et al., 2019). ^a Fatigue includes asthenia, fatigue, lethargy. ^b Injection site reactions includes injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria. ^c Edema includes edema, edema peripheral, face edema, generalized edema, peripheral swelling. ^d Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, spinal pain. ^e Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness. ^f Rash includes dermatitis bullous, erythema, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, rash pustular, recall phenomenon, seborrheic dermatitis, skin exfoliation. ^g Cardiac arrhythmias includes bradycardia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia.		

Clinically relevant adverse reactions in < 10% of patients who received EPKINLY included ICANS, sepsis, pleural effusion, COVID-19, pneumonia (including pneumonia and COVID-19 pneumonia), tumor flare, febrile neutropenia, upper respiratory tract infections, and tumor lysis syndrome.

Table 10 summarizes laboratory abnormalities in EPCORE NHL-1.

Table 10: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Relapsed or Refractory LBCL Who Received EPKINLY in EPCORE NHL-1

Laboratory Abnormality*	EPKINLY ¹	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	87	77
Hemoglobin decreased	62	12
White blood cells decreased	53	22
Neutrophils decreased	50	32
Platelets decreased	48	12
Chemistry		
Sodium decreased	56	2.6
Phosphate decreased ²	56	N/A
Aspartate aminotransferase increased	48	4.6
Alanine aminotransferase increased	45	5.3
Potassium decreased	34	5.3
Magnesium decreased	31	0
Creatinine increased	24	3.3
Potassium increased	21	1.3
<p>* Laboratory abnormalities were graded based on CTCAE Version 5.0</p> <p>¹ The denominator used to calculate the rate varied from 146 to 153 based on the number of patients with a baseline value and at least one post-treatment value.</p> <p>² CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).</p>		

Relapsed or Refractory Follicular Lymphoma (FL)

EPCORE NHL-1

The safety of EPKINLY was evaluated in EPCORE NHL-1, a single-arm study of patients with relapsed or refractory FL after two or more lines of systemic therapy who received EPKINLY following a 2-step up dosage schedule (N=127) [see [Clinical Studies \(14.2\)](#)]. A separate dose optimization cohort evaluated the recommended 3-step up dosage schedule for CRS mitigation (N=86), where EPKINLY was administered via subcutaneous injection until disease progression or unacceptable toxicities according to the following 28-day cycle schedule:

- Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 3 mg on Day 15, and 48 mg on Day 22
- Cycle 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: EPKINLY 48 mg on Days 1 and 15

- Cycles 10 and beyond: EPKINLY 48 mg on Day 1

With the exception of CRS, the safety results presented below and in tables 11 and 12 represent data from patients who received the 2-step up dosage schedule. The data presented for CRS reflects the 86 patients who received the recommended 3-step up dosage schedule. The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infection, any patients with known impaired T-cell immunity, creatinine clearance < 45 ml/min, alanine aminotransferase > 3 times the upper limit of normal, and a cardiac ejection fraction < 45%.

Recommended 3-step up Dosage Schedule

Of the 86 patients with relapsed or refractory FL who received EPKINLY following the recommended 3-step up dosage schedule, the median age was 63.5 years (range: 33-90), 57% were male, and 100% had an ECOG performance status of 0 or 1.

The median duration of exposure was 5 cycles (range: 1 to 12 cycles). CRS occurred in 49% of patients, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Serious adverse reactions due to CRS occurred in 28% of patients who received EPKINLY. Dose interruptions due to CRS occurred in 19% of patients who received EPKINLY.

2-step up Dosage Schedule

Of the 127 patients with relapsed or refractory FL who received EPKINLY following a 2-step up dosage schedule, the median age was 65 years (range: 39 to 84), 62% were male, and 95% had an ECOG performance status of 0 or 1 [see [Clinical Studies \(14.2\)](#)]. The median duration of exposure for patients receiving EPKINLY was 8 cycles (range: 1 to 33 cycles).

Serious adverse reactions occurred in 66% of patients who received EPKINLY. Serious adverse reactions in $\geq 5\%$ of patients included CRS, COVID-19, pneumonia, and second primary malignancies.

