



Approved: ~90-minute infusion\*

## GAZYVA: for follicular lymphoma that has not responded to or has returned after treatment

\*Initiate from Cycle 2 onwards for eligible FL patients who do not experience a severe or life-threatening IRR during Cycle 1. Cycle 1 should be administered at standard infusion rate.

*GAZYVA is a prescription medicine used with the chemotherapy drug, bendamustine, followed by GAZYVA alone for follicular lymphoma (FL) in adults who did not respond to a rituximab-containing regimen, or whose FL returned after such treatment.*

### WHAT IS THE MOST IMPORTANT SAFETY INFORMATION I SHOULD KNOW ABOUT GAZYVA?

Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that can become serious or life-threatening, including:

- **Hepatitis B Virus (HBV):** Hepatitis B can cause liver failure and death. If you have a history of hepatitis B infection, GAZYVA could cause it to return. You should not receive GAZYVA if you have active hepatitis B liver disease. Your doctor or healthcare team will need to screen you for hepatitis B before, and monitor you during and after, your treatment with GAZYVA. Sometimes this will require treatment for hepatitis B. Symptoms of hepatitis include: worsening of fatigue and yellow discoloration of skin or eyes
- **Progressive Multifocal Leukoencephalopathy (PML):** PML is a rare and serious brain infection caused by a virus. PML can be fatal. Your weakened immune system could put you at risk. Your doctor will watch for symptoms. Symptoms of PML include: confusion, difficulty talking or walking, dizziness or loss of balance, and vision problems

Please see pages 16-22 and accompanying full Prescribing Information for additional Important Safety Information, including **BOXED WARNINGS**.

**GAZYVA**  
obinutuzumab  
injection | 1,000mg/40mL

## *This brochure will provide information about:*

- Follicular lymphoma that has not responded to or has returned after treatment with a regimen containing rituximab
- Treatment with GAZYVA® (obinutuzumab), including how GAZYVA works and what you can expect from treatment

**Please contact your healthcare treatment team with any questions that you may have.**

### **Who should not receive GAZYVA?**

- **Do NOT** receive GAZYVA if you have had an allergic reaction (e.g., anaphylaxis or serum sickness) to GAZYVA. Tell your healthcare provider if you have had an allergic reaction to obinutuzumab or any other ingredients in GAZYVA in the past

The information provided in this brochure is meant for informational purposes only. It is not meant to replace your physician's medical advice.

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**Underlined, bold medical terms used in this guide will be defined in the Glossary.**

## About follicular lymphoma

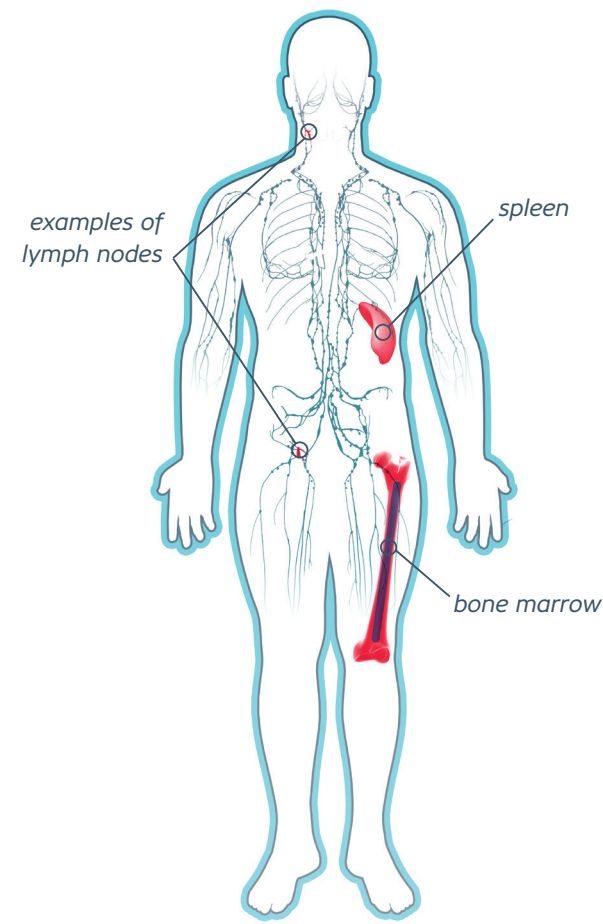
### What is follicular lymphoma?

Non-Hodgkin's lymphoma (NHL) is a blood cancer that involves **lymphocytes**—white blood cells that help fight infections. Abnormal lymphocytes build up in the **lymph nodes**, **bone marrow**, and **spleen**. NHL can be indolent (slow-growing) or aggressive.

**Follicular lymphoma** is the most common type of indolent NHL and can be a chronic disease.

### Understanding relapsed or refractory follicular lymphoma

If your doctor refers to your follicular lymphoma as “**relapsed**,” this might mean it has returned after responding to previous treatment. If your follicular lymphoma has not responded to previous treatment, your doctor may refer to your disease as “**refractory**.”



## What are the symptoms of relapsed or refractory follicular lymphoma?

When a patient's follicular lymphoma has not responded to or has returned after treatment, symptoms can be similar to those symptoms which were present at initial diagnosis and can also vary from patient to patient. It is important to pay attention to how your follicular lymphoma may be affecting you. Tell your doctor if you notice any symptoms or changes in your health.

### Possible symptoms you should watch for include:

- Enlarged lymph nodes
- Easy bruising or bleeding
- Fever, fatigue, and night sweats
- Numbness or tingling in feet and/or hands
- Unexplained weight loss
- Headaches and/or blurry vision
- Severe or frequent infections

Symptoms of follicular lymphoma may be seen in other conditions as well. Only your doctor will be able to tell if your symptoms are related to follicular lymphoma.

While you are being treated and after your treatment concludes, your doctor will continue to monitor your follicular lymphoma.

### Your doctor may be looking for:

- Swelling in your lymph nodes, liver, or spleen
- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells

### Common tests include:

- Routine tests such as physical exam, blood cell counts, and bone marrow biopsy
- **Flow cytometry**—a sample of your cells is examined using a laser beam and a computer to find out the type of cancer and the number of cells involved
- Imaging tests such as **PET-CT** or **CT scans**—these scans produce pictures of the inside of your body that help show where follicular lymphoma is

## What are treatment goals for relapsed or refractory follicular lymphoma?

There is no cure for follicular lymphoma. As a result, the goals of treatment are to relieve symptoms, stop the cancer from getting worse, or achieve **remission**.

**If your follicular lymphoma has not responded to or has returned after your previous treatment, your doctor may decide you need to return to treatment based on factors such as:**

- Your symptoms
- Your results from medical tests

Relapsed or refractory follicular lymphoma can be treated in a number of ways, including **antibody therapy** and/or **chemotherapy**. Often, doctors will combine these two types of treatment. After treatment, patients can go into remission for a period of time. However, the disease often comes back.

