

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BIZENGRI® safely and effectively. See full prescribing information for BIZENGRI.

BIZENGRI (zenocutuzumab-zbco) injection, for intravenous use

Initial U.S. Approval: 2024

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning. Embryo-Fetal Toxicity: Exposure to BIZENGRI during pregnancy can cause embryo-fetal harm. Advise patients of this risk and the need for effective contraception [see Warnings and Precautions (5.4), Use on Specific Populations (8.1, 8.3)].

INDICATIONS AND USAGE

BIZENGRI® is a bispecific HER2- and HER3-directed antibody indicated for the treatment of:

- Adults with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.* (1.1)
- Adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.* (1.2)

*This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

- Select patients for treatment with BIZENGRI based on the presence of an *NRG1* gene fusion. (2.1)
- Evaluate left ventricular ejection fraction (LVEF) before initiating BIZENGRI. (2.2)
- The recommended dosage of BIZENGRI is 750 mg every 2 weeks until disease progression or unacceptable toxicity. (2.3)
- Administer premedications before each infusion to reduce the risk of infusion-related reactions. (2.4)
- Administer as an intravenous infusion, after dilution, over 4 hours. (2.7)

DOSAGE FORMS AND STRENGTHS

Injection: 375 mg/18.75 mL (20 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Infusion-Related Reactions (IRR)/Hypersensitivity/Anaphylactic Reactions:** Administer BIZENGRI in a setting with emergency resuscitation equipment and staff who are trained to monitor for IRRs and to administer emergency medications. Monitor for signs and symptoms of IRR. Interrupt infusion in patients with \leq Grade 3 IRRs and administer symptomatic treatment as needed. Resume infusion at a reduced rate after resolution of symptoms. Immediately stop the infusion and permanently discontinue BIZENGRI for Grade 4 or life-threatening IRR or hypersensitivity/anaphylaxis. (5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis:** Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Permanently discontinue BIZENGRI in patients with \geq Grade 2 ILD/pneumonitis. (5.2)
- Left Ventricular Dysfunction:** Assess LVEF before initiating BIZENGRI and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue BIZENGRI in patients with symptomatic congestive heart failure (CHF). (5.3)

ADVERSE REACTIONS

- The most common adverse reactions ($\geq 10\%$) in patients were diarrhea, musculoskeletal pain, fatigue, nausea, infusion-related reactions (IRR), dyspnea, rash, constipation, vomiting, abdominal pain, and edema. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities ($\geq 2\%$) were increased GGT, decreased hemoglobin, decreased sodium, decreased platelets, increased AST, increased ALT, increased alkaline phosphatase, decreased magnesium, decreased phosphate, increased aPTT and increased bilirubin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Partner Therapeutics, Inc. at 1-888-479-5385 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Verify pregnancy status of females prior to initiation of BIZENGRI. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: EMBRYO-FETAL TOXICITY

1 INDICATIONS AND USAGE

- Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Non-Small Cell Lung Cancer
- Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Pancreatic Adenocarcinoma

2 DOSAGE AND ADMINISTRATION

- Patient Selection
- Recommended Evaluation Before Initiating BIZENGRI
- Recommended Dosage
- Recommended Premedications
- Dosage Modifications for Adverse Reactions
- Preparation
- Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Infusion-Related Reactions/Hypersensitivity/Anaphylactic Reactions
- Interstitial Lung Disease/Pneumonitis
- Left Ventricular Dysfunction
- Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential
- Pediatric Use
- Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics
- Immunogenicity

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Non-Small Cell Lung Cancer
- Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Pancreatic Adenocarcinoma

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Embryo-Fetal Toxicity: Exposure to BIZENGRI during pregnancy can cause embryo-fetal harm. Advise patients of this risk and the need for effective contraception [see *Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)*].

1 INDICATIONS AND USAGE

1.1 Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Non-Small Cell Lung Cancer

BIZENGRI is indicated for the treatment of adults with advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.

This indication is approved under accelerated approval based on overall response rate and duration 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 Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Pancreatic Adenocarcinoma

BIZENGRI is indicated for the treatment of adults with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.

This indication is approved under accelerated approval based on overall response rate and duration 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 Patient Selection

Select patients for treatment with BIZENGRI based on the presence of an *NRG1* gene fusion in tumor specimens [see *Clinical Studies (14.1, 14.2)*].

An FDA-approved test for the detection of *NRG1* gene fusions is not currently available.

2.2 Recommended Evaluation Before Initiating BIZENGRI

Before initiating BIZENGRI, evaluate left ventricular ejection fraction (LVEF) [see *Warnings and Precautions (5.3)*].

2.3 Recommended Dosage

- The recommended dosage of BIZENGRI is 750 mg as an intravenous (IV) infusion every 2 weeks until disease progression or unacceptable toxicity [see *Dosage and Administration (2.7)*].
- Administer premedications before each BIZENGRI infusion as recommended to reduce the risk of infusion-related reactions [see *Dosage and Administration (2.4)*].