Fatal adverse reactions occurred in 9% of patients who received EPKINLY, including COVID-19 (5%), pneumonitis (1.6%), cardiac failure (0.8%), pneumonia (0.8%), and sepsis (0.8%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 19% of patients who received EPKINLY. Adverse reactions which resulted in permanent discontinuation of EPKINLY in $\geq 2\%$ of patients included COVID-19, Hepatitis E, pneumonitis, and second primary malignancy.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 59% of patients who received EPKINLY. Adverse reactions which required dosage interruption in $\geq 5\%$ of patients included COVID-19, CRS, pneumonia, upper respiratory tract infection, and fatigue.

The most common ($\geq 20\%$) adverse reactions were injection site reactions, CRS, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, pyrexia, cough, and headache. The most common Grade 3 to 4 laboratory abnormalities ($\geq 10\%$) were decreased

lymphocyte count, decreased neutrophil count, decreased white blood cell count, and decreased hemoglobin.

Table 11 summarizes the adverse reactions in EPCORE NHL-1.

Table 11: Adverse Reactions ($\geq 10\%$) in Patients with Relapsed or Refractory FL Who Received EPKINLY in EPCORE NHL-1

Adverse Reaction [§]	EPKINLY	
	All Grades (%)	Grade 3 or 4 (%)
(N=86) ⁺		
Immune system disorders		
Cytokine release syndrome ^{†*}	49	0
(N=127)		
General disorders and administration site conditions		
Injection site reactions ^a	58	0
Fatigue ^a	37	5 [#]
Pyrexia ^a	26	2 [#]
Edema ^a	17	0
Infections and Infestations		
COVID-19 ^b	40	19
Upper respiratory tract infection ^c	29	2 [#]
Pneumonia ^d	17	13 [#]
Urinary tract infection ^a	13	5 [#]
Herpesvirus infection ^e	12	1.6 [#]
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^a	28	0.8 [#]
Arthralgia	14	0.8 [#]
Skin and subcutaneous disorders		
Rash ^a	28	0
Gastrointestinal disorders		
Diarrhea	26	1.6 [#]
Nausea	17	0
Abdominal pain ^a	17	0.8 [#]
Constipation	16	0
Mucositis ^f	12	0
Respiratory disorders		
Cough ^a	20	0
Dyspnea ^a	17	0
Nervous system disorders		
Headache	20	0
Neurological changes ^g	13	0
Peripheral neuropathy and paresthesia ^h	13	1.6 [#]
Dizziness	11	0

Psychiatric disorders		
Insomnia	13	0
Renal and urinary disorders		
Renal insufficiency ⁱ	10	1.6 [#]
<p>§ Adverse reactions were graded based on CTCAE Version 5.0.</p> <p>† The frequency of CRS is based on 86 patients with FL who received the recommended 3-step up dosage schedule in EPCORE NHL-1 [see <i>Dosage and Administration (2.2)</i>].</p> <p>‡ CRS was graded using ASTCT consensus criteria (Lee et al., 2019).</p> <p>* The frequency of CRS based on the 127 patients with FL who received the 2-step up dosage schedule in EPCORE NHL-1 was the following: Any grade CRS 66%; Grade 1 CRS: 50%; Grade 2 CRS: 26%; Grade 3 CRS: 1.6%.</p> <p># Only grade 3 adverse reactions occurred.</p> <p>^a Includes related grouped terms.</p> <p>^b COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive.</p> <p>^c Upper respiratory tract infection includes preferred terms with upper respiratory infection and sinusitis, laryngitis viral, nasopharyngitis, oropharyngitis fungal, pharyngitis, rhinitis, rhinovirus infection, tonsillitis.</p> <p>^d Pneumonia includes preferred terms with pneumonia, bronchopulmonary aspergillosis, infectious pleural effusion, infective exacerbation of bronchiectasis, Pneumocystis jirovecii pneumonia, pneumonia respiratory syncytial viral.</p> <p>^e Herpesvirus infection includes herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, varicella zoster virus infection.</p> <p>^f Mucositis includes aphthous ulcer, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, stomatitis, tongue ulceration.</p> <p>^g Neurological changes includes amnesia, aphasia, balance disorder, brain fog, confusional state, dysphonia, encephalopathy, extrapyramidal disorder, hallucination, hypoacusis, memory impairment, mental status changes, tremor, vertigo.</p> <p>^h Peripheral neuropathy and paresthesia includes bell's palsy, hypoesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy.</p> <p>ⁱ Renal insufficiency includes acute kidney injury, blood creatinine increased, renal impairment.</p>		