## Antibody therapy

Antibody therapy is used to find and destroy specific cells within the body. It can use your body's **immune system** to help fight cancer. It can also harm healthy cells in the body. It is often an important part of follicular lymphoma treatment plans and can be given along with chemotherapy.

### How it works

Antibody therapy targets a protein found on the surface of follicular lymphoma cells and some healthy blood cells. It is thought to use your body's immune system to find and kill lymphoma and healthy cells.

## Chemotherapy

Chemotherapy is a drug treatment that destroys growing cells, including cancer cells. It is also an important part of follicular lymphoma treatment plans. It can be given as a single drug or a combination of drugs including antibody therapy.

### How it works

Chemotherapy attacks growing cancer cells in the body. It also attacks growing healthy cells in the body, such as those for hair and the intestinal lining.

*GAZYVA® (obinutuzumab) is a prescription medicine used with the chemotherapy drug, bendamustine, followed by GAZYVA alone for follicular lymphoma (FL) in adults who did not respond to a rituximab-containing regimen, or whose FL returned after such treatment.*

## What is GAZYVA?

GAZYVA is a type of antibody therapy that targets and attaches to the CD20 proteins found on follicular lymphoma cells as well as some healthy blood cells.

**Once attached to the CD20 protein, GAZYVA is thought to work in different ways, including:**

- By helping your own immune system destroy the cancer cells
- By destroying the cancer cells directly

In addition, GAZYVA can harm healthy cells in your body.

## Starting treatment with GAZYVA



GAZYVA is given as an infusion. This means it goes directly into your vein through a needle in your arm. You'll get your treatment with GAZYVA at a clinic or infusion center.

On the days you receive GAZYVA® (obinutuzumab), you should expect to spend most of the day at the clinic or infusion center.



Your doctor may have you take medications one hour before you begin taking GAZYVA. Your doctor may refer to this kind of medication as premedication.

Common premedications include acetaminophen, antihistamines, and steroid medications. Taking the suggested medication before treatment may reduce the chance of possible side effects during your GAZYVA infusion. Be sure to check with your medical team about the proper premedication you should take before receiving GAZYVA.

About GAZYVA

# How and when am I given GAZYVA?



GAZYVA in combination with bendamustine is given for a total of 6 cycles, or rounds, of treatment. Each cycle will last 28 days. If your disease has not progressed during the initial 6 cycles, your doctor may recommend GAZYVA alone once every 2 months for 2 years. Treatment occurs only on certain days of each cycle, and that is usually followed by several weeks of rest and recovery.

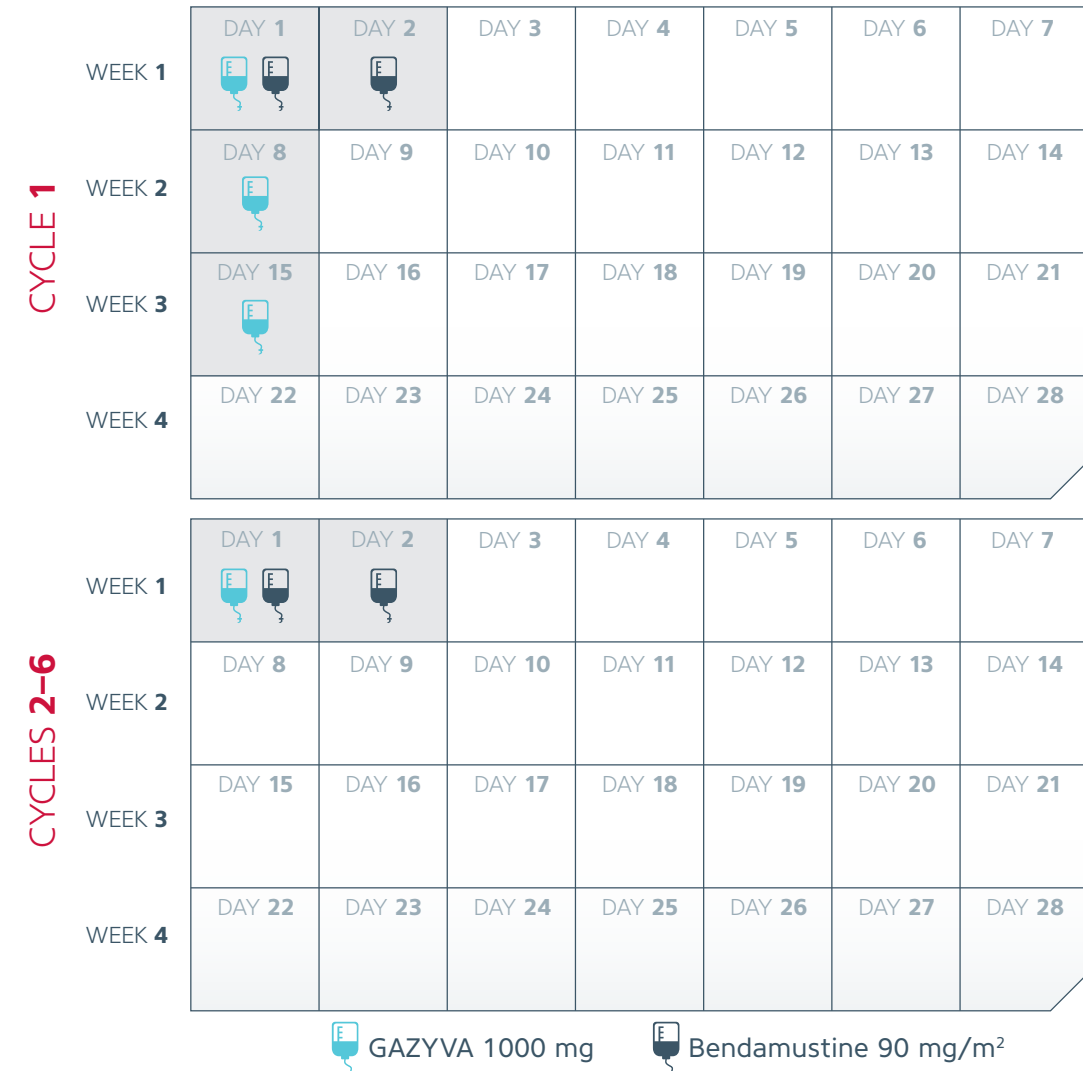
Each dose of GAZYVA is the same. Some patients may have side effects during the infusion process. Please refer to page 15 for more information about these reactions.

**The standard GAZYVA infusion is administered over 3-5 hours. A shorter ~90-minute infusion beginning in Cycle 2 is available if you do not have a severe or life-threatening infusion-related reaction during Cycle 1, given as a standard infusion. Ask your doctor if a shorter-duration infusion may be right for you.**

*Speak with your doctor if you miss a dose of GAZYVA.*

*GAZYVA® (obinutuzumab) is a prescription medicine used with the chemotherapy drug, bendamustine, followed by GAZYVA alone for follicular lymphoma (FL) in adults who did not respond to a rituximab-containing regimen, or whose FL returned after such treatment.*

Below is a chart that shows when you should receive GAZYVA® (obinutuzumab) and bendamustine infusions.