2.4 Recommended Premedications

Prior to each infusion of BIZENGRI, administer premedications to reduce the risk of infusion-related reactions (IRRs) [see *Warnings and Precautions (5.1)*] (see [Table 1](#)).

Table 1: Premedications Prior to BIZENGRI Infusions

Medication	Dose	Route of Administration
Corticosteroid ¹	Dexamethasone (10 mg)	Oral or intravenous
Antipyretic	Acetaminophen (1,000 mg)	Oral or intravenous
H1 Antihistamine	Dexchlorpheniramine (5 mg) or other anti-H1 equivalent	Intravenous or oral

¹ Optional after initial BIZENGRI infusion

2.5 Dosage Modifications for Adverse Reactions

No dose reduction is recommended for BIZENGRI. The recommended dosage modifications of BIZENGRI for adverse reactions are provided in [Table 2](#).

Table 2: Recommended BIZENGRI Dosage Modifications and Management for Adverse Reactions

Adverse Reaction	Severity	Dose Modifications and Management
Infusion-related reactions (IRRs)/Hypersensitivity/Anaphylactic Reactions [see <i>Warnings and Precautions (5.1)</i>]	≤ Grade 3 IRR	<ul style="list-style-type: none"> • Interrupt BIZENGRI infusion if IRR is suspected and monitor patient until reaction symptoms resolve. • Provide symptomatic treatment as needed. • Resume the infusion at 50% of the infusion rate at which the reaction occurred. The infusion rate may be escalated if there are no additional symptoms. • Corticosteroid premedication can be used as necessary for subsequent BIZENGRI infusions [see <i>Recommended Premedications (2.4)</i>].

	Grade 4 IRR or any grade hypersensitivity/ anaphylactic reaction	<ul style="list-style-type: none"> • Permanently discontinue BIZENGRI.
Interstitial Lung Disease (ILD)/Pneumonitis <i>[see Warnings and Precautions (5.2)]</i>	Grade 1	<ul style="list-style-type: none"> • Interrupt BIZENGRI until recovery. • Consider prompt initiation of corticosteroids when the diagnosis is suspected. • Resume treatment after resolution.
	≥ Grade 2	<ul style="list-style-type: none"> • Permanently discontinue BIZENGRI. • Promptly treat with corticosteroids.
Left Ventricular Dysfunction <i>[see Warnings and Precautions (5.3)]</i>	LVEF is 45-49% and absolute decrease from baseline ≥10% or LVEF less than 45%	<ul style="list-style-type: none"> • Interrupt BIZENGRI. • Repeat LVEF assessment within 3 weeks. • If LVEF is less than 45% or LVEF has not recovered to within 10% from baseline, permanently discontinue BIZENGRI. • If LVEF is 50% or greater or LVEF is 45-49% and recovered to within 10% of baseline, resume BIZENGRI and monitor LVEF every 12 weeks while on treatment and as clinically indicated.
	Symptomatic congestive heart failure (CHF)	<ul style="list-style-type: none"> • Permanently discontinue BIZENGRI.
Other Clinically Relevant Adverse Reactions <i>[see Adverse Reactions (6.1)]</i>	Grade 3 or 4	<ul style="list-style-type: none"> • Withhold BIZENGRI until recovery to ≤ Grade 1 or baseline. • Provide symptomatic treatment as needed. • Resume treatment after resolution of symptoms.

2.6 Preparation

Dilute and prepare BIZENGRI for intravenous infusion before administration.

For the initial infusion, prepare BIZENGRI as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion-related reaction.

- Check that the BIZENGRI solution is clear to slightly opalescent, colorless to slightly yellow. Parenteral drug products should be inspected visually for particulate matter and

discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present.

- Withdraw and then discard 37.5 mL 0.9% Sodium Chloride Injection from the 250 mL infusion bag. Only use infusion bags made of polyvinylchloride (PVC), polyolefin or polyolefin/polyamide coextruded plastic.
- Withdraw a total of 37.5 mL of BIZENGRI from 2 vials and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Discard any unused portion left in the vial.
- Gently invert the bag to mix the solution. Do not shake.
- If not used immediately, store the diluted solution refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light after preparation unless the infusion is initiated within 2 hours of preparation.