Clinically relevant adverse reactions in < 10% of patients (N=127) who received EPKINLY included vomiting, pruritis, hepatotoxicity, ICANS, lower respiratory tract infections, cardiac arrhythmias, respiratory tract infections, pneumonitis, second primary malignancy, vision changes, cellulitis, febrile neutropenia, cardiac failure, cytomegalovirus infection and sepsis.

Table 12 summarizes laboratory abnormalities in EPCORE NHL-1.

Table 12: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Relapsed or Refractory FL Who Received EPKINLY in EPCORE NHL-1

Laboratory Abnormality [*]	EPKINLY ¹ (N=127)	
	All Grades	Grade 3 or 4 (%)
Hematology		
Lymphocytes decreased	94	82
Hemoglobin decreased	59	10
White blood cells decreased	58	19
Neutrophils decreased	55	30
Platelets decreased	49	8
Chemistry		
Sodium decreased	51	1.6

Laboratory Abnormality*	EPKINLY ¹ (N=127)	
	All Grades	Grade 3 or 4 (%)
ALT increased	47	8
AST increased	44	6
Creatinine increased	36	0.8
Alkaline phosphatase increased	29	0
Bilirubin increased	28	1.6
Potassium decreased	20	3.1
Magnesium decreased	20	0.8
* Laboratory abnormalities were graded based on CTCAE Version 5.0		
¹ The denominator used to calculate the rate varied from 123 to 127 based on the number of patients with a baseline value and at least one post-treatment value.		

7 DRUG INTERACTIONS

For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with EPKINLY.

Epcoritamab-bysp causes release of cytokines [see [Clinical Pharmacology \(12.2\)](#)] that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of EPKINLY and up to 14 days after the first 48 mg dose, and during and after CRS [see [Warnings and Precautions \(5.1\)](#)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman [see [Clinical Pharmacology \(12.1\)](#)]. There are no available data on the use of EPKINLY in pregnant women to evaluate for a drug-associated risk. No animal reproductive or developmental toxicity studies have been conducted with epcoritamab-bysp.

Epcoritamab-bysp causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD20 on B-cells and the finding of B-cell depletion in non-pregnant animals, epcoritamab-bysp can cause B-cell lymphocytopenia in infants exposed to epcoritamab-bysp in-utero. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, EPKINLY has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of epcoritamab-bysp in human milk, the effect on the breastfed child, or milk production. Because maternal IgG is present in human milk, and there is potential for epcoritamab-bysp absorption leading to serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

8.4 Pediatric Use

The safety and efficacy of EPKINLY in pediatric patients have not been established.

8.5 Geriatric Use

LBCL

In patients with relapsed or refractory LBCL who received EPKINLY in EPCORE NHL-1, 77 (49%) were 65 years of age and older, and 29 (19%) were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients with relapsed or refractory LBCL who were 65 years of age and older compared with younger adult patients

FL

In patients with relapsed or refractory FL who received EPKINLY in EPCORE NHL-1, 66 (52%) were 65 years of age or older, and 16 (13%) were 75 years of age and older.

In patients with relapsed or refractory FL, there was a higher rate of fatal adverse reactions, primarily infections, including COVID-19, in patients older than 65 years of age compared to younger adult patients. No overall difference in efficacy was observed in patients with relapsed or refractory FL who were 65 years of age and older compared with younger adult patients.

