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

GAZYVA® (obinutuzumab) injection, for intravenous infusion
Initial U.S. Approval: 2013

WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

• Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)
• Progressive Multifocal Leukoencephalopathy (PML) resulting in death. (5.2)

RECENT MAJOR CHANGES

Indications and Usage, Follicular Lymphoma (1.2)	2/2016
Dosage and Administration (2)	2/2016
Warnings and Precautions (5.3, 5.6, 5.7)	2/2016
Warnings and Precautions, Tumor Lysis Syndrome (5.4)	9/2015

INDICATIONS AND USAGE

GAZYVA (obinutuzumab) is a CD20-directed cytolytic antibody and is indicated:

- in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia. (1, 14)
- in combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen. (1, 14)

DOSAGE AND ADMINISTRATION

- Premedicate for infusion reactions and tumor lysis syndrome. (2.2, 5.3, 5.4)
- Dilute and administer as intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
- Recommended dose for 6 cycles (28-day cycles):
  - The dose for chronic lymphocytic leukemia is 100 mg on day 1 and 900 mg on day 2 Cycle 1, 1000 mg on day 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6. (2.1)
  - The dose for follicular lymphoma is 1000 mg on day 1, 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2-6, and then every 2 months for 2 years. (2.1)

DOSAGE FORMS AND STRENGTHS

- 1000 mg/40 mL (25 mg/mL) single-dose vial. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Infusion reactions: Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions. (2.2, 5.3)
- Tumor Lysis Syndrome: Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance. (5.4)
- Neutropenia: Monitor for infection. (5.6)
- Thrombocytopenia: Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support. (5.7)
- Immunization: Do not administer live virus vaccines prior to or during GAZYVA treatment. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 10%) were:

- CLL: infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea. (6)
- Indolent NHL: infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Likely to cause fetal B-cell depletion. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2016

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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

FULL PRESCRIBING INFORMATION

WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation *[see Warnings and Precautions (5.1)]*.**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) *[see Clinical Studies (14.1)]*.

1.2 Follicular Lymphoma

GAZYVA, in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

- Premedicate before each infusion *[see Dosage and Administration (2.2)]*.
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk of tumor lysis syndrome *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.
- Administer only as an intravenous infusion through a dedicated line *[see Dosage and Administration (2.5)]*.
- Do not administer as an intravenous push or bolus.
- Monitor blood counts at regular intervals.
- GAZYVA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur *[see Warnings and Precautions (5.3)]*.

Chronic Lymphocytic Leukemia

Each dose of GAZYVA is 1000 mg, administered intravenously, with the exception of the first infusions in Cycle 1, which are administered on day 1 (100 mg) and day 2 (900 mg).

Table 1 Dose of GAZYVA to Be Administered During 6 Treatment Cycles, Each of 28 days Duration, for Patients with CLL

Day of treatment cycle		Dose of GAZYVA	Rate of infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)
Cycle 1 (loading doses)	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible and adjust dosing schedule accordingly. If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose.

Follicular Lymphoma

Each dose of GAZYVA is 1000 mg administered intravenously according to Table 2. Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles of GAZYVA treatment in combination with bendamustine should continue on GAZYVA 1000 mg as monotherapy for two years.

Table 2 Dose of GAZYVA to Be Administered During 6 Treatment Cycles, Each of 28 days Duration, Followed by GAZYVA Monotherapy for Patients with FL

Day of treatment cycle		Dose of GAZYVA	Rate of infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)
Cycle 1 (loading doses)	Day 1	1000 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 8	1000 mg	If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	
Monotherapy	Every two months for two years	1000 mg	

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible. During GAZYVA and bendamustine treatment, adjust the dosing schedule accordingly. During monotherapy, maintain the original dosing schedule for subsequent doses.

Management of Infusion Reactions in CLL and FL Patients

If a patient with CLL or FL experiences an infusion reaction of any grade during infusion, adjust the infusion as follows *[see Warnings and Precautions (5.3)]*:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue GAZYVA therapy.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if patients experience a Grade 3 infusion-related symptom at rechallenge.
    - For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.
- Grade 1–2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.
    - For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.

2.2 Recommended Premedication

Infusion Reactions

Premedication to reduce the risk of infusion reactions is outlined in Table 3 *[see Warnings and Precautions (5.3)]*.

Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration *[see Warnings and Precautions (5.3)]*.

Tumor Lysis Syndrome

Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L) or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with anti-hyperuricemics (e.g., allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed *[see Warnings and Precautions (5.4)]*.

Table 3 Premedication for GAZYVA Infusion to Reduce Infusion-Related Reactions (IRR)

Day of Treatment Cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: **CLL Day 1, Day 2** **FL Day 1**	All patients	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[1]	Completed at least 1 hour prior to GAZYVA infusion.
		650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	
All subsequent infusions	All patients	650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
	Patients with an IRR (Grade 1-2) with the previous infusion	650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	
	Patients with a Grade 3 IRR with the previous infusion OR with a lymphocyte count > 25×10^9/L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone[1]	Completed at least 1 hour prior to GAZYVA infusion.
		650–1000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	

[1] Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.

2.3 Antimicrobial Prophylaxis

Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

2.4 Treatment Interruption for Toxicity

Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥ Grade 2 non-hematologic toxicity.

2.5 Preparation and Administration

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

- Inspect visually for any particulate matter and discoloration prior to administration.
- Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%).

Chronic Lymphocytic Leukemia

- Preparation of solution for infusion on day 1 (100 mg) and day 2 (900 mg) of Cycle 1:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 4 mL (100 mg) of GAZYVA into a 100 mL 0.9% sodium chloride infusion bag for immediate administration.
  - Dilute the remaining 36 mL (900 mg) into a 250 mL 0.9% sodium chloride infusion bag at the same time for use on day 2 and store at 2°C to 8°C (36°F to 46°F) for up to 24 hours. After allowing the diluted bag to come to room temperature, use immediately.
  - Clearly label each infusion bag.
- Preparation of solution for infusion on day 8 and 15 of Cycle 1 and day 1 Cycles 2–6:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag.