2.7 Administration

- If the infusion time exceeds the recommended storage time, the infusion bag must be discarded and a new infusion bag prepared to continue the infusion. Diluted BIZENGRI solution must be administered within:
 - 6 hours from end of preparation of infusion solution stored at room temperature [15°C to 25°C (59°F to 77°F)]
 - 28 hours from end of preparation of infusion solution stored refrigerated [2°C to 8°C (36°F to 46°F)]
- If the diluted BIZENGRI solution has been refrigerated, allow it to reach room temperature (approximately 30 minutes) prior to administration.
- Administer diluted BIZENGRI solution [*see Dosage and Administration (2.6)*] by intravenous infusion using an infusion set made of either PVC, polyethylene (PE), polyurethane (PUR) or polybutadiene (PB) with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer).
- Do not infuse BIZENGRI concomitantly in the same IV line with other agents.
- Administer BIZENGRI infusion via a peripheral or central line.
- Monitor patients closely for signs and symptoms of infusion-related reactions during BIZENGRI infusion and monitor patients for at least 1 hour following completion of the first BIZENGRI infusion and as clinically indicated [*see Warnings and Precautions (5.1)*].

- Administer intravenous infusion over 4 hours.

3 DOSAGE FORMS AND STRENGTHS

Injection: 375 mg/18.75 mL (20 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions/Hypersensitivity/Anaphylactic Reactions

BIZENGRI can cause serious and life-threatening infusion-related reactions (IRRs), hypersensitivity and anaphylactic reactions. Signs and symptoms of IRR may include chills, nausea, fever, and cough.

In the eNRGy study, 13% of patients experienced IRRs, all were Grade 1 or 2; 91% occurred during the first infusion. The median time to onset was 63 minutes (range: 13 minutes to 240 minutes) from the start of infusion.

Administer BIZENGRI in a setting with emergency resuscitation equipment and staff who are trained to monitor for IRRs and to administer emergency medications. Monitor patients closely for signs and symptoms of infusion reactions during infusion and for at least 1 hour following completion of first BIZENGRI infusion and as clinically indicated. Prior to the first BIZENGRI infusion, premedicate with a corticosteroid, an H1 antihistamine and acetaminophen to reduce the risk of IRRs [see *Dosage and Administration (2.4)*]. Corticosteroid premedication can be used as necessary for subsequent BIZENGRI infusions.

Interrupt BIZENGRI infusion in patients with \leq Grade 3 IRRs and administer symptomatic treatment as needed. Resume infusion at a reduced rate after resolution of symptoms [see *Dosage and Administration (2.5)*]. Immediately stop the infusion and permanently discontinue BIZENGRI for Grade 4 or life-threatening IRR or hypersensitivity/anaphylaxis reactions.

5.2 Interstitial Lung Disease/Pneumonitis

BIZENGRI can cause serious and life-threatening interstitial lung disease (ILD)/pneumonitis.

In the eNRGy study [see *Adverse Reactions (6.1)*], ILD/pneumonitis occurred in 2 (1.1%) patients treated with BIZENGRI. Grade 2 ILD/pneumonitis (Grade 2) resulting in permanent discontinuation of BIZENGRI occurred in 1 (0.6%) patient.

Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold BIZENGRI in patients with suspected

ILD/pneumonitis and administer corticosteroids as clinically indicated. Permanently discontinue BIZENGRI if ILD/pneumonitis \geq Grade 2 is confirmed [see *Dosage and Administration (2.5)*].

5.3 Left Ventricular Dysfunction

BIZENGRI can cause left ventricular dysfunction.

Left ventricular ejection fraction (LVEF) decrease occurred with anti-HER2 therapies, including BIZENGRI. Treatment with BIZENGRI has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.

In the eNRGy study [see *Adverse Reactions (6.1)*], Grade 2 LVEF decrease [Grade 2 LVEF decrease (40%-50%; 10 - 19% drop from baseline)] occurred in 2% of evaluable patients. Cardiac failure without LVEF decrease occurred in 1.7% of patients including 1 (0.6%) fatal event.

Before initiating BIZENGRI, evaluate LVEF and monitor at regular intervals during treatment as clinically indicated. For LVEF of less than 45% or less than 50% with absolute decrease from baseline of 10% or greater is confirmed, permanently discontinue BIZENGRI. Permanently discontinue BIZENGRI in patients with symptomatic congestive heart failure (CHF) [see *Dosage and Administration (2.5)*].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, BIZENGRI can cause fetal harm when administered to a pregnant woman. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Animal studies have demonstrated that inhibition of HER2 and/or HER3 results in impaired embryo-fetal development, including effects on cardiac, vascular and neuronal development, and embryoletality. Advise patients of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of BIZENGRI. Advise females of reproductive potential to use effective contraception during treatment with BIZENGRI and for 2 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:

- Infusion-Related Reactions/Hypersensitivity/Anaphylaxis [see *Warnings and Precautions (5.1)*]
- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions (5.2)*]
- Left Ventricular Dysfunction [see *Warnings and Precautions (5.3)*]