11 DESCRIPTION

Epcoritamab-bysp is a bispecific CD20-directed CD3 T-cell engager; it is a humanized bispecific IgG1 antibody. Epcoritamab-bysp is manufactured in Chinese hamster ovary (CHO) cells using recombinant DNA technology and has an approximate molecular weight of 149 kDa.

EPKINLY (epcoritamab-bysp) injection for subcutaneous use is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles.

Each single-dose 4 mg/0.8 mL vial contains epcoritamab-bysp (4 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

Each single-dose 48 mg/0.8 mL vial contains epcoritamab-bysp (48 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epcoritamab-bysp is a T-cell engaging bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells.

In vitro, epcoritamab-bysp activated T-cells, caused the release of proinflammatory cytokines, and induced lysis of B-cells.

12.2 Pharmacodynamics

Circulating B-Cell Count

Circulating B-cells decreased to undetectable levels (< 10 cells/microliter) after administration of the approved recommended dosage of EPKINLY in patients who had detectable B-cells at treatment initiation by Cycle 1 Day 15 and the depletion was sustained while patients remained on treatment.

Cytokine Concentrations

Plasma concentrations of cytokines (IL-2, IL-6, IL-10, TNF- α , and IFN- γ) were measured. Transient elevation of circulating cytokines was observed at dose levels of 0.04 mg and above. After administration of the approved recommended dosages of EPKINLY, cytokine levels increased within 24 hours after the first dose on Cycle 1 Day 1, generally reached maximum levels after the first 48 mg dose, and returned to baseline prior to the second 48 mg full dose.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were evaluated at the approved recommended dosage (48 mg) and are presented as geometric mean (CV%) unless otherwise specified.

Epcoritamab-bysp area under the concentration-time curve (AUC) increased more than proportionally over a full dosage range from 1.5 to 60 mg (0.03125 to 1.25 times the approved recommended dosage).

Epcoritamab-bysp maximum concentration (10.2 mcg/mL [43.2%]) is achieved after the first dose of the Q2W regimen (i.e., the first dose of Cycle 4). No clinically significant differences in pharmacokinetic parameters were observed between patients with relapsed or refractory LBCL and patients with relapsed or refractory FL. PK exposures are summarized for the recommended dosage of EPKINLY in Table 13.

Table 13: Exposure Parameters of Epcoritamab-bysp in Subjects with Relapsed or Refractory LBCL and Relapsed or Refractory FL Following Recommended Dosage

	C_{avg} (mcg/mL)¹	C_{max} (mcg/mL)¹	C_{trough} (mcg/mL)¹
First full 48 mg dose ²	1.3 (113.3%)	1.7 (106.7%)	1.4 (100.9%)
End of weekly dosing (end of Cycle 3)	9.1 (45.9%)	9.9 (43.4%)	7.8 (52.4%)
End of every 2-week dosing (end of Cycle 9)	5.3 (57%)	6.7 (49.4%)	3.6 (81.5%)
Steady state ³ with every 4-week dosing	2.4 (73.3%)	4.2 (59.8%)	1.1 (134.1%)
¹ Values are geometric mean with geometric CV%. ² First full 48 mg dose is on the first day of Week 3 in subjects with relapsed or refractory LBCL and on the first day of Week 4 in subjects with relapsed or refractory FL. ³ Steady state values are approximated at Cycle 15 (Week 60).			

Absorption

The median (range) T_{max} of epcoritamab-bysp after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively.

Distribution

The apparent total volume of distribution is 25.6 L (82%).

Elimination

The half-life of full dose epcoritamab-bysp (48 mg) was approximately 22 days (58%) at the end of Cycle 3, with apparent total clearance of approximately 0.53 L/day (40%) after the end of Cycle 3.

Metabolism

Epcoritamab-bysp is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in the PK of epcoritamab-bysp were observed based on age (20 to 89 years), sex, race (White or Asian), mild to moderate renal impairment (creatinine clearance [CLcr] 30 to < 90 mL/min as estimated by Cockcroft-Gault formula), and mild hepatic impairment (total bilirubin \leq ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in bodyweight.