- For Cycle 1, you will receive:
- GAZYVA on Days 1, 8, and 15
  - Bendamustine on Days 1 and 2

- For Cycles 2 through 6, you will receive:
- GAZYVA on the first day of each cycle (once every 28 days)
  - Bendamustine on Days 1 and 2

**If you complete Cycles 1 through 6 and your disease has not progressed, your doctor may recommend GAZYVA alone once every 2 months for 2 years.**

## Preparing for your infusion

### One week before:

- Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements
- **Speak to your doctor if you take medications to control your blood pressure. He/she may ask you to not take them on the day of your GAZYVA® (obinutuzumab) infusion**
- Arrange a ride—after your infusion, you may feel drowsy or dizzy. It is a good idea to have someone else drive you home
- Check with your doctor to see if you will need medication to help reduce side effects from the fast breakdown of cancer cells. You may also need to start drinking extra water a few days before your first infusion

### One day before:

- Remember to follow any changes your doctor made to your regular medication schedule

### The day of your infusion

#### At home:

- Wear or bring loose clothing so you can be comfortable during your infusion
- Pack food and drink—bringing some snacks or a packed meal can help you get through the day
- Bring a book or activities to help pass the time

#### At the clinic or infusion center:

- Take the medications prescribed by your doctor to help reduce the side effects of the infusion process
- Relax during your infusion, but be aware of what is happening to your body. Tell your doctor or nurse right away if you feel any side effects, including the symptoms of an infusion-related reaction

#### Before Cycle 2:

- Cycle 2 may start with an ~90-minute infusion of GAZYVA vs the standard infusion if you do not have a severe or life-threatening infusion-related reaction in Cycle 1. Before starting this cycle, ask your doctor if this treatment option is right for you

### Infusion-Related Reactions (IRRs):

These side effects may occur during or within 24 hours of any GAZYVA® (obinutuzumab) infusion. Some IRRs can be serious, including, but not limited to, severe allergic reactions (anaphylaxis), acute life-threatening breathing problems, or other life-threatening IRRs. If you have a reaction, the infusion is either slowed or stopped until your symptoms are resolved. Most patients are able to complete infusions and receive medication again. However, if the IRR is life-threatening, the infusion of GAZYVA will be permanently stopped. Your healthcare team will take steps to help lessen any side effects you may have to the infusion process. You may be given medicines to take before each GAZYVA treatment.

#### Symptoms of IRRs may include:

- Fast heartbeat
- Tiredness
- Dizziness
- Headache
- Redness of the face
- Nausea
- Chills
- Fever
- Vomiting
- Diarrhea
- Rash
- High blood pressure
- Low blood pressure
- Difficulty breathing
- Chest discomfort



## Important safety information about GAZYVA



### What is the most important safety information I should know about GAZYVA® (obinutuzumab)?

Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that can become serious or life threatening, including:

#### Hepatitis B Virus (HBV)

Hepatitis B can cause liver failure and death. If you have a history of hepatitis B infection, GAZYVA could cause it to return. You should not receive GAZYVA if you have active hepatitis B liver disease. Your doctor or healthcare team will need to screen you for hepatitis B before, and monitor you during and after, your treatment with GAZYVA. Sometimes this will require treatment for hepatitis B. Symptoms of hepatitis include: worsening of fatigue and yellow discoloration of skin or eyes

#### Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare and serious brain infection caused by a virus. PML can be fatal. Your weakened immune system could put you at risk. Your doctor will watch for symptoms. Symptoms of PML include: confusion, difficulty talking or walking, dizziness or loss of balance, and vision problems

#### Who should not receive GAZYVA?

**Do NOT** receive GAZYVA if you have had an allergic reaction (e.g., anaphylaxis or serum sickness) to GAZYVA. Tell your healthcare provider if you have had an allergic reaction to obinutuzumab or any other ingredients in GAZYVA in the past

### What are the additional possible serious side effects of GAZYVA® (obinutuzumab)?

Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that may become severe or life-threatening, including:

#### Infusion-Related Reactions (IRRs)

These side effects may occur during or within 24 hours of any GAZYVA infusion. Some IRRs can be serious, including, but not limited to, severe allergic reactions (anaphylaxis), acute life-threatening breathing problems, or other life-threatening IRRs. If you have a reaction, the infusion is either slowed or stopped until your symptoms are resolved. Most patients are able to complete infusions and receive medication again. However, if the IRR is life-threatening, the infusion of GAZYVA will be permanently stopped. Your healthcare team will take steps to help lessen any side effects you may have to the infusion process. You may be given medicines to take before each GAZYVA treatment. Symptoms of IRRs may include: fast heartbeat, tiredness, dizziness, headache, redness of the face, nausea, chills, fever, vomiting, diarrhea, rash, high blood pressure, low blood pressure, difficulty breathing, and chest discomfort

#### Hypersensitivity Reactions Including Serum Sickness

Some people receiving GAZYVA may have severe or life-threatening allergic reactions. This reaction may be severe, may happen during or after an infusion, and may affect many areas of the body. If an allergic reaction occurs, your doctor will stop the infusion and permanently discontinue GAZYVA

## *Important safety information about GAZYVA (cont'd)*

### **Tumor Lysis Syndrome (TLS)**

Tumor lysis syndrome, including fatal cases, has been reported in patients receiving GAZYVA® (obinutuzumab). GAZYVA works to break down cancer cells quickly. As cancer cells break apart, their contents are released into the blood. These contents may cause damage to organs and the heart, and may lead to kidney failure requiring the need for dialysis treatment. Your doctor may prescribe medication to help prevent TLS. Your doctor will also conduct regular blood tests to check for TLS. Symptoms of TLS may include nausea, vomiting, diarrhea, and tiredness

### **Infections**

While you're taking GAZYVA, you may develop infections. Some of these infections may be fatal and severe, so be sure to talk to your doctor if you think you have an infection. Patients administered GAZYVA in combination with chemotherapy, followed by GAZYVA alone are at a high risk of infections during and after treatment. Patients with a history of recurring or chronic infections may be at an increased risk of infection. Patients with an active infection should not be treated with GAZYVA. Patients taking GAZYVA plus bendamustine may be at higher risk for fatal or severe infections compared to patients taking GAZYVA plus CHOP or CVP

### **Low White Blood Cell Count**

When you have an abnormally low count of infection-fighting white blood cells, it is called neutropenia. While you are taking GAZYVA® (obinutuzumab), your doctor will do blood work to check your white blood cell count. Severe and life-threatening neutropenia can develop during or after treatment with GAZYVA. Some cases of neutropenia can last for more than one month. If your white blood cell count is low, your doctor may prescribe medication to help prevent infections

### **Low Platelet Count**

Platelets help stop bleeding or blood loss. GAZYVA may reduce the number of platelets you have in your blood; having low platelet count is called thrombocytopenia. This may affect the clotting process. While you are taking GAZYVA, your doctor will do blood work to check your platelet count. Severe and life-threatening thrombocytopenia can develop during treatment with GAZYVA. Fatal bleeding events have occurred in patients treated with GAZYVA. If your platelet count gets too low, your treatment may be delayed or reduced

### **Disseminated Intravascular Coagulation (DIC)**

Fatal and severe DIC has been reported in people receiving GAZYVA. DIC is a rare and serious abnormal blood clotting condition that should be monitored and managed by your doctor as it can lead to uncontrollable bleeding.