- Embryo-Fetal Toxicity [*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.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflects exposure to BIZENGRI as a single agent at 750 mg administered intravenously every 2 weeks until disease progression or unacceptable toxicity in 175 patients with *NRG1* gene fusion positive tumors in the eNRGy study. Of these, there were 99 patients with NSCLC, 39 patients with pancreatic adenocarcinoma and 37 patients with other solid tumors [*see Clinical Studies (14.1, 14.2)*]. Among the 175 patients who received BIZENGRI, the median duration of exposure to BIZENGRI was 5.3 months (range: 0.1 to 36), including 45% of patients exposed for at least 6 months and 15% of patients exposed for at least 1 year. In this pooled safety population, the most common ($\geq 10\%$) adverse reactions were diarrhea, musculoskeletal pain, fatigue, nausea, infusion-related reactions (IRR), dyspnea, rash, constipation, vomiting, abdominal pain, and edema. The most common Grade 3 or 4 laboratory abnormalities ($\geq 2\%$) were increased GGT, decreased hemoglobin, decreased sodium, decreased platelets, increased AST, increased ALT, increased alkaline phosphatase, decreased magnesium, decreased phosphate, increased aPTT and increased bilirubin.

NRG1 Gene Fusion Positive Unresectable or Metastatic NSCLC

eNRGy Study

The safety of BIZENGRI was evaluated in the eNRGy study in 99 patients with unresectable or metastatic NSCLC with *NRG1* gene fusions [*see Clinical Studies (14.1)*]. Patients received BIZENGRI as a single agent at 750 mg intravenously every 2 weeks until disease progression or unacceptable toxicity. Among patients who received BIZENGRI, 47% were exposed for 6 months or longer and 17% were exposed for greater than one year.

The median age was 66 years (range: 27 to 88), 54% were 65 years or older; 62% were female; 37% were White, 53% were Asian, 2% were Black or African American; and 1% were Hispanic or Latino.

Serious adverse reactions occurred in 25% of patients who received BIZENGRI. Serious adverse reactions in $\geq 2\%$ of patients included pneumonia (n=4) dyspnea and fatigue (n=2 each). Serious adverse reactions occurring in one patient each were: abdominal pain, acute kidney injury, ascites, bradycardia, carotid artery stenosis, cellulitis, acute cholecystitis, COVID-19, decreased appetite, dehydration, dizziness, dysphagia, hyponatremia, ileus, lymphadenitis, nausea, gastric obstruction, pericardial effusion, pneumonitis, pulmonary hypertension, sepsis, staphylococcal infection, tumor pain, urinary tract infection, viral infection and vomiting. Fatal adverse reactions occurred in 3 (3%) patients and included respiratory failure (n=2) and cardiac failure (n=1).

Permanent discontinuation of BIZENGRI due to an adverse reaction occurred in 3% of patients. Adverse reactions resulting in permanent discontinuation of BIZENGRI included dyspnea, pneumonitis and sepsis (n=1 each).

Dosage interruptions of BIZENGRI due to an adverse reaction, excluding temporary interruptions of BIZENGRI due to infusion-related reactions, occurred in 29% of patients. Adverse reactions leading to dosage interruptions in $\geq 2\%$ of patients included dyspnea, COVID-19, arrhythmia, increased ALT, increased AST, and pneumonia.

Table 3 summarizes the adverse reactions in the eNRGy study in patients with *NRG1* gene fusion positive unresectable or metastatic NSCLC.

Table 3: Adverse Reactions ($\geq 10\%$) in Patients with *NRG1* Gene Fusion Positive NSCLC Who Received BIZENGRI in the eNRGy Study

Adverse Reaction ¹	BIZENGRI (N=99)	
	All Grades %	Grade 3 or 4 %
Gastrointestinal disorders		
Diarrhea ²	25	2
Nausea	10	1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ³	23	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea ⁴	18	5
Cough ⁵	15	1
General disorders and administration site conditions		
Fatigue ⁶	17	2
Edema ⁷	11	0
Skin and subcutaneous tissue disorders		
Rash ⁸	14	0
Injury, poisoning and procedural complications		
Infusion-related reactions ⁹	12	0
Metabolism and nutrition disorders		
Decreased appetite	11	1

¹ Based on NCI CTCAE v4.03 and MedDRA v26.0

² Includes post-procedural diarrhea

³ Includes back pain, pain in extremity, musculoskeletal chest pain, myalgia, arthralgia, non-cardiac chest pain, bone pain, musculoskeletal stiffness, neck pain, spinal pain.

⁴ Includes dyspnea exertional

⁵ Includes productive cough

⁶ Includes asthenia

⁷ Includes breast edema, peripheral edema, face edema

⁸ Includes eczema, erythema, dermatitis, dermatitis contact, rash maculopapular, rash erythematous.

⁹ Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting. AEs that were considered IRRs were counted under the composite term 'IRR', irrespective of the reported PT.