The effects of severe renal impairment (CLcr 15 to < 30 mL/min), end-stage renal disease (CLcr < 15 mL/min), or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on the PK of epcoritamab-bysp are unknown.

Body Weight

In patients who received the recommended dosage of EPKINLY, geometric mean average concentration following the first full 48 mg dose was 31% lower in the higher body weight (BW) group (85 to 172 kg) and 13% higher in the lower BW group (39 to 65 kg) compared to patients with BW of 65 to less than 85 kg.

Drug Interaction Studies

No clinical studies evaluating the drug interaction potential of epcoritamab-bysp have been conducted.

12.6 Immunogenicity

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

Anti-epcoritamab-bysp antibodies developed in 2.6% of patients (4 of 156) with LBCL and 4.2% of patients (8 of 190) with FL treated with EPKINLY in Study EPCORE NHL-1 (up to 10 cycles) [*see Clinical Studies (14.1, 14.2)*] using an electrochemiluminescence immunoassay (ECLIA). Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the PK, pharmacodynamics, safety, and effectiveness of epcoritamab-bysp is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with epcoritamab-bysp.

No dedicated studies have been conducted to evaluate the effects of epcoritamab-bysp on fertility.

14 CLINICAL STUDIES

14.1 DLBCL and High-grade B-cell Lymphoma

The efficacy of EPKINLY was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial in 157 patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infection, and any patients with known impaired T-cell immunity. Patients received EPKINLY monotherapy at the recommended 2-step up dosage schedule:

- Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22
- Cycles 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: EPKINLY 48 mg on Days 1 and 15
- Cycles 10 and beyond: EPKINLY 48 mg on Day 1

Patients continued to receive EPKINLY until disease progression or unacceptable toxicity. In the setting of a suspected tumor flare reaction, continued treatment was permitted.

The efficacy population includes 148 patients with DLBCL, not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma. Of the 148 patients, the median age was 65 years (range: 22 to 83), 62% were male, 97% had an ECOG performance status of 0 or 1, and 3% had an ECOG performance status of 2. Race was reported in 125 (84%) patients; of these patients, 61% were White, 20% were Asian, and 0.7% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The diagnosis was DLBCL NOS in 86%, including 27% with DLBCL transformed from indolent lymphoma, and high-grade B-cell lymphoma in 14%. The median number of prior therapies was 3 (range: 2 to 11), with 30% receiving 2 prior therapies, 30% receiving 3 prior therapies, and 40% receiving 4 or more prior therapies. Eighteen percent had prior autologous HSCT, and 39% had prior chimeric antigen receptor (CAR) T-cell therapy. Eighty-two percent of patients had disease refractory to last therapy and 29% of patients were refractory to CAR T-cell therapy.

Efficacy was established based on overall response rate (ORR) determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and duration of response. The efficacy results are summarized in Table 14.

Table 14: Efficacy Results in EPCORE NHL-1 in Patients with DLBCL and High-grade B-cell Lymphoma

Endpoint ^a	EPKINLY (N=148)
ORR^b, n (%)	90 (61)
(95% CI)	(52.5, 68.7)
CR, n (%)	56 (38)
(95% CI)	(30.0, 46.2)
PR, n (%)	34 (23)
(95% CI)	(16.5, 30.6)
DOR	
Median (95% CI), months	15.6 (9.7, NR)
9-month estimate ^c % (95% CI)	63 (51.5, 72.4)
ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response; NR = not reached. ^a Determined by Lugano criteria (2014) as assessed by independent review committee (IRC). ^b Early response assessments were evaluated in the context of potential flare reactions. Of 90 patients who achieved an objective response, 9 patients had early flare reactions identified with objective response demonstrated on subsequent imaging per Lugano criteria. ^c Kaplan-Meier estimate.	

The median time to response was 1.4 months (range: 1 to 8.4 months). Among responders, the median follow-up for DOR was 9.8 months (range: 0.0 to 17.3 months).