Follicular Lymphoma

- Preparation of solution for infusion:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag.

- Mix diluted solution by gentle inversion. Do not shake or freeze.
- For microbiological stability, the diluted GAZYVA infusion solution should be used immediately. Dilute under appropriate aseptic conditions. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use.

The product can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.

Administration for CLL and FL Patients

- Administer as an intravenous infusion only.
- Do not administer as an intravenous push or bolus.
- Do not mix GAZYVA with other drugs.
- No incompatibilities between GAZYVA and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed *[see How Supplied/Storage and Handling (16.1)]*.

3 DOSAGE FORMS AND STRENGTHS

1000 mg/40 mL (25 mg/mL) single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with GAZYVA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with GAZYVA. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving GAZYVA, immediately discontinue GAZYVA and any concomitant chemotherapy and institute appropriate treatment. Resumption of GAZYVA in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming GAZYVA in patients who develop HBV reactivation.

5.2 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with GAZYVA. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.3 Infusion Reactions

GAZYVA can cause severe and life-threatening infusion reactions. Sixty-five percent of patients with CLL experienced a reaction to the first 1000 mg infused of GAZYVA. Thirty-eight percent of iNHL patients experienced a reaction on Day 1 of GAZYVA infusion. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills *[see Adverse Reactions (6.1)]*.

Premedicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed. Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving GAZYVA have occurred *[see Dosage and Administration (2)]*.

For patients with any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction: Stop the GAZYVA infusion. Permanently discontinue GAZYVA therapy.

For patients with Grade 1, 2, or 3 infusion reactions: Interrupt GAZYVA for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms *[see Dosage and Administration (2)]*.

For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the GAZYVA infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each GAZYVA infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here.

5.4 Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS), including fatal cases, has been reported in patients receiving GAZYVA. Patients with high tumor burden, high circulating lymphocyte count ($> 25 \times 10^9$/L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA *[see Dosage and Administration (2.2)]*.

During the initial days of GAZYVA treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

5.5 Infections

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. Fatal infections have been reported with GAZYVA. Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

5.6 Neutropenia

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Patients with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider administration of granulocyte colony-stimulating factors (G-CSF) in patients with Grade 3 or 4 neutropenia.

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Consider dose delays in the case of Grade 3 or 4 neutropenia. Patients with severe and long lasting (>1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

5.7 Thrombocytopenia

Severe and life threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chlorambucil or bendamustine. Fatal hemorrhagic events during Cycle 1 have also been reported in patients with CLL treated with GAZYVA.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of GAZYVA and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

5.8 Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following GAZYVA therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatitis B reactivation *[see Warnings and Precautions (5.1)]*
- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.2)]*
- Infusion reactions *[see Warnings and Precautions (5.3)]*
- Tumor lysis syndrome *[see Warnings and Precautions (5.4)]*
- Infections *[see Warnings and Precautions (5.5)]*
- Neutropenia *[see Warnings and Precautions (5.6)]*
- Thrombocytopenia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial 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.

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data described in Tables 4-5 below are based on a safety population of 773 previously untreated patients with CLL. Patients were treated with chlorambucil alone, GAZYVA in combination with chlorambucil, or rituximab in combination with chlorambucil. The Stage 1 analysis compared GAZYVA in combination with chlorambucil vs. chlorambucil alone, and Stage 2 compared GAZYVA in combination with chlorambucil vs. rituximab in combination with chlorambucil. Adverse reactions rates and laboratory abnormalities from the Stage 2 phase are presented below and are consistent with the rates in Stage 1. In addition to the adverse reactions observed in Stage 2, in Stage 1 back pain (5% vs. 2%), anemia (12% vs. 10%) and cough (10% vs. 7%) were observed at a higher incidence in the obinutuzumab treated patients. The incidence of Grade 3-4 back pain (<1% vs. 0%), cough (0% vs. <1%) and anemia (5% vs. 4%) was similar in both treatment arms. With regard to laboratory abnormalities, in Stage 1 hyperkalemia (33% vs. 18%), creatinine increased (30% vs. 20%) and alkaline phosphatase

increased (18% vs. 11%) were observed at a higher incidence in patients treated with obinutuzumab with similar incidences of Grade 3-4 abnormalities between the two arms.

Patients received three 1000 mg doses of GAZYVA on the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with chlorambucil (6 cycles of 28 days each in total). In the last 140 patients enrolled, the first dose of GAZYVA was split between day 1 (100 mg) and day 2 (900 mg) *[see Dosage and Administration (2.1)]*. In total, 81% of patients received all 6 cycles (of 28 days each) of GAZYVA-based therapy.

The most common adverse reactions (incidence ≥ 10%) observed in patients with CLL in the GAZYVA containing arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

The most common Grade 3-4 adverse reactions (incidence ≥ 10%) observed in patients with CLL in the GAZYVA containing arm were neutropenia, infusion reactions, and thrombocytopenia.

Table 4 Summary of Adverse Reactions Reported in ≥ 5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

Adverse Reactions System Organ Class	GAZYVA + Chlorambucil n = 336		Rituximab + Chlorambucil n = 321	
	All Grades %	Grades 3–4 %	All Grades %	Grades 3–4 %
Injury, poisoning and procedural complications				
Infusion reactions	66	20	38	4
Blood and lymphatic system disorders[a]				
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
Leukopenia	6	4	2	< 1
General disorders and administration site conditions				
Pyrexia	9	< 1	7	< 1
Gastrointestinal disorders				
Diarrhea	10	2	8	< 1
Constipation	8	0	5	0
Infections and infestations				
Nasopharyngitis	6	< 1	3	0
Urinary tract infection	5	1	2	< 1

[a] Adverse reactions reported under "Blood and lymphatic system disorders" reflect those reported by investigator as clinically significant.