Clinically relevant adverse reactions in <10% of patients receiving BIZENGRI were stomatitis (7%), vomiting (8%), cardiac failure and pneumonitis (2% each).

Table 4 summarizes the laboratory abnormalities in the eNRGy study in patients with *NRG1* gene fusion positive unresectable or metastatic NSCLC.

Table 4: Select Laboratory Abnormalities \geq 20% that Worsened from Baseline in Patients with *NRG1* Gene Fusion Positive NSCLC Who Received BIZENGRI in the eNRGy Study

Laboratory Abnormality	BIZENGRI ¹	
	All Grades %	Grade 3 or 4 %
Hematology		
Decreased hemoglobin	35	4.2
Chemistry		
Increased alanine aminotransferase	30	3.1
Decreased magnesium	28	4.3
Increased alkaline phosphatase	27	0
Decreased phosphate	26	1.1
Increased gamma-glutamyl transpeptidase	23	5
Increased aspartate aminotransferase	22	3.1
Decreased potassium	21	2.1

¹ The denominator used to calculate the rate varied from 93 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

NRG1 Gene Fusion Positive Unresectable or Metastatic Pancreatic Adenocarcinoma

eNRGy Study

The safety of BIZENGRI was evaluated in the eNRGy study in 39 patients with unresectable or metastatic pancreatic adenocarcinoma with *NRG1* gene fusions [see *Clinical Studies (14.2)*]. Patients received BIZENGRI as a single agent at 750 mg intravenously every 2 weeks until

disease progression or unacceptable toxicity. Among patients who received BIZENGRI, 50% were exposed for 6 months or longer and 13% were exposed for greater than one year.

The median age was 51 years (range: 21 to 74), 23% were 65 years or older; 49% were female; 82% were White, 13% were Asian, 2.6% were Black or African American; and 5% were Hispanic or Latino.

Serious adverse reactions occurred in 23% of patients who received BIZENGRI. Serious adverse reactions occurring in one patient each were: anemia, thrombocytopenia, tachycardia, abdominal pain, hemorrhoidal hemorrhage, nausea, cholestatic jaundice, COVID-19, liver abscess, traumatic fracture, blood creatinine increased, back pain, myelodysplastic syndrome, and respiratory disorder. There were 2 fatal adverse reactions, one due to COVID-19 and one due to respiratory failure.

Dosage interruptions of BIZENGRI due to an adverse reaction, excluding temporary interruptions of BIZENGRI due to infusion-related reactions, occurred in 33% of patients. Adverse reactions leading to dosage interruptions in $\geq 2\%$ of patients included COVID-19, pneumonia, increased AST, neutropenia, abdominal pain, agitation, increased blood alkaline phosphatase, increased blood bilirubin, constipation, increased creatinine, hemorrhage, hyperbilirubinemia, cholestatic jaundice, tachycardia, traumatic fracture, and upper respiratory infection.

Table 5 summarizes the adverse reactions in the eNRGy study in patients with *NRG1* gene fusion positive pancreatic adenocarcinoma.

Table 5: Adverse Reactions ($\geq 10\%$) in Patients with *NRG1* Gene Fusion Positive Pancreatic Adenocarcinoma Who Received BIZENGRI in the eNRGy Study

Adverse Reaction ¹	BIZENGRI (N=39)	
	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Diarrhea	36	5
Nausea	23	5
Vomiting	23	2.6
Abdominal pain	18	5
Constipation	15	0
Abdominal distension	13	0
Stomatitis	10	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ²	28	2.6
General disorders and administration site conditions		
Fatigue ³	21	5

Edema ⁴	13	0
Pyrexia	10	0
Infections and infestations		
COVID-19	18	0
Injury, poisoning and procedural complications		
Infusion-related reactions ⁵	15	0
Vascular disorders		
Hemorrhage ⁶	13	5
Psychiatric disorders		
Anxiety	10	0
Skin and subcutaneous tissue disorders		
Dry skin	10	0

¹ Based on NCI CTCAE v4.03 and MedDRA v26.0

² Includes back pain, pain in extremity, musculoskeletal chest pain, myalgia, arthralgia, non-cardiac chest pain, bone pain, musculoskeletal stiffness, neck pain, spinal pain

³ Includes asthenia

⁴ Includes peripheral edema, face edema, localized edema, peripheral swelling

⁵ Includes chills, IRR, nausea, cough, diarrhea, back pain, body temperature increased, dyspnea, face edema, fatigue, non-cardiac chest pain, oropharyngeal discomfort, paresthesia, pyrexia, and vomiting

⁶ Includes epistaxis, hematochezia, hematuria, hemorrhoidal hemorrhage

Clinically relevant adverse reactions in <10% of patients receiving BIZENGRI were decreased appetite (5%), and rash (8%) [including dermatitis acneiform, erythema, dermatitis, dermatitis contact, rash maculopapular, rash erythematous].