The most common side effects seen with GAZYVA in a study that included relapsed or refractory FL patients were infusion-related reactions, fatigue, low white blood cell counts, cough, upper respiratory tract infection, and joint or muscle pain.

## Important safety information about GAZYVA (cont'd)

### What other information should I tell my doctor before receiving GAZYVA?

You should talk to your doctor about:

#### Immunizations

Before receiving GAZYVA® (obinutuzumab) therapy, tell your healthcare provider if you have recently received or are scheduled to receive a vaccine. People who are treated with GAZYVA should not receive live vaccines

#### Pregnancy

Tell your doctor if you are pregnant, think you may be pregnant, or plan to become pregnant. GAZYVA may harm your unborn baby. Speak to your doctor about using GAZYVA while you are pregnant. Talk to your doctor or your child's doctor about the safety and timing of live virus vaccinations to your infant if you received GAZYVA during pregnancy. Women of childbearing potential should use effective contraception while taking GAZYVA and for 6 months after your GAZYVA treatment

#### Breastfeeding

Because of the potential risk of serious side reactions in breastfed children, women should not breastfeed while taking GAZYVA and for 6 months after your last dose

### Most common side effects

## Side effects in a clinical trial

The safety of GAZYVA® (obinutuzumab) was evaluated based on 392 patients with relapsed or refractory NHL, of whom 81% had follicular lymphoma. The following side effects have occurred with GAZYVA infusions:

- Infusion-related reactions – 69%
- Low counts of certain cells within the blood
  - White blood cells – 35%
  - Platelets – 15%
  - Red blood cells – 12%
- Nausea – 54%
- Fatigue – 39%
- Cough – 26%
- Diarrhea – 27%
- Constipation – 19%
- Fever – 18%
- Vomiting – 22%
- Upper respiratory tract infection – 13%
- Decreased appetite – 18%
- Joint or muscle pain – 12%
- Sinusitis – 12%
- General weakness – 11%
- Urinary tract infection – 10%

## Important safety information about GAZYVA (cont'd)

Tell your doctor about any side effects.

These are not all of the possible side effects of GAZYVA® (obinutuzumab). For more information, ask your doctor or pharmacist.

GAZYVA is available by prescription only.

**You may report side effects to the FDA at (800) FDA-1088, or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**You may also report side effects to Genentech at (888) 835-2555.**

**Please see the accompanying full Prescribing Information, including BOXED WARNINGS, for additional Important Safety Information.**

*Remember to tell your healthcare team exactly how you feel. This will allow them to take the proper actions to help you.*

### Glossary

**Antibody therapy:** A type of therapy used to find and destroy specific cells within the body (for example, the cells where follicular lymphoma starts). Antibody therapy can also harm healthy cells in the body. This is a type of immunotherapy.

**Bone marrow:** The soft spongy material that fills the inside of bones. Bone marrow is the source of new blood cells, and platelets are made in the bone marrow.

**Chemotherapy:** A drug treatment that destroys growing cells, including cancer cells.

**CT (computed tomography) scan:** A medical test that uses a computer linked to an x-ray machine to take pictures of the inside of the body.

**Flow cytometry:** This test identifies the type of blood cancer and number of cells involved.

**Follicular lymphoma:** The most common type of indolent non-Hodgkin's lymphoma (NHL). With NHL, abnormal lymphocytes build up in the lymph nodes, bone marrow, and spleen. Follicular lymphoma can be a chronic disease.

**Immune system:** The group of organs and cells that defends the body from infections.

**Immunotherapy:** A treatment (such as antibodies) that uses your body's immune system to help fight cancer. Immunotherapy can also harm healthy cells in the body.

**Lymph node:** A small bean-shaped organ that stores white blood cells.

**Lymphocytes:** A type of white blood cell that has an important role in fighting infection.

**PET (Positron emission tomography) scan:** A medical test that uses a form of radioactive sugar that can be traced by a special camera. This can help tell if an area contains lymphoma and if that lymphoma is responding to treatment.

**PET-CT (Positron emission tomography-computed tomography) scan:** A medical test that combines the PET scan with a CT scan. This lets the doctor compare areas with lymphoma on the PET scan with the more detailed appearance of that area on the CT scan.

**Refractory:** A term used to describe disease that has not responded to previous treatment.

**Relapsed:** A term used to describe disease that has returned after responding to previous treatment.

**Remission:** A term used to describe a response to treatment. Partial remission means the cancer is significantly improved, but evidence of the cancer remains. Complete remission means all evidence of the cancer is gone for a period of time.

**Spleen:** An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach.

## Support and resources

# Support from Genentech

## The Genentech Oncology Co-pay Assistance Program\*

Genentech Co-pay Programs help people with commercial health insurance. This might be a plan you get through your employer or one you purchased through a Health Insurance Marketplace like HealthCare.gov. To qualify, you must also meet other criteria.

\*This Genentech Co-pay Program is valid ONLY for patients with commercial insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medication. Patients using Medicare, Medicaid, or any other federal or state government program to pay for their medications are not eligible. Under the program, the patient will pay a co-pay. After reaching the maximum program benefit, the patient will be responsible for all out-of-pocket expenses. All participants are responsible for reporting the receipt of all program benefits as required by any insurer or by law. No party may seek reimbursement for all or any part of the benefit received through this program. The program is only valid in the United States and U.S. Territories. This program is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. The patient, guardian, prescriber, hospital and any other person using the program agree not to seek reimbursement for all or any part of the benefit received by the patient through the offer of this program. Genentech reserves the right to rescind, revoke, or amend the Program without notice at any time. Additional terms and conditions apply. See full terms and conditions at [www.copayassistancenow.com](http://www.copayassistancenow.com).

## Independent Co-pay Assistance Foundations†

If you need help with the co-pay for your Genentech medicine, Genentech Access Solutions can refer you to an independent co-pay assistance foundation. Independent co-pay assistance foundations help patients with public or commercial health insurance.

†Independent co-pay assistance foundations have their own rules for eligibility. We cannot guarantee a foundation will help you. We only can refer you to a foundation that supports your disease state. We do not endorse or show financial preference for any particular foundation. The foundations we refer you to are not the only ones that might be able to help you.