Table 5 Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

Laboratory Abnormalities	GAZYVA + Chlorambucil n = 336		Rituximab + Chlorambucil n = 321	
	All Grades %	Grades 3–4 %	All Grades %	Grades 3–4 %
Hematology				
Neutropenia	76	46	69	41
Lymphopenia	80	39	50	16
Leukopenia	84	35	62	16
Thrombocytopenia	48	13	40	8
Anemia	39	10	37	10
Chemistry				
Hypocalcemia	37	3	32	<1
Hypokalemia	14	1	10	<1
Hyponatremia	26	7	18	2
AST/SGOT increased	27	2	21	<1

Laboratory Abnormalities	GAZYVA + Chlorambucil n = 336		Rituximab + Chlorambucil n = 321	
	All Grades %	Grades 3–4 %	All Grades %	Grades 3–4 %
ALT/SGPT increased	28	2	21	1
Hypoalbuminemia	23	<1	16	<1

Summary of Clinical Trial Experience in Non-Hodgkin Lymphoma

The safety of GAZYVA was evaluated based on a safety population of 392 patients with indolent NHL, of whom 81% had FL. In the population of patients with FL, the profile of adverse reactions was consistent with the overall indolent NHL population. Patients were treated with either GAZYVA in combination with bendamustine, followed by GAZYVA monotherapy in patients that have not progressed, or with bendamustine alone.

Patients randomized to the GAZYVA + bendamustine arm received three weekly 1000 mg doses of GAZYVA in the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with bendamustine 90 mg/m^2 on Days 1 and 2 in all 6 cycles. Patient randomized to the bendamustine alone arm received 120 mg/m^2 on Days 1 and 2. This regimen continued for 6 cycles of 28 days in duration. For patients who did not progress on GAZYVA in combination with bendamustine, a single dose of 1000 mg GAZYVA monotherapy was given every two months until progression or for a maximum of two years. During combination therapy with GAZYVA and bendamustine, 79% of patients received all 6 treatment cycles of GAZYVA and 76% received all 6 treatment cycles of bendamustine compared to 67% of patients in the bendamustine alone arm.

The most common adverse reactions (incidence ≥ 10%) observed in patients with iNHL in the GAZYVA containing arm were infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection.

The most common Grade 3-4 adverse reactions (incidence ≥ 10%) observed in patients with iNHL in the GAZYVA containing arm were neutropenia, thrombocytopenia and infusion reactions.

Table 6 Summary of Adverse Reactions Reported in ≥5% of Patients with Indolent NHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm

Adverse Reactions System Organ Class	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194		Bendamustine n = 198	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Injury, Poisoning and Procedural Complications				
Infusion related reactions[a]	69	11	63	6
Blood and Lymphatic System Disorders				
Neutropenia	35	33	28	26
Gastrointestinal Disorders				
Constipation	19	0	16	0
Dyspepsia	5	0	3	0
General Disorders and Administration Site Conditions				
Pyrexia	18	1	14	0

Adverse Reactions System Organ Class	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194		Bendamustine n = 198	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Asthenia	11	1	8	0
Infections and Infestations				
Upper Respiratory Tract Infection	13	2	8	1
Sinusitis	12	1	5	0
Urinary Tract Infection	10	3	6	0
Nasopharyngitis	9	0	4	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	12	0	5	0
Pain in Extremity	9	1	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	26	0	17	0
Nasal Congestion	7	0	2	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	9	0	6	0

[a] Defined as any related adverse reaction that occurred during or within 24 hours of infusion.

During the monotherapy period with GAZYVA, the most common adverse reactions in patients with iNHL were cough (15%), upper respiratory tract infections (12%), neutropenia (11%), sinusitis (10%), diarrhea (8%), infusion related reactions (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), pyrexia (6%), nasopharyngitis (6%), and urinary tract infections (6%). The most common Grade 3-4 adverse reactions during the monotherapy period were neutropenia (10%), and anemia, febrile neutropenia, thrombocytopenia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1%).

Table 7 Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with iNHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm[a]

Laboratory Abnormalities	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194		Bendamustine n = 198	
	All Grades %	Grades 3–4 %	All Grades %	Grades 3–4 %
Hematology				
Neutropenia	75	52	77	42
Leukopenia	86	47	88	34
Lymphopenia	99	93	99	85
Chemistry				
Hypocalcemia	38	2	26	2
Hypophosphatemia	41	7	38	7
ALT/SGPT increased	35	1	31	4
Elevated creatinine	87	4	92	2
Creatinine Clearance (decreased)	58	6	61	4

[a] Two percent different in either the All Grades or Grade 3-4 Lab Abnormalities.

In the monotherapy phase of treatment with GAZYVA, the most frequently reported hematological laboratory abnormalities were lymphopenia (80%), leukopenia (63%), low hemoglobin (50%) and neutropenia (46%). The most frequently reported hematological Grade 3-

4 laboratory abnormalities during the monotherapy period were lymphopenia (52%), neutropenia (27%) and leukopenia (20%).

In the monotherapy phase of treatment with GAZYVA, the most frequently reported chemistry laboratory abnormalities were elevated creatinine (69%), decreased creatinine clearance (43%), hypophosphatemia (25%), AST/SGOT increased (24%) and ALT/SGPT increased (21%). The most frequently reported chemistry Grade 3-4 laboratory abnormalities during the monotherapy period were hypophosphatemia (5%) and hyponatremia (3%).