14.2 Follicular Lymphoma

The efficacy of EPKINLY was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial that included patients with relapsed or refractory follicular lymphoma (FL) after at least 2 lines of systemic therapy. The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, ongoing active infection, any patients with known impaired T-cell immunity, creatinine clearance < 45 mL/min, alanine aminotransferase > 3 times the upper limit of normal, and a cardiac ejection fraction < 45%. Patients received EPKINLY monotherapy following a 2-step up dosage schedule:

- Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22
- Cycles 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22
- Cycles 4-9: EPKINLY 48 mg on Days 1 and 15
- Cycles 10 and beyond: EPKINLY 48 mg on Day 1

Patients continued to receive EPKINLY until disease progression or unacceptable toxicity.

Among the 127 patients with FL, the median age was 65 years (range: 39 to 84), 52% were 65 years of age or older, and 62% were male. Race was reported in 85 (67%) patients; of these patients, 89% were White, and 8% were Asian. A total of 85% had stage III-IV disease, 25% had

bulky disease, 95% had an ECOG performance status of 0 or 1, and 6% had an ECOG performance status of 2. The median number of prior therapies was 3 (range: 2 to 9), with 36% receiving 2 prior lines of systemic therapy, 32% receiving 3 prior therapies, and 32% receiving 4 or more prior therapies.

Seventy-nine percent of patients were refractory to prior anti-CD20 monoclonal antibody therapy, 70% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 21% had prior rituximab plus lenalidomide therapy, 19% received prior autologous HSCT, and 5% received prior chimeric antigen receptor (CAR) T-cell therapy. Fifty-two percent of patients had progression of disease within 24 months of first systemic therapy.

Efficacy was established based on overall response rate (ORR) determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and duration of response. The median follow-up for DOR was 14.8 months. The efficacy results are summarized in Table 15.

Table 15: Efficacy Results in EPCORE NHL-1 in Patients with FL

Endpoint^a	EPKINLY (N=127)
ORR, n (%)	104 (82)
(95% CI)	(74.1, 88.2)
CR, n (%)	76 (60)
(95% CI)	(50.8, 68.4)
PR, n (%)	28 (22)
(95% CI)	(15.2, 30.3)
DOR	
Median (95% CI), months	NR (13.7, NR)
12-month estimate ^b % (95% CI)	68.4 (57.6, 77.0)
ORR = overall response rate; CI = confidence interval; CR = complete response; PR = partial response; DOR = duration of response; NR = not reached. ^a Determined by Lugano criteria (2014) as assessed by independent review committee (IRC). ^b Kaplan-Meier estimate.	

The median time to first response was 1.4 months (range: 1 to 3 months).

In a separate dose optimization cohort in EPCORE NHL-1, 86 patients received the recommended 3-step up dosage schedule in Cycle 1 [see [Adverse Reactions \(6.1\)](#)]. The efficacy results in this cohort were comparable to the primary efficacy population.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

EPKINLY (epcoritamab-bysp) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles, supplied in glass vials as follows:

Carton contents	NDC number
One 4 mg/0.8 mL single-dose vial	NDC 82705-002-01
One 48 mg/0.8 mL single-dose vial	NDC 82705-010-01

The vial stopper is not made with natural rubber latex.

Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep in the original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Cytokine Release Syndrome (CRS)

Inform patients of the risk of CRS, and to immediately contact their healthcare provider should signs and symptoms associated with CRS (e.g., pyrexia, hypotension, hypoxia, chills, tachycardia, headache, and dyspnea) occur at any time. Advise patients with DLBCL or high-grade B-cell lymphoma that they should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg. Advise all patients who experience symptoms that impair consciousness not to drive and refrain from operating heavy or potentially dangerous machinery until events resolve [see [Warnings and Precautions \(5.1\)](#)].

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Advise patients of the risk of ICANS, to immediately contact their healthcare provider for signs and symptoms associated with ICANS, which may manifest, for example, as confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus, and that the onset of events may be delayed. Advise patients who experience symptoms of ICANS that impair consciousness to refrain from driving or operating heavy or potentially dangerous machinery until symptoms of ICANS resolve [see [Warnings and Precautions \(5.2\)](#)].