## Support from Genentech (cont'd)

### Genentech Patient Foundation\*

The Genentech Patient Foundation gives free Genentech medicine to people who need it.

\*If you have health insurance, you should try to get other types of financial assistance, if available. You also need to meet income requirements. If you do not have insurance, or if your insurance does not cover your Genentech medicine, you must meet different income requirements.

To learn more about how we can help,

**CALL (877) GENENTECH/(877) 436-3683**

VISIT [www.genentech-access.com/GAZYVA/patients](http://www.genentech-access.com/GAZYVA/patients)

## Helpful resources

Many patient support groups offer helpful information about cancer. Some may also help you connect with a local support group. You can share your experiences and learn more about follicular lymphoma. Many people find this helps them stay informed and stay positive.

### Cancer organizations

#### American Cancer Society

1-800-ACS-2345 (1-800-227-2345)

[www.cancer.org](http://www.cancer.org)

#### CancerCare, Inc.

1-800-813-HOPE (1-800-813-4673)

[www.cancercare.org](http://www.cancercare.org)

#### National Cancer Institute

1-800-4-CANCER (1-800-422-6237)

[www.cancer.gov](http://www.cancer.gov)

#### National Comprehensive Cancer Network

[www.nccn.org/patients](http://www.nccn.org/patients)

### Lymphoma organizations

#### Lymphoma Research Foundation

1-800-500-9976

[www.lymphoma.org](http://www.lymphoma.org)

#### The Leukemia & Lymphoma Society

1-800-955-4572

[www.lls.org](http://www.lls.org)

### Support organizations

#### Cancer Support Community

1-888-793-WELL (1-888-793-9355)

[www.cancersupportcommunity.org](http://www.cancersupportcommunity.org)

#### Patient Advocate Foundation

1-800-532-5274

[www.patientadvocate.org](http://www.patientadvocate.org)

Genentech is not affiliated with any of these organizations. The information provided by Genentech or these organizations is meant for informational purposes only. It is not meant to replace your physician's medical advice.

## Questions to ask your doctor

Before returning to treatment, it is important to ask your doctor or nurse any questions you may have. It's a good idea to write down a list of questions before your appointment. Bring a family member or friend to your appointment for support. They can also help you keep track of the answers.

### Here are some questions to consider asking:

- What are my treatment options?
- What will my treatment schedule be?
- Do I need to take medication at home as well?
- What are the possible side effects of treatment?
- Is there more I can do to make the most of my treatment?
- Where can I get more information about relapsed or refractory follicular lymphoma?
- Where can I find information about support to help me pay for my GAZYVA® (obinutuzumab) therapy?
- How will treatment with GAZYVA affect my lifestyle (working, traveling, etc)?
- Am I eligible for the shorter, ~90-minute infusion beginning with Cycle 2?

Use this space to write down additional information or questions.

Notes: \_\_\_\_\_

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**Notes**

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**Contacts**

Use this space to help keep track of important contact information.

Doctor (Name): \_\_\_\_\_



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\_\_\_\_\_

Nurse (Name): \_\_\_\_\_



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Hospital (Name): \_\_\_\_\_



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Pharmacy (Name): \_\_\_\_\_



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\_\_\_\_\_

Emergency (Name): \_\_\_\_\_



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**GAZYVA**<sup>®</sup>  
obinutuzumab  
injection | 1,000mg/40mL

***For more information, visit [GAZYVA.com](https://www.gazyva.com).***

Images in this brochure do not depict actual patients.

*Please see pages 16-22 and accompanying full Prescribing Information for Important Safety Information, including BOXED WARNINGS.*

**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 use  
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**-----  
Dosage and Administration, Recommended Dosage for Follicular Lymphoma (2.3) 2/2022  
Dosage Modifications for Adverse Reactions (2.5) 2/2022  
Dosage and Administration, Preparation and Administration (2.6) 2/2022  
Warnings and Precautions, Thrombocytopenia (5.8) and Disseminated Intravascular Coagulation (5.9) 7/2022

-----**INDICATIONS AND USAGE**-----  
GAZYVA is a CD20-directed cytolytic antibody 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 who relapsed after, or are refractory to, a rituximab-containing regimen. (1, 14)
- in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma. (1, 14)

-----**DOSAGE AND ADMINISTRATION**-----  

- Premedicate for infusion-related reactions and tumor lysis syndrome. (2.1, 5.3, 5.4)
- Administer only as intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
- The recommended dosage for chronic lymphocytic leukemia is 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1,000 mg on day 8 and 15 of Cycle 1, and 1,000 mg on day 1 of Cycles 2–6. (2.2)
- The recommended dosage for follicular lymphoma is 1,000 mg on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years. (2.3)

-----**DOSAGE FORMS AND STRENGTHS**-----  
Injection: 1,000 mg/40 mL (25 mg/mL) single-dose vial. (3)

-----**CONTRAINDICATIONS**-----  
GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use. (4)

-----**WARNINGS AND PRECAUTIONS**-----  

- **Infusion-Related Reactions:** Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt, reduce rate, or discontinue for infusion-related reactions based on severity. (2.1, 5.3)
- **Hypersensitivity Reactions Including Serum Sickness:** Discontinue GAZYVA permanently. (5.4)
- **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. (5.5)
- **Infections:** 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:** In patients with Grade 3 to 4 neutropenia, monitor laboratory tests until resolution and for infection. Consider dose delays and infection prophylaxis, as appropriate. (5.7)
- **Thrombocytopenia:** Monitor for decreased platelet counts and bleeding. Transfusion may be necessary. (5.8)
- **Disseminated Intravascular Coagulation:** Evaluate cause and monitor for bleeding, thrombosis, and need for supportive care. (5.9)
- **Immunization:** Avoid administration of live virus vaccines during GAZYVA treatment and until B-cell recovery. (5.10)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception. (5.11)

-----**ADVERSE REACTIONS**-----  
The most common adverse reactions (incidence ≥ 20% and ≥ 2% greater in the GAZYVA treated arm) were:  

- **Previously untreated CLL:** infusion-related reactions and neutropenia. (6)
- **Relapsed or refractory NHL:** infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain. (6)
- **Previously untreated NHL:** infusion-related reactions, neutropenia, upper respiratory tract infections, cough, constipation, and diarrhea. (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](http://www.fda.gov/medwatch).**

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

- **Lactation:** Advise not to breastfeed. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

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## 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 (CLL)**

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia.

### **1.2 Follicular Lymphoma (FL)**

GAZYVA, in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosing Information**

- Premedicate before each infusion [see *Dosage and Administration* (2.4)].
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk of tumor lysis syndrome [see *Dosage and Administration* (2.4) and *Warnings and Precautions* (5.4)].
- Administer only as an intravenous infusion through a dedicated line [see *Dosage and Administration* (2.6)].
- 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-related reactions that can be fatal if they occur [see *Warnings and Precautions* (5.3)].