Infusion Reactions:

Chronic Lymphocytic Leukemia

The incidence of infusion reactions was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 infusion reactions was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1000 mg and < 1% thereafter. No Grade 3 or 4 infusion reactions were reported beyond the first 1000 mg infused.

Of the first 53 patients receiving GAZYVA on the trial, 47 (89%) experienced an infusion reaction. After this experience, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on day 1 and 900 mg on day 2). For the 140 patients for whom these mitigation measures were implemented, 74 patients (53%) experienced a reaction with the first 1000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and < 3% thereafter *[see Dosage and Administration (2)]*.

Non-Hodgkin Lymphoma

Overall, 69% of patients experienced an infusion reaction (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3-4 infusion reactions was 11%. In Cycle 1, the incidence of infusion reactions (all grades) was 55% in patients receiving GAZYVA in combination with bendamustine with Grade 3-4 infusion reactions reported in 9%. In patients receiving GAZYVA in combination with bendamustine, the incidence of infusion reactions was highest on Day 1 (38%), and gradually decreased on Days 2, 8 and 15 (25%, 7% and 4%, respectively).

During Cycle 2, the incidence of infusion reactions was 24% in patients receiving GAZYVA in combination with bendamustine and decreased with subsequent cycles.

During GAZYVA monotherapy, infusion reactions (all grades) were observed in 8% of patients. No grade 3-4 infusion reactions were reported during GAZYVA monotherapy.

Overall, 2% of patients experienced an infusion reaction leading to discontinuation of GAZYVA.

Neutropenia:

Chronic Lymphocytic Leukemia

The incidence of neutropenia reported as an adverse reaction was 38% in the GAZYVA treated arm and 32% in the rituximab treated arm, with the incidence of serious adverse events being 1% and < 1%, respectively (Table 4). Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the GAZYVA treated arm and 12% in the rituximab treated arm.

Non-Hodgkin Lymphoma

The incidence of neutropenia was higher in the GAZYVA plus bendamustine arm (38%) compared to the arm treated with bendamustine alone (32%). Cases of prolonged neutropenia

(3%) and late onset neutropenia (7%) were also reported in the GAZYVA plus bendamustine arm.

Infection:

Chronic Lymphocytic Leukemia

The incidence of infections was similar between GAZYVA and rituximab treated arms. Thirty-eight percent of patients in the GAZYVA treated arm and 37% in the rituximab treated arm experienced an infection, with Grade 3–4 rates being 11% and 13%, respectively. Fatal events were reported in 1% of patients in both arms.

Non-Hodgkin Lymphoma

The incidence of infection was 66% in the GAZYVA plus bendamustine arm and 56% in the bendamustine arm, with Grade 3-4 events reported in 16% and 14%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 4% in the bendamustine arm.

Thrombocytopenia:

Chronic Lymphocytic Leukemia

The overall incidence of thrombocytopenia reported as an adverse reaction was higher in the GAZYVA treated arm (14%) compared to the rituximab treated arm (7%), with the incidence of Grade 3–4 events being 10% and 3%, respectively (Table 4). The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle were 11% in the GAZYVA and 3% in the rituximab treated arms, with Grade 3–4 rates being 8% and 2%, respectively. Four percent of patients in the GAZYVA treated arm experienced acute thrombocytopenia (occurring within 24 hours after the GAZYVA infusion).

The overall incidence of hemorrhagic events and the number of fatal hemorrhagic events were similar between the treatment arms, with 3 in the rituximab and 4 in the GAZYVA treated arms. However, all fatal hemorrhagic events in patients treated with GAZYVA occurred in Cycle 1.

Non-Hodgkin Lymphoma

The incidence of thrombocytopenia was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (24%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 11% and 10%, respectively. Grade 3-4 hemorrhagic events were similar in both treatment arms (5% in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm).

Tumor Lysis Syndrome: The incidence of Grade 3 or 4 tumor lysis syndrome in patients with CLL was 2% in the GAZYVA treated arm, and in patients with iNHL was 0.5% in the GAZYVA plus bendamustine treated arm.

Musculoskeletal Disorders:

Chronic Lymphocytic Leukemia

Adverse events related to musculoskeletal disorders (all events from the System Organ Class), including pain, have been reported in the GAZYVA treated arm with higher incidence than in the rituximab treated arm (18% vs. 15%).

Non-Hodgkin Lymphoma

Adverse events related to musculoskeletal disorders (all events from the System Organ Class), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (41% vs. 29%).

Liver Enzyme Elevations: Hepatic enzyme elevations have occurred in CLL patients who received GAZYVA in clinical trials and had normal baseline hepatic enzyme levels (AST, ALT, and ALP). The events occurred most frequently within 24-48 hours of the first infusion. In some patients, elevations in liver enzymes were observed concurrently with infusion reactions or tumor lysis syndrome. In the pivotal CLL study, there was no clinically meaningful difference in overall hepatotoxicity adverse events between all arms (4% of patients in the GAZYVA treated arm). Medications commonly used to prevent infusion reactions (e.g., acetaminophen) may also be implicated in these events. Monitor liver function tests during treatment, especially during the first cycle. Consider treatment interruption or discontinuation for hepatotoxicity.

Gastro-Intestinal Perforation: Cases of gastro-intestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

6.2 Immunogenicity

Serum samples from patients with previously untreated CLL were tested during and after treatment for antibodies to GAZYVA. Of the GAZYVA treated patients with CLL, 7% (18/271) tested positive for anti-GAZYVA antibodies at one or more time points. In the pivotal iNHL trial, two out of 194 (1%) patients in the GAZYVA plus bendamustine arm tested positive for anti-GAZYVA antibodies at baseline and experienced infusion reactions. No patients with iNHL developed anti-GAZYVA antibodies during or following GAZYVA treatment. Neutralizing activity of anti-GAZYVA antibodies has not been assessed.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. Therefore, comparison of the incidence of antibodies to GAZYVA with the incidence of antibodies to other products may be misleading. Clinical significance of anti-GAZYVA antibodies is not known.