Infections

Advise patients of the risk of serious infections, and to contact their healthcare professional for signs or symptoms of serious infection [see [Warnings and Precautions \(5.3\)](#)].

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia [see [Warnings and Precautions \(5.4\)](#)].

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 [Use in Specific Populations \(8.1\)](#)]. Advise females of reproductive potential to use effective contraception

during treatment with EPKINLY and for 4 months after the last dose [*see Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose [*see Use in Specific Populations (8.2)*].

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Marketed by:

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MEDICATION GUIDE
EPKINLY® (ep-KIN-lee)
(epcoritamab-bysp)
injection, for subcutaneous use

What is the most important information I should know about EPKINLY?

EPKINLY can cause serious side effects, including:

- **Cytokine Release Syndrome (CRS).** CRS is common during treatment with EPKINLY and can also be serious or life-threatening. Tell your healthcare provider or get medical help right away if you develop any signs or symptoms of CRS, including:
 - fever of 100.4°F (38°C) or higher
 - dizziness or light-headedness
 - trouble breathing
 - chills
 - fast heartbeat
 - feeling anxious
 - headache
 - confusion
 - shaking (tremors)
 - problems with balance and movement, such as trouble walking

Due to the risk of CRS, you will receive EPKINLY on a “step-up dosing schedule”.

- The step-up dosing schedule is when you receive 2 or 3 smaller “step-up” doses of EPKINLY during your first cycle of treatment (Cycle 1).
- You will receive your first full dose of EPKINLY a week after your last step-up dose (this will be Day 15 or Day 22 of Cycle 1).
- If your dose of EPKINLY is delayed for any reason, you may need to repeat the “step-up dosing schedule”.
- Before each dose in Cycle 1, you will receive medicines to help reduce your risk of CRS. You will also receive medicine for 3 days after each dose in Cycle 1. Your healthcare provider will decide if you need to receive medicine to help reduce your risk of CRS with future cycles.
- See “**How will I receive EPKINLY?**” for more information about how you will receive EPKINLY.
- **Neurologic problems.** EPKINLY can cause serious neurologic problems that can be life-threatening and lead to death. Neurologic problems may happen days or weeks after you receive EPKINLY. Your healthcare provider may refer you to a healthcare provider who specializes in neurologic problems. Tell your healthcare provider right away if you develop any signs or symptoms of neurologic problems, including:
 - trouble speaking or writing
 - confusion and disorientation
 - drowsiness
 - tiredness or lack of energy
 - muscle weakness
 - shaking (tremors)
 - seizures
 - memory loss

Your healthcare provider will monitor you for signs and symptoms of CRS and neurologic problems during treatment with EPKINLY, as well as other side effects and treat you if needed. Your healthcare provider may temporarily stop or completely stop your treatment with EPKINLY if you develop CRS, neurologic problems, or any other side effects that are severe.

People with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma should be hospitalized for 24 hours after receiving their first full dose of EPKINLY on Day 15 of Cycle 1 due to the risk of CRS and neurologic problems.

See “**What are the possible side effects of EPKINLY?**” for more information about side effects.

What is EPKINLY?

EPKINLY is a prescription medicine used to treat adults with certain types of DLBCL, high-grade B-cell lymphoma, or follicular lymphoma:

- that has come back (relapsed) or that did not respond to previous treatment (refractory), **and**
- who have already received 2 or more treatments for their cancer.

It is not known if EPKINLY is safe and effective in children.

Before receiving EPKINLY, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection.
- are pregnant or plan to become pregnant. EPKINLY may harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with EPKINLY.
- You should use effective birth control (contraception) during treatment and for 4 months after your last dose of EPKINLY.
- Tell your healthcare provider if you become pregnant or think that you may be pregnant during treatment with EPKINLY.
- are breastfeeding or plan to breastfeed. It is not known if EPKINLY passes into your breast milk. Do not breastfeed during treatment and for 4 months after your last dose of EPKINLY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive EPKINLY?