Table 6 summarizes the laboratory abnormalities in the eNRGy study in patients with *NRG1* gene fusion positive pancreatic adenocarcinoma.

Table 6: Select Laboratory Abnormalities \geq 20% That Worsened from Baseline in Patients with *NRG1* Gene Fusion Positive Pancreatic Adenocarcinoma Who Received BIZENGRI in the eNRGy Study

Laboratory Abnormality	BIZENGRI ¹ (N=39)	
	All Grades (%)	Grade 3 or 4 (%)
Chemistry		
Increased alanine aminotransferase	51	5
Increased aspartate aminotransferase	31	5
Increased bilirubin	31	5
Decreased phosphate	31	2.9
Increased alkaline phosphatase	28	8
Decreased sodium	28	10

Decreased albumin	26	0
Decreased potassium	26	2.6
Decreased magnesium	24	2.6
Increased gamma-glutamyl transpeptidase	23	15
Hematology		
Decreased platelets	26	10
Decreased hemoglobin	23	10
Decreased leukocytes	21	2.6

¹ The denominator used to calculate the rate varied from 35 to 39, based on the number of patients with a baseline value and at least one post-treatment value.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BIZENGRI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of BIZENGRI in pregnant women to inform a drug-associated risk.

Animal studies have demonstrated that HER2 and/or HER3 deficiency results in embryo-fetal malformation, including effects on cardiac, vascular and neuronal development, and embryolethality (see *Data*).

Human IgG1 is known to cross the placenta; therefore, BIZENGRI has the potential to be transmitted from the mother to the developing fetus. Advise patients of the potential risk to a fetus.

There are clinical considerations if BIZENGRI is used in pregnant women, or if a patient becomes pregnant within 2 months after the last dose of BIZENGRI (see *Clinical Considerations*).

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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received BIZENGRI during pregnancy or within 2 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of BIZENGRI in pregnant women. In literature reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received HER2-directed antibody alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with zenocutuzumab-zbco. A literature-based assessment of the effects on reproduction demonstrated that HER2 and HER3 are critically important in embryo-fetal development. HER2 knockout mice or mice expressing catalytically inactive HER2 die at mid-gestation due to cardiac dysfunction. HER2 knockout mice have also shown abnormal sympathetic nervous system development. In HER3-deficient mice, embryoletality occurred on embryonic day 13.5 due to cardiac and vascular defects, as well as abnormalities in other organs (neural crest, pancreas, stomach, and adrenal). In addition, HER3 is shown to be involved in mammary gland ductal morphogenesis in mice. Zenocutuzumab-zbco can cause embryo-fetal toxicity based on its mechanism of action.

8.2 Lactation

Risk Summary

There are no data on the presence of zenocutuzumab-zbco in human milk, the effects on the breastfed child, or the effects on milk production. Maternal IgG1 is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to BIZENGRI are unknown. Consider the developmental and health benefits of breast feeding along with the mother's clinical need for BIZENGRI treatment and any potential adverse effects on the breastfed child from BIZENGRI or from the underlying maternal condition. This consideration should also take into account the elimination half-life of zenocutuzumab-zbco and washout period of 2 months.

8.3 Females and Males of Reproductive Potential

BIZENGRI can 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 BIZENGRI [*see Use in Specific Populations (8.1)*].

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BIZENGRI and for 2 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of BIZENGRI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 175 patients with *NRG1* gene fusion positive tumors in the eNRGy study treated with BIZENGRI at 750 mg every 2 weeks, 75 patients (43%) were 65 years of age or older and 26 patients (15%) were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥ 65 years of age and younger patients.

11 DESCRIPTION

Zenocutuzumab-zbco is a low-fucose humanized full-length immunoglobulin G1 (IgG1) bispecific HER2- and HER3-directed antibody. It has a molecular weight of approximately 146 kDa and is produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

BIZENGRI is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free injection for intravenous infusion in single-dose vials. The pH is 6.0. Each BIZENGRI vial contains 375 mg/18.75 mL zenocutuzumab-zbco at a concentration of 20 mg/mL. Each vial also contains the following inactive ingredients: histidine (34.9 mg), L-histidine hydrochloride monohydrate (51.1 mg), polysorbate 20 (3.7 mg), trehalose (1412 mg), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zenocutuzumab-zbco is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 expressed on the surface of cells, including tumor cells, inhibiting HER2:HER3 dimerization and preventing *NRG1* binding to HER3. Zenocutuzumab-zbco decreased cell proliferation and signaling through the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway. In addition, zenocutuzumab-zbco mediates antibody-dependent cellular cytotoxicity (ADCC). Zenocutuzumab-zbco showed antitumor activity in mouse models of *NRG1* fusion-positive lung and pancreatic cancers.