6.3 Additional Clinical Trial Experience

Worsening of Pre-existing Cardiac Conditions: Fatal cardiac events have been reported in patients treated with GAZYVA.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with GAZYVA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GAZYVA is likely to cause fetal B-cell depletion based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are no data with GAZYVA use in pregnant women to inform a drug-associated risk. Monoclonal antibodies are transferred across the placenta. In animal reproduction studies, weekly intravenous administration of obinutuzumab to pregnant cynomolgus monkeys from day 20 of pregnancy

until parturition which includes the period of organogenesis at doses with exposures up to 2.4 times the exposure at the clinical dose of 1000 mg monthly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys *[see Data]*. Consider the potential risk to the fetus when prescribing GAZYVA to a pregnant woman.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

GAZYVA is likely to cause fetal B-cell depletion *[see Data]*. Avoid administering live vaccines to neonates and infants exposed to GAZYVA in utero until B-cell recovery occurs *[see Warnings and Precautions (5.8)] and Clinical Pharmacology (12.2)]*.

Data

Animal Data

In a pre- and post-natal development study, pregnant cynomolgus monkeys received weekly intravenous doses of 25 or 50 mg/kg obinutuzumab from day 20 of pregnancy until parturition, which includes the period of organogenesis. The high dose results in an exposure (AUC) that is 2.4 times the exposure in patients with CLL at the recommended label dose. There were no embryo-toxic or teratogenic effects in animals. Secondary opportunistic infections, immune complex mediated hypersensitivity reactions, or a combination of both were observed in exposed dams. When first measured on day 28 postpartum, obinutuzumab was detected in offspring at levels in the range of maternal serum levels on the same day, and B-cells were completely depleted. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months after birth.

Obinutuzumab was measured in the milk of lactating cynomolgus monkeys on day 28 postpartum after weekly intravenous administration from day 20 of pregnancy until parturition. Concentrations in milk were approximately 0.04% and 0.13% of concentrations in maternal serum in the 25 and 50 mg/kg groups, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of GAZYVA in human milk, the effects on the breastfed infant, or the effects on milk production. However, low levels of obinutuzumab were present in the milk of lactating cynomolgus monkeys *[see Use in Specific Populations (8.1)]*. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GAZYVA and any potential adverse effects on the breastfed infant from GAZYVA or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

Chronic Lymphocytic Leukemia

Of 336 patients with previously untreated CLL who received GAZYVA in combination with chlorambucil, 81% were 65 years and older, while 46% were 75 and older. Of the patients 75 years and older, 46% experienced serious adverse events and 7% experienced adverse events leading to death. Of the patients younger than 75, 33% experienced a serious adverse event and 2% an adverse event leading to death. No significant differences in efficacy were observed between younger and older patients *[see Clinical Studies (14.1)]*.

Non-Hodgkin Lymphoma

Of 194 patients with iNHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 52% of patients experienced serious adverse events and 26% experienced adverse events leading to treatment withdrawal while in patients under 65, 28% and 12% experienced serious adverse events and adverse events leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients.

10 OVERDOSAGE

There has been no experience with overdose in human clinical trials. Doses ranging from 50 mg up to and including 2000 mg per infusion have been administered in clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of GAZYVA and supportive therapy.

11 DESCRIPTION

GAZYVA (obinutuzumab) is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B cells. The molecular mass of the antibody is approximately 150 kDa.

GAZYVA is produced by mammalian cell (CHO) suspension culture. GAZYVA was engineered for reduced fucose content as compared to a typical IgG1 produced in CHO cells. GAZYVA is a sterile, clear, colorless to slightly brown, preservative-free liquid concentrate for intravenous administration. GAZYVA is supplied at a concentration of 25 mg/mL in 1000 mg single-use vials. The product is formulated in 20 mM L-histidine/L-histidine hydrochloride, 240 mM trehalose, 0.02% poloxamer 188. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre B- and mature B-lymphocytes. Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.

As an antibody with reduced fucose content, obinutuzumab induces greater ADCC activity than rituximab in vitro using human cancer cell lines. Obinutuzumab also demonstrated an increased ability to induce direct cell death when compared to rituximab. Obinutuzumab binds to FcγRIII

using purified proteins with a higher affinity than rituximab. Obinutuzumab and rituximab bind with similar affinity to overlapping epitopes on CD20.

12.2 Pharmacodynamics

In clinical trials in patients with CLL, GAZYVA caused CD19 B-cell depletion (defined as CD19 B-cell counts < 0.07 x 10^9/L). Initial CD19 B-cell recovery was observed in some patients approximately 9 months after the last GAZYVA dose. At 18 months of follow-up, some patients remain B-cell depleted.

Although the depletion of B cells in the peripheral blood is a measurable pharmacodynamic effect, it is not directly correlated with the depletion of B cells in solid organs or in malignant deposits. B-cell depletion has not been shown to be directly correlated to clinical response.

Cardiac Electrophysiology

The potential effects of GAZYVA on the QTc interval have not been studied.

12.3 Pharmacokinetics

The elimination of obinutuzumab is comprised of a linear clearance pathway and a time-dependent non-linear clearance pathway. As GAZYVA treatment progresses, the impact of the time-dependent pathway diminishes in a manner suggesting target-mediated drug disposition (TMDD) and saturation of the TMDD at the end of the treatment cycle at the proposed clinical dose regimen. Based on a population pharmacokinetic analysis, in patients with CLL the geometric mean (CV%) obinutuzumab volume of distribution at steady state, clearance after TMDD saturation and terminal half-life are approximately 4.1 (20%) L, 0.11 (53%) L/day and 26.4 (48%) days, respectively. In patients with iNHL the geometric mean (CV%) obinutuzumab volume of distribution at steady state, clearance after TMDD saturation and terminal half-life are approximately 4.3 (22%) L, 0.08 (45%) L/day and 36.8 (40%) days, respectively.