### **2.2 Recommended Dosage for Chronic Lymphocytic Leukemia**

Each dose of GAZYVA is 1,000 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) according to Table 1.

**Table 1 Dose of GAZYVA to be Administered During Six 28-Day Treatment Cycles for Patients with CLL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
<b>Cycle 1 (loading doses)</b>	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	If no infusion-related reaction (IRR) occurred during the previous infusion, 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. If an IRR occurred during the previous infusion, administer at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1,000 mg	If no IRR 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	1,000 mg	
<b>Cycles 2–6</b>	Day 1	1,000 mg	If an infusion-related reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

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

### 2.3 Recommended Dosage for Follicular Lymphoma

Each dose of GAZYVA is 1,000 mg administered intravenously according to Table 2.

For patients with relapsed or refractory FL, administer GAZYVA in combination with bendamustine in six 28-day cycles. Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles should continue on GAZYVA 1,000 mg as monotherapy for up to two years.

For patients with previously untreated FL, administer GAZYVA with one of the following chemotherapy regimens:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by 2 additional 21-day cycles of GAZYVA alone
- Eight 21-day cycles in combination with CVP

Patients with previously untreated FL who achieve a complete response or partial response to the initial 6 or 8 cycles should continue on GAZYVA 1,000 mg as monotherapy for up to two years.

GAZYVA should be administered at the standard infusion rate in Cycle 1 (see Table 2). In patients with FL who do not experience a Grade 3 or higher IRR during Cycle 1, GAZYVA may be administered as a shorter, approximately 90-minute infusion from Cycle 2 onwards (see Table 3) with continued premedication.

**Table 2 Dose and Standard Infusion Rate of GAZYVA to be Administered During 6–8 Treatment Cycles, Followed by GAZYVA Monotherapy for Patients with FL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
Cycle 1 (loading doses)	Day 1	1,000 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	1,000 mg	If no infusion-related reaction or an infusion-related reaction of Grade 1 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	1,000 mg	
Cycles 2–6 or 2–8	Day 1	1,000 mg	If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
Monotherapy	Every two months for up to two years	1,000 mg	

**Table 3 Dose and Infusion Rate of a GAZYVA 90-Minute Infusion for Patients with FL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
Cycle 1	Days 1, 8, 15	1,000 mg	See Table 2
Cycles 2–6* or 2-8*	Day 1	1,000 mg	If no Grade 3 or higher IRR occurred during Cycle 1: 100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes.
Monotherapy*	Every two months for up to two years	1,000 mg	If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 or higher IRR occurred during the previous approximately 90-minute infusion, administer all subsequent GAZYVA infusions at the standard infusion rate (see Table 2).

\* Consider an approximately 90-minute infusion in patients with FL who do not experience a Grade 3 or higher infusion-related reaction to GAZYVA in Cycle 1 and subsequent cycles.

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible. During GAZYVA and chemotherapy treatment, adjust the dosing schedule accordingly to maintain the time interval between chemotherapy cycles. During monotherapy, maintain the original dosing schedule for subsequent doses. Initiate monotherapy approximately two months after the last dose of GAZYVA administered during the induction phase.

## 2.4 Recommended Premedication and Prophylactic Medications

### Infusion-Related Reactions

Premedication to reduce the risk of IRRs is outlined in Table 4 [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)*].

**Table 4 Premedication for GAZYVA Infusion to Reduce Infusion-Related Reactions**

Day of Treatment Cycle	Patients requiring premedication	Premedication	Administration
<b>Cycle 1:</b>  <b>CLL</b> <b>Day 1,</b> <b>Day 2</b>  <b>FL</b> <b>Day 1</b>	All patients	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone <sup>1,2</sup>	Completed at least 1 hour prior to GAZYVA infusion.
		650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	
<b>All subsequent infusions, CLL or FL</b>	All patients	650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
	Patients with an IRR (Grade 1-2) with the previous infusion	650–1,000 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 x 10 <sup>9</sup> /L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone <sup>1</sup>	Completed at least 1 hour prior to GAZYVA infusion.
		650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	

Premedication applies to both standard and approximately 90-minute infusions.

<sup>1</sup> Hydrocortisone is not recommended as it has not been effective in reducing the rate of IRRs.

<sup>2</sup> If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

### Tumor Lysis Syndrome Prophylaxis

Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10<sup>9</sup>/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)*].

### 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. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (> 1 week) neutropenia.

## **2.5 Dosage Modifications for Adverse Reactions**

### Infusion-Related Reactions

If a patient experiences an IRR, adjust the infusion as follows [see *Warnings and Precautions (5.3)*]:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue GAZYVA.
- Grade 3 (severe): Interrupt infusion and manage symptoms.
  - For patients who experience Grade 3 IRRs during standard infusion, 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 IRR reaction occurred), and if patient does not experience any further IRR 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 or higher IRR at rechallenge.
  - For patients with FL who experience Grade 3 IRRs during the approximately 90-minute infusion, upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than 400 mg/hr. Administer subsequent infusions at the standard rate. Permanently discontinue treatment if patients experience a Grade 3 or higher IRR 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 manage symptoms. Upon resolution of symptoms, continue or resume GAZYVA infusion, and if patient does not experience any further IRR 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.

### Other Adverse Reactions

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

## **2.6 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.
- Use a sterile needle and syringe to prepare GAZYVA.
- Dilute into a 0.9% Sodium Chloride Injection, USP PVC or non-PVC polyolefin infusion bag.

*Chronic Lymphocytic Leukemia*



- Preparation of solution for infusion on day 1 (100 mg) and day 2 (900 mg) of Cycle 1:
  - Prepare day 1 (100 mg) and day 2 (900 mg) infusion bags at the same time using one vial (1,000 mg/40 mL) on day 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 Injection, USP infusion bag for immediate administration.
  - Dilute the remaining 36 mL (900 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP 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 of Cycles 2–6:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag.

#### *Follicular Lymphoma*

- Preparation of solution for infusion:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag.
- Mix diluted solution by gentle inversion. Do not shake or freeze.
- For microbiological stability, immediately use diluted GAZYVA infusion solution. If not used immediately, store 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.

#### Storage

Use the diluted solution immediately. If not used immediately, store for up to 24 hours at 2°C to 8°C. Discard after 24 hours.

#### Administration

- 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.

### **3 DOSAGE FORMS AND STRENGTHS**

Injection: 1,000 mg/40 mL (25 mg/mL) clear, colorless to slightly brown solution in single-dose vial.

## 4 CONTRAINDICATIONS

GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use [*see Warnings and Precautions (5.4)*].