- EPKINLY will be given to you by your healthcare provider as an injection under your skin (subcutaneous injection), usually in the lower part of your stomach-area (abdomen) or thigh.
- Your EPKINLY treatment schedule is divided into cycles that are usually 28 days (4 weeks) long.
- EPKINLY is usually given every week during Cycles 1 to 3, every 2 weeks during Cycles 4 to 9, and every 4 weeks starting with Cycle 10.
- Your healthcare provider will decide how many treatment cycles you will receive.
- See **“What is the most important information I should know about EPKINLY?”** for more information about how you will receive EPKINLY.

What should I avoid while receiving EPKINLY?

Do not drive, operate heavy machinery, or do other dangerous activities if you develop dizziness, confusion, tremors, sleepiness, or any other symptoms that impair consciousness until your signs and symptoms go away. These may be signs and symptoms of CRS or neurologic problems.

See **“What is the most important information I should know about EPKINLY?”** for more information about signs and symptoms of CRS and neurologic problems.

What are the possible side effects of EPKINLY?

EPKINLY can cause serious side effects, including:

- See **“What is the most important information I should know about EPKINLY?”**
- **Infections.** EPKINLY can cause serious infections that may lead to death. Your healthcare provider will check you for signs and symptoms of infection before and during treatment with EPKINLY. Your healthcare provider should prescribe medicines before you start treatment to help prevent infection and treat you as needed if you develop an infection during treatment with EPKINLY. Tell your healthcare provider right away if you develop any signs or symptoms of infection during treatment with EPKINLY, including:
 - fever of 100.4°F (38°C) or higher
 - cough
 - chest pain
 - tiredness
 - shortness of breath
 - painful rash
 - sore throat
 - pain during urination
 - feeling weak or generally unwell
- **Low blood cell counts.** EPKINLY can cause low blood cell counts which can be serious or severe. Your healthcare provider will check your blood cell counts during treatment with EPKINLY. EPKINLY may cause the following low blood cell counts:
 - **low white blood cell counts (neutropenia).** Low white blood cells can increase your risk for infection.
 - **low red blood cell counts (anemia).** Low red blood cells can cause tiredness and shortness of breath.
 - **low platelet counts (thrombocytopenia).** Low platelet counts can cause bruising or bleeding problems.

Your healthcare provider may temporarily stop or completely stop treatment with EPKINLY if you develop certain side effects.

The most common side effects of EPKINLY in DLBCL or high-grade B-cell lymphoma include:

- | | | |
|----------------------------|---------------------------------|------------|
| • tiredness | • fever | • nausea |
| • muscle and bone pain | • stomach-area (abdominal) pain | • diarrhea |
| • injection site reactions | | |

The most common severe abnormal laboratory test results with EPKINLY in DLBCL or high-grade B-cell lymphoma include: decreased white blood cells, decreased red blood cells, and decreased platelets.

The most common side effects of EPKINLY in follicular lymphoma include:

- | | | |
|-------------------------------------|------------------------|------------|
| • injection site reactions | • muscle and bone pain | • fever |
| • COVID-19 | • rash | • cough |
| • tiredness | • diarrhea | • headache |
| • upper respiratory tract infection | | |

The most common severe abnormal laboratory test results with EPKINLY in follicular lymphoma include: decreased white blood cells and decreased red blood cells.

These are not all of the possible side effects of EPKINLY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of EPKINLY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about EPKINLY that is written for health professionals.

What are the ingredients in EPKINLY?

Active ingredient: epcoritamab-bysp

Inactive ingredients: acetic acid, polysorbate 80, sodium acetate, sorbitol and Water for Injection.

Manufactured by: Genmab US, Inc., Plainsboro, NJ 08536

U.S. License Number: 2293

Marketed by: Genmab US, Inc., Plainsboro, NJ 08536 and AbbVie Inc., North Chicago, IL 60064

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For more information, go to www.EPKINLY.com or call 1-855-4GENMAB (1-855-443-6622)

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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