Specific Populations:

Age: Age did not affect the pharmacokinetics of GAZYVA.

Body Weight: Volume of distribution and steady-state clearance both increased with body weight; however, the expected change in exposure does not warrant a dose modification.

Renal Impairment: Based on the population pharmacokinetic analysis, a baseline creatinine clearance (CrCl) > 30 mL/min does not affect the pharmacokinetics of GAZYVA. GAZYVA has not been studied in patients with a baseline CrCl < 30 mL/min.

Hepatic Impairment: GAZYVA has not been studied in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with obinutuzumab.

No specific studies have been conducted to evaluate potential effects on fertility; however, no adverse effects on male or female reproductive organs were observed in the 26-week repeat-dose toxicity study in cynomolgus monkeys.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia

GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (Study 1) in 781 patients with previously untreated CD20+ chronic lymphocytic leukemia requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) < 70 mL/min. Patients with CrCl < 30 mL/min, active infections, positive hepatitis B (HBsAg or anti-HBc positive; patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, or immunization with live virus vaccine within 28 days prior to randomization were excluded from the trial. Patients were treated with chlorambucil control (Arm 1), GAZYVA in combination with chlorambucil (Arm 2), or rituximab in combination with chlorambucil (Arm 3). The safety and efficacy of GAZYVA was evaluated in a Stage 1 comparison of Arm 1 vs. Arm 2 in 356 patients and a Stage 2 comparison of Arm 2 vs. Arm 3 in 663 patients.

The majority of patients received 1000 mg of GAZYVA on days 1, 8, and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of GAZYVA was divided between day 1 (100 mg) and day 2 (900 mg) *[see Dosage and Administration (2.1)]*, which was implemented in 140 patients. Chlorambucil was given orally at 0.5 mg/kg on day 1 and day 15 of all treatment cycles (1 to 6).

In Study 1, the median age was 73 years, 62% were male, and 95% were Caucasian. Sixty-five percent had a CrCl < 70 mL/min and 76% had multiple coexisting medical conditions. Twenty-two percent of patients were Binet stage A, 42% were stage B, and 36% were stage C. The median estimated CrCl was 62 mL/min. Eighty-one percent of patients treated with GAZYVA in combination with chlorambucil received all 6 cycles compared to 89% of patients in the rituximab treated arm and 67% in the chlorambucil alone arm.

In the Stage 1 analysis of Study 1, the median progression-free survival (PFS) in the GAZYVA in combination with chlorambucil arm was 27.2 months and 11.2 months in the chlorambucil alone arm (median observation time 22.8 months) as assessed by independent review and is consistent with investigator-assessed PFS. The median overall survival (OS) was not yet reached with a total of 46 deaths: 22 (9%) in the GAZYVA in combination with chlorambucil arm and 24 (20%) in the chlorambucil arm. The hazard ratio for OS was 0.41 (95% CI: 0.23-0.74).

In the Stage 2 analysis of Study 1, the median PFS was 26.7 months in the GAZYVA arm and 14.9 months in the rituximab arm with a median observation time of 18.7 months (HR: 0.42, 95% CI: 0.33-0.54, p-value <0.0001). These results were assessed by independent review and are consistent with investigator-assessed PFS. Minimal Residual Disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cutoff for a negative status was one CLL cell per 10^4 leukocytes in the sample (i.e., an MRD value of $<10^{-4}$ was considered negative). Among patients who achieved complete response (CR) and complete response with incomplete marrow recovery (CRi) (94 patients in the GAZYVA arm and 34 patients in the rituximab arm), 18 patients (19%) had negative MRD in the bone marrow in the GAZYVA arm compared to 2 patients (6%) in the rituximab arm. Out of the patients who achieved CR and CRi, 39 patients (41%) in the GAZYVA arm and 4 patients (12%) in the rituximab arm were MRD negative in peripheral blood samples collected at least 3 months after the end of treatment.

Efficacy results are shown in Table 8, and the Kaplan-Meier curves for Stage 1a Overall Survival and Stage 2 PFS are shown in Figures 1 and 2, respectively.