12.2 Pharmacodynamics

The exposure-response relationship and time-course of pharmacodynamic response for zenocutuzumab-zbco have not been fully characterized.

12.3 Pharmacokinetics

Zenocutuzumab-zbco pharmacokinetic parameters are expressed as mean unless otherwise specified. Zenocutuzumab-zbco exposure increases proportionally over a dose range from 480 mg (0.6 times the approved recommended dosage) to 900 mg (1.2 times the approved recommended dosage). The median time to steady state of zenocutuzumab-zbco concentrations is 8 weeks and the median accumulation ratio is 1.6-fold at the approved recommended dosage.

Distribution

Zenocutuzumab-zbco volume of distribution is 6 L (CV 18%).

Elimination

The steady state zenocutuzumab-zbco half-life is 8 days (SD \pm 1.3 days) with a clearance of 22 mL/h (CV 37%).

Metabolism

Zenocutuzumab-zbco is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in the pharmacokinetics of zenocutuzumab-zbco were observed based on age (22 to 88 years), sex, race [White or Asian], body weight (38 to 126 kg), albumin level (20 to 49 g/L), mild or moderate renal impairment (creatinine clearance (CL_{cr}) 30 to 89 mL/min), and mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST > ULN).

The pharmacokinetics of zenocutuzumab-zbco in patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to 3 times ULN with any AST) or severe renal impairment (CL_{cr} < 30 mL/min) is unknown.

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 comparison of the incidence of anti-drug antibodies in the studies below with the incidence of anti-drug antibodies in other studies, including those of BIZENGRI or of other zenocutuzumab products.

In patients who received BIZENGRI at the approved recommended dosage for up to 30 months, 7 of 153 (4.6%) patients developed anti-zenocutuzumab antibodies. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and efficacy of zenocutuzumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the carcinogenic or mutagenic potential of zenocutuzumab-zbco.

Animal fertility studies have not been conducted with zenocutuzumab-zbco.

14 CLINICAL STUDIES

14.1 Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of BIZENGRI was evaluated in the eNRGy study (NCT02912949) a multicenter, open-label, multi-cohort clinical study. The study enrolled adult patients with advanced or metastatic *NRG1* fusion-positive NSCLC who had disease progression following standard of care treatment for their disease. Identification of positive *NRG1* gene fusion status was prospectively determined based on next generation sequencing (NGS) assays performed at local laboratories or central laboratories. Patients received BIZENGRI as an intravenous infusion, 750 mg every 2 weeks, until unacceptable toxicity or disease progression. Tumor assessments were performed every 8 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR) as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Efficacy was evaluated in 64 patients with *NRG1* fusion-positive NSCLC previously treated with systemic therapy enrolled in eNRGy.

The trial population characteristics were: median age 63.5 years (range: 32 to 86) with 47% of patients \geq 65 years of age; 64% female; 56% Asian, 33% White, and 11% other races or not reported; none were Hispanic or Latino; baseline ECOG performance status of 0 or 1 (97%) or 2 (3%) and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 to 6); 95% had prior platinum chemotherapy and 64% had prior anti-PD-1/PD-L1 therapy. A total of 54 patients (84%) had an *NRG1* gene fusion detected by RNA-based NGS that may include DNA sequencing and 9 (14%) had an *NRG1* gene fusion detected by DNA-based NGS.

Efficacy results are summarized in [Table 7](#) and [Table 8](#).

Table 7: Efficacy Results for Advanced Unresectable or Metastatic *NRG1* Fusion-Positive NSCLC in the eNRGy Study

Efficacy Parameter	BIZENGRI
	Previously Treated with Systemic Therapy (n = 64)
Overall response rate ¹ (95% CI)	33% (22%, 46%)
Complete response rate	1.6%
Partial response rate	31%
Duration of response	
Median (95% CI) (months)	7.4 (4.0, 16.6)
Patients with DOR ≥6 months ²	43%

¹ Confirmed overall response rate assessed by BICR

² Based on observed duration of response

Table 8: Efficacy Results by *NRG1* Gene Fusion Partner in *NRG1* Fusion-Positive NSCLC Patients in the eNRGy Study

<i>NRG1</i> Partner ¹	BIZENGRI (n = 64)	ORR		DOR
		n (%)	95% CI	Range (Months)
<i>CD74</i>	37	12 (32)	(18, 50)	1.8+; 20.3+
<i>SLC3A2</i>	14	5 (36)	(13, 65)	3.6; 20.8+
<i>SDC4</i>	7	2 (29)	(3.7, 71)	7.4; 16.6
<i>CDH1</i>	2	1 (50)	(1.3, 99)	1.9+
<i>FUT10</i>	1	PD	NA	NA
<i>PVALB</i>	1	PD	NA	NA
<i>ST14</i>	1	PD	NA	NA
<i>VAMP2</i>	1	PR	NA	5.6

¹ Fusion partners identified in this primary analysis set (n=64) may not represent all potential fusion partners.