## 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 healthcare providers 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 healthcare providers 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

John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, occurred 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-Related Reactions

GAZYVA can cause severe and life-threatening infusion-related reactions (IRRs). Sixty-five percent of patients with CLL experienced a reaction to the first 1,000 mg of GAZYVA infused. Thirty-seven percent of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of GAZYVA infusion. IRRs have occurred within 24 hours of receiving GAZYVA. IRRs 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). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills [*see Adverse Reactions (6.1)*].

Premedicate patients with acetaminophen, anti-histamine, and a glucocorticoid [see *Dosage and Administration* (2.4)]. Closely monitor patients during the entire infusion. Reduce infusion rate, interrupt infusion or permanently discontinue GAZYVA for IRRs based on severity [see *Dosage and Administration* (2.5)]. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed.

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 IRR to GAZYVA. 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 Hypersensitivity Reactions Including Serum Sickness**

Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from IRRs. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure.

If a hypersensitivity reaction is suspected during or after an infusion, stop the infusion and permanently discontinue treatment. GAZYVA is contraindicated in patients with known hypersensitivity reactions to GAZYVA, including serum sickness with prior GAZYVA use [see *Contraindications* (4)].

#### **5.5 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.

Administer appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA for patients at risk for TLS [see *Dosage and Administration* (2.4)]. 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.

#### **5.6 Infections**

Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by GAZYVA monotherapy as in the GALLIUM study, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment [see *Adverse Reactions* (6.1)].

In GALLIUM, more Grade 3 to 5 infections were reported in the recipients of GAZYVA and bendamustine (117/410 patients, 29%) as compared to GAZYVA plus CHOP or CVP (43/281 patients, 15%). More fatal infections were reported in patients treated with GAZYVA and bendamustine (3%), as compared to GAZYVA plus CHOP or CVP ( $< 1\%$ ), including during the monotherapy phase and after completion of treatment.

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.

## 5.7 Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider dose delays for Grade 3 or 4 neutropenia. Consider administration of granulocyte colony-stimulating factors (GCSF) 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). 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. Consider antiviral and antifungal prophylaxis.

## 5.8 Thrombocytopenia

Severe and life-threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL and CLL treated with GAZYVA in combination with chemotherapy, including during Cycle 1.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle and if clinically indicated, evaluate laboratory coagulation parameters [*see Warnings and Precautions (5.9)*]. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider 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 that may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

## 5.9 Disseminated Intravascular Coagulation (DIC)

Fatal and severe DIC has been reported in patients receiving GAZYVA for treatment of follicular lymphoma and chronic lymphocytic leukemia. The majority of DIC cases have involved changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, DIC was associated with IRRs, TLS, or both [*see Adverse Reactions (6.1)*]. In patients with suspected DIC, evaluate potential causes, and monitor coagulation parameters, platelet counts, and for signs and symptoms of bleeding or thrombosis. Manage according to standard guidelines for DIC. Supportive care, including transfusion of blood products and other medical management, may be necessary.

## 5.10 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.

## 5.11 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, GAZYVA can cause B-cell depletion in infants exposed to obinutuzumab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving GAZYVA and for 6 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:

- Hepatitis B virus reactivation [*see Warnings and Precautions (5.1)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.2)*]
- Infusion-related reactions [*see Warnings and Precautions (5.3)*]

- Hypersensitivity reactions including serum sickness [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Neutropenia [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
- Disseminated intravascular coagulation [see Warnings and Precautions (5.9)]

## 6.1 Clinical Trials Experience

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

### Chronic Lymphocytic Leukemia

The data below are based on a safety population of 773 previously untreated patients with CLL in the CLL11 study. Patients were treated with chlorambucil alone, GAZYVA in combination with chlorambucil, or rituximab product 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 product 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 GAZYVA treated patients. The incidence of Grade 3 to 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 GAZYVA with similar incidences of Grade 3 to 4 abnormalities between the two arms.

Patients received three 1,000 mg doses of GAZYVA on the first cycle and a single dose of 1,000 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 (2.2)]. In total, 81% of patients received all 6 cycles (of 28 days each) of GAZYVA-based therapy.

Adverse reactions in  $\geq 10\%$  of patients in the GAZYVA containing arm were infusion-related reactions, neutropenia, thrombocytopenia, and diarrhea. The most common Grade 3 to 4 adverse reactions (incidence  $\geq 10\%$ ) in the GAZYVA containing arm were neutropenia, infusion-related reactions, and thrombocytopenia.

**Table 5 Adverse Reactions (Incidence  $\geq 5\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with CLL (Stage 2)**

Body System Adverse Reactions	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion-Related Reaction	66	20	38	4
<b>Blood and Lymphatic System Disorders<sup>a</sup></b>				
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
<b>Gastrointestinal Disorders</b>				
Diarrhea	10	2	8	< 1

Body System Adverse Reactions	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Constipation	8	0	5	0
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	9	< 1	7	< 1
<b>Infections and Infestations</b>				
Nasopharyngitis	6	< 1	3	0
Urinary Tract Infection	5	1	2	< 1

<sup>a</sup> Adverse reactions reported under "Blood and lymphatic system disorders" reflect those reported by investigator as clinically significant.

**Table 6 Post-Baseline Laboratory Abnormalities (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with CLL (Stage 2)**

Laboratory Abnormalities	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Leukopenia	84	35	62	16
Lymphopenia	80	39	50	16
Neutropenia	76	46	69	41
Thrombocytopenia	48	13	40	8
Anemia	39	10	37	10
<b>Chemistry</b>				
Hypocalcemia	37	3	32	< 1
ALT increased	28	2	21	1
AST increased	27	2	21	< 1
Hyponatremia	26	7	18	2
Hypoalbuminemia	23	< 1	16	< 1
Hypokalemia	14	1	10	< 1

## Non-Hodgkin Lymphoma

### *GADOLIN*

The GADOLIN study evaluated safety in 407 patients with relapsed or refractory NHL, including FL (81%), small lymphocytic lymphoma and marginal zone lymphoma (a disease for which GAZYVA is not indicated), who did not respond to or progressed within 6 months of treatment with rituximab product or a rituximab product-containing regimen. In the population of patients with FL, the profile of adverse reactions was consistent with the overall NHL population. Patients received either GAZYVA in combination with bendamustine (204 patients), followed by GAZYVA monotherapy in patients that had not progressed, or bendamustine alone (203 patients).

Patients randomized to the GAZYVA + bendamustine arm received three weekly 1,000 mg doses of GAZYVA in the first cycle and a single dose of 1,000 mg once every 28 days for 5 additional cycles, in combination with bendamustine 90 mg/m<sup>2</sup> intravenously on Days 1 and 2 in all 6 cycles. Patients who did not progress on the combination received a single 1,000 mg dose of GAZYVA monotherapy every two months until progression or for a maximum of two years. The control arm received bendamustine 120 mg/m<sup>2</sup> on Days 1 and 2 of each cycle for 6 cycles, with a cycle length of 28 days. In the GAZYVA arm, 78% of patients received 6 cycles of bendamustine and 82% received their full 6 cycles of GAZYVA; 72 (46%) of the 158 patients who began GAZYVA monotherapy received all planned doses. In the control arm, 72% of patients received 6 cycles of bendamustine.