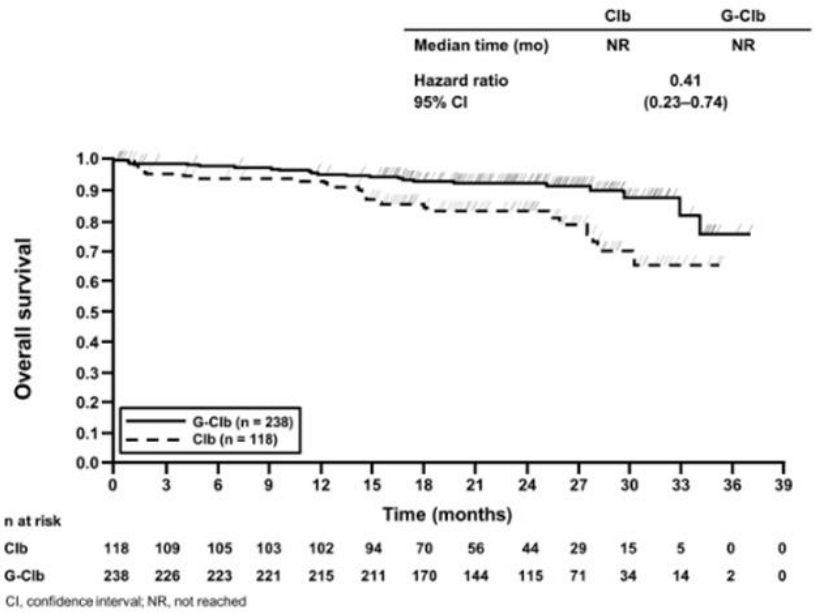
Table 8 Efficacy Results for Study 1

Endpoint	Stage 1 of Study 1		Stage 2 of Study 1	
	GAZYVA + Chlorambucil* **n = 238**	**Chlorambucil** **n = 118**	**GAZYVA + Chlorambucil*** **n = 333**	**Rituximab + Chlorambucil** **n = 330**
Median Progression-Free Survival[a]	27.2 months (HR 0.19 [0.14; 0.27], p-value < 0.0001 stratified log-rank test)	11.2 months	26.7 months (HR 0.42 [0.33; 0.54], p-value < 0.0001 stratified log-rank test)	14.9 months
Overall Response Rate[b]	78.2%	33.1%	79.6%	66.3%
Complete Response	28.2%	0	26.1%	8.8%
Complete Response with Incomplete Marrow Recovery	2.5%	1.7%	2.1%	1.5%
Partial Response	45.0%	30.5%	48.6%	54.1%
Nodular Partial Response	2.5%	0.8%	2.7%	1.8%
Median Duration of Response	22.4 months	4.7 months	19.6 months	9.7 months
Overall Survival	HR 0.41 [0.23; 0.74]		Not Yet Mature	

[a] As defined by independent review. Investigator-assessed PFS was consistent with data from independent review.
[b] Defined as best overall response rate (ORR = CR + CRi + PR + nPR).
*All Stage 1 GClb patients (n = 238) were included in the Stage 2 GClb population (n = 333).

Figure 1

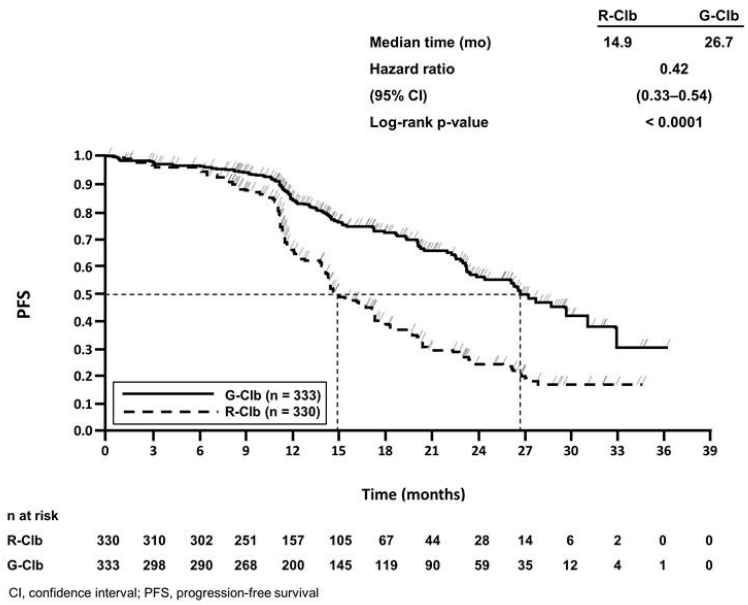
Kaplan-Meier Curve of Overall Survival in Patients with CLL in Study 1 (Stage 1)



CI, confidence interval; NR, not reached

Figure 2

Kaplan-Meier Curve of Progression-Free Survival in Patients with CLL in Study 1 (Stage 2)



CI, confidence interval; PFS, progression-free survival

14.2 Follicular Lymphoma

Study 2 is an open-label, multicenter, randomized study including 321 patients with follicular lymphoma (FL) who had no response to or have progressed during or within 6 months of rituximab or a rituximab-containing regimen. These patients were randomized to receive either bendamustine alone (n = 166) or GAZYVA in combination with bendamustine (n = 155) for 6 cycles, each of 28 days duration. Patients in the GAZYVA plus bendamustine arm who did not have disease progression [patients with a complete response (CR), partial response (PR) or stable disease (SD)] at the end of the 6 cycles continued receiving GAZYVA monotherapy for 2 years. Patients were stratified according to rituximab-refractory type (refractory to prior rituximab monotherapy versus rituximab in combination with chemotherapy) and the number of prior therapies (≤2 versus >2).

GAZYVA was given by intravenous infusion as a flat dose of 1000 mg on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2-6, and then every 2 months until disease progression for up to 2 years. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (1-6) at 90 mg/m^2/day when given in combination with GAZYVA or 120 mg/m^2/day when given alone.

In Study 2, patients had a median age of 63 years, 88% were Caucasian, and 56% were male. Thirty-four percent had bulky disease (>6 cm), 15% had at least one B-symptom at baseline and 95% had an ECOG performance status of 0-1 at baseline. The median time since initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10). Forty-six percent of patients received 1 prior therapy and 33% of patients received 2 prior therapies. Twenty percent of patients were refractory to prior rituximab monotherapy, 37% of patients were refractory to prior rituximab plus chemotherapy induction treatment, and 41% of patients were refractory to rituximab maintenance treatment received following rituximab plus chemotherapy induction. Seventy-nine percent of patients were refractory to both rituximab and an alkylating agent during any prior regimen (double refractory).

The primary objective of the study was to evaluate progression-free survival as determined by an independent review committee (IRC). Median observation time was 21.1 months. The median PFS in the bendamustine arm was 13.8 months. Median PFS was not reached in the GAZYVA plus bendamustine arm (PFS HR = 0.48, 95% CI: 0.34-0.68; stratified log-rank test p-value < 0.0001). The investigator assessed PFS result was consistent with the IRC-assessed PFS. The median investigator-assessed PFS in the bendamustine arm was 13.7 months and the median in the GAZYVA containing arm was 29.2 months (PFS HR = 0.48, 95% CI: 0.35-0.67; stratified log-rank test p-value < 0.0001). Efficacy results are summarized in Table 9. Kaplan-Meier curves for PFS are shown in Figure 3.