PR=partial response; PD=progressive disease; NA=not applicable; “+” indicates ongoing response-

14.2 Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Pancreatic Adenocarcinoma

The efficacy of BIZENGRI was evaluated in the eNRGy study (NCT02912949), a multicenter, open-label, multi-cohort clinical study. The study enrolled 30 adult patients with advanced or metastatic *NRG1* fusion-positive pancreatic adenocarcinoma who had disease progression following standard of care treatment. Identification of an *NRG1* gene fusion was prospectively determined in local laboratories using next generation sequencing (NGS). Patients received BIZENGRI as an intravenous infusion, 750 mg every 2 weeks, until unacceptable toxicity or disease progression. Tumor assessments were performed every 8 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR) as determined by a blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The trial population characteristics were: median age 49 years (range: 21 to 72) with 10% of patients \geq 65 years of age; 43% female; 87% White, 7% Asian, 3.3% Black or African American, and 3.3% other races or not reported; 3.3% were Hispanic or Latino; baseline ECOG performance status of 0 (53%) or 1 (47%) and all patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 0 to 5); 97% had prior systemic therapy with FOLFIRINOX, gemcitabine/taxane-based therapy, or both. A total of 27 patients (90%) had an *NRG1* gene fusion detected by RNA-based NGS that may include DNA sequencing and 3 (10%) had an *NRG1* gene fusion detected by DNA-based NGS.

Efficacy results are summarized in [Table 9](#) and [Table 10](#).

Table 9: Efficacy Results for Advanced Unresectable or Metastatic *NRG1* Fusion-Positive Pancreatic Adenocarcinoma in the eNRGy Study

Efficacy Parameter	BIZENGRI (n = 30)
Overall response rate ¹ (95% CI)	40% (23%, 59%)
Complete response rate	3.3%
Partial response rate	37%
Duration of response	
Range (months)	3.7, 16.6
Patients with DOR \geq 6 months ²	67%

¹ Confirmed overall response rate assessed by BICR

² Based on observed duration of response

Table 10: Efficacy Results by *NRG1* Gene Fusion Partner in *NRG1* Fusion-Positive Pancreatic Adenocarcinoma Patients in the eNRGy Study

<i>NRG1</i> Partner ¹	BIZENGRI (n = 30)	ORR		DOR
		n (%)	95% CI	Range (Months)
<i>ATP1B1</i>	14	7 (50)	(23, 77)	3.7, 16.6
<i>CD44</i>	3	0	(0, 71)	NA
<i>NOTCH2</i>	3	1 (33)	(0.8, 91)	7.4+
<i>SLC4A4</i>	3	2 (67)	(9, 99)	7.5+, 15.2+
<i>AGRN</i>	1	PR	NA	9.1+
<i>APP</i>	1	PR	NA	3.7
<i>CDH1</i>	2	SD, SD	NA	NA
<i>SDC4</i>	1	SD	NA	NA
<i>THBS1</i>	1	PD	NA	NA
<i>VTCN1</i>	1	SD	NA	NA

¹ Fusion partners identified in this primary analysis set (n=30) may not represent all potential fusion partners.

PR=partial response; PD=progressive disease; SD=stable disease; NA=not applicable; “+” indicates ongoing response

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

BIZENGRI (zenocutuzumab-zbco) injection is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free solution for intravenous infusion. Each single-dose vial contains 375 mg/18.75 mL (20 mg/mL) BIZENGRI. Two vials (equivalent to 1 dose) are packed in a single carton. (NDC 71837-1000-1 for individual vial and NDC 71837-1000-2 for a single carton).

Storage and Handling

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in 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 (Patient Information).

Infusion-Related Reactions/Hypersensitivity/Anaphylaxis

Advise patients that BIZENGRI can cause serious and life-threatening infusion-related reactions (IRRs). Advise patients to alert their healthcare provider immediately for any signs or symptoms of IRRs during and following the infusion [*see Warnings and Precautions (5.1)*].

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients that BIZENGRI can cause serious and life threatening ILD/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [*see Warnings and Precautions (5.2)*].

Left Ventricular Dysfunction

Inform patients that BIZENGRI can cause serious and life threatening left ventricular dysfunction. Advise patients to immediately contact their healthcare provider for new or worsening cardiovascular symptoms [*see Warnings and Precautions (5.3)*].

Embryo-Fetal Toxicity

- Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider with a known or suspected pregnancy [*see Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment with BIZENGRI and for 2 months after the last dose [*see Use in Specific Populations (8.1, 8.3)*].

Lactation

Advise women not to breastfeed during treatment with BIZENGRI and for 2 months after the last dose [*see Use in Specific Populations (8.2)*].

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