An analysis conducted with 24.1 months of median observation time revealed that the median overall survival was not yet reached in either arm. Kaplan-Meier curves for OS are shown in Figure 4.

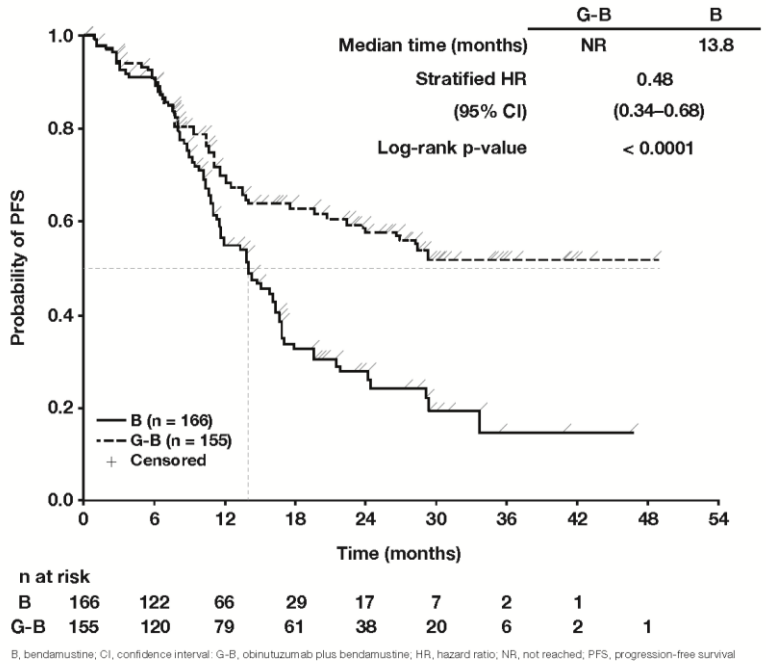
Table 9 Efficacy Results from Study 2[a, b]

Endpoint	Study 2	
	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 155	**Bendamustine n = 166**
Median Progression-Free Survival	NR	13.8 months (HR = 0.48 [0.34; 0.68], p-value < 0.0001 stratified log-rank test)
Best Overall Response[c]	78.7%	74.7%
Complete Response	15.5%	18.7%
Partial Response	63.2%	56.0%
Median duration of DOR (months)	NR	11.6 months

[a]Based on FL population.
[b]As defined by independent review.
[c]Best response of CR/PR within 12 months of study start.

Figure 3

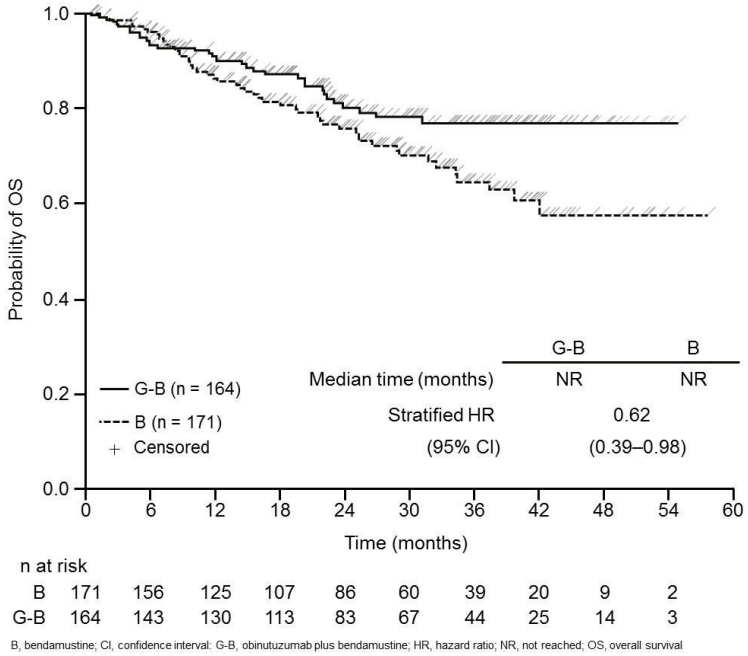
Kaplan-Meier Curve of Progression Free Survival in Patients with FL



B, bendamustine; CI, confidence interval; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NR, not reached; PFS, progression-free survival

Figure 4

Kaplan-Meier Curve of Overall Survival in Patients with FL



B, bendamustine; CI, confidence interval; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NR, not reached; OS, overall survival

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

GAZYVA 1000 mg/40 mL (25 mg/mL) single-dose vials containing preservative-free solution (NDC 50242-070-01) are stable at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. Protect GAZYVA vials from light. DO NOT FREEZE. DO NOT SHAKE.

For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C (36°F to 46°F) followed by 48 hours (including infusion time) at room temperature (≤ 30°C/86°F). GAZYVA does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2 to 8°C. No incompatibilities between GAZYVA and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of GAZYVA with 0.9% sodium chloride.

17 PATIENT COUNSELING INFORMATION

Advise patients to seek immediate medical attention for any of the following:

- Signs and symptoms of infusion reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, breathing problems, or chest pain *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.
- Symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.
- Signs of infections including fever and cough *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.1)]*.
- New or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.2)]*.

Advise patients of the need for:

- Periodic monitoring of blood counts *[see Warnings and Precautions (5.6 and 5.7) and Adverse Reactions (6.1)]*.
- Avoid vaccinations with live viral vaccines *[see Warnings and Precautions (5.8)]*.
- Patients with a history of hepatitis B infection (based on the blood test) should be monitored and sometimes treated for their hepatitis *[see Warnings and Precautions (5.1)]*.

Advise pregnant women of potential fetal B-cell depletion *[see Use in Specific Populations (8.1)]*.

GAZYVA® (obinutuzumab)

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