Serious adverse reactions occurred in 45% of the GAZYVA arm and 37% of the bendamustine-only arm. Fatal adverse reactions within 90 days of treatment occurred in 3.4% and 2.5%, respectively. During treatment and follow-up combined, fatal adverse reactions occurred in 10% of GAZYVA

recipients and in 7.4% of recipients of bendamustine alone, with infection and second primary malignancies being the leading causes.

Dose modification due to adverse reactions occurred in 50% of the GAZYVA arm and 42% of the control arm, and discontinuation of any study drug due to adverse reactions occurred in 20% and 17%, respectively.

Table 7 presents selected adverse reactions in GADOLIN. The most common adverse reactions (incidence  $\geq 20\%$ ) in GAZYVA recipients included infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain.

**Table 7 Adverse Reactions (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Relapsed or Refractory NHL (GADOLIN)**

Body System Adverse Reactions <sup>a, b</sup>	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 204		Bendamustine n = 203	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
<b>Procedural Complications</b>				
Infusion-Related Reaction <sup>c</sup>	67	11	63	5
<b>General Disorders</b>				
Fatigue	40	3	36	3
Pyrexia	19	1	15	1
<b>Blood and Lymphatic System Disorders</b>				
Neutropenia	37	35 <sup>d</sup>	29	27
<b>Infections and Infestations</b>				
Upper Respiratory Tract Infection	36	3	23	1
Respiratory Tract Infection, Unspecified	14	1	8	0
Urinary Tract Infection	13	3	7	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	31	<1	21	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal Pain	28	1	20	0
Arthralgia	12	<1	5	0
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	17	<1	14	<1
Pruritus	11	0	6	0

<sup>a</sup> Includes adverse reactions reported throughout study treatment and follow-up.

<sup>b</sup> Includes grouped terms.

<sup>c</sup> Except where noted, individual events that meet the definition of “infusion-related reaction” are excluded from Table 7 above, as they are included in the grouped term “Infusion-Related Reaction”.

<sup>d</sup> Includes 1 fatal event.

**Infusion-related reactions** are defined as any related adverse reaction that occurred during or within 24 hours of infusion.

**Fatigue** includes fatigue, lethargy, asthenia.

**Pyrexia** includes pyrexia, hyperthermia, body temperature increased.

**Cough** includes cough, productive cough, upper-airway cough syndrome.

**Neutropenia** includes neutropenia, agranulocytosis, granulocytopenia, neutrophil count decreased.

**Upper respiratory tract infection** includes upper respiratory tract congestion, upper respiratory tract inflammation, upper respiratory fungal infection, rhinovirus infection, and all terms containing: upper respiratory tract infection, laryngitis, nasopharyngitis, pharyngitis, rhinitis, tonsillitis, and sinusitis with the exception of sinobronchitis.

**Respiratory tract infection unspecified** includes respiratory tract infection, respiratory tract infection viral, influenza, influenza-like illness, sinobronchitis, respiratory syncytial virus infection.

**Urinary tract infection** includes all terms containing: urinary tract infection, cystitis, pyelonephritis.

**Musculoskeletal pain** includes non-cardiac chest pain, bone pain, spinal pain, myalgia, back pain, neck pain, musculoskeletal discomfort, pain in extremity, and all terms containing “musculoskeletal pain”.

**Rash** includes drug eruption, skin reaction, all terms containing “rash”, urticaria, and selected terms containing “dermatitis”.

**Pruritus** includes pruritus, pruritus generalized.

Other clinically relevant adverse reactions (incidence < 10% and ≥ 2% greater in the GAZYVA arm) included:

- *Blood and lymphatic system disorders:* febrile neutropenia (6%)
- *Infection:* sepsis (7%)

During GAZYVA monotherapy (158 patients), adverse reactions in ≥ 10% of patients included upper and lower respiratory tract infections, cough, neutropenia, musculoskeletal pain, fatigue, diarrhea, rash, and urinary tract infection.

Table 8 presents selected new or worsening laboratory abnormalities in the GADOLIN trial.

**Table 8 New or Worsening Laboratory Abnormalities (Incidence ≥ 10% and ≥ 2% Greater in the GAZYVA Arm<sup>a</sup>) in Patients with Relapsed or Refractory NHL (GADOLIN)**

Laboratory Abnormalities	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 204		Bendamustine n = 203	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Lymphopenia	97	92	96	84
Leukopenia	84	47	87	34
Neutropenia	76	53	75	42
<b>Chemistry</b>				
Hypophosphatemia	41	8	38	7
Hypocalcemia	39	3	24	1
ALT/SGPT increased	36	2	31	3
Alkaline phosphatase increased	27	0	23	0
Hyperbilirubinemia	21	2	17	2
Hyperkalemia	20	3	18	0

<sup>a</sup> Two percent difference in either any-grade or Grade 3 to 4 laboratory abnormalities.

In the GAZYVA monotherapy phase, new or worsening grade 3 or 4 abnormalities included neutropenia in 25% of patients (Grade 4, 10%) and lymphopenia in 23% (Grade 4, 5%).

### GALLIUM

A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%). Patients received chemotherapy (bendamustine, CHOP, or CVP) combined with either GAZYVA (691 patients) or rituximab product (694 patients), followed in responding patients by GAZYVA or rituximab product monotherapy every two months until disease progression or for a maximum of two years. The study excluded patients having an absolute neutrophil count (ANC) < 1500 / μL, platelets < 75,000 / μL, CLcr < 40 mL/min and, unless attributable to lymphoma, hepatic transaminases > 2.5 x upper limit of normal.

The median age was 60 (range: 23-88), 47% were male, 82% were white, and 97% had an ECOG performance status of 0 or 1. The chemotherapy was bendamustine in 59%, CHOP in 31% and CVP in 10% of patients. Following combination therapy, 624 patients (90%) in the GAZYVA arm and 612 patients (88%) in the rituximab product arm received monotherapy.

Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab product arm, most often from infections in the GAZYVA arm. During treatment and follow-up combined, fatal adverse reactions were reported in 5% of the GAZYVA arm and 4% of the rituximab product arm, with infections and second malignancies being leading causes. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to < 1% in the rituximab product arm.



During combination therapy, 93% of patients received all treatment cycles in the GAZYVA arm, and 92% received all treatment cycles in the rituximab product arm. Of the responding patients who began monotherapy with GAZYVA or rituximab product, 76% and 73%, respectively, completed the full course. Dose modification due to adverse reactions occurred in 74% of the GAZYVA arm and 63% of the rituximab product arm throughout study treatment, and discontinuation of any study drug due to adverse reactions occurred in 18% and 15%, respectively.

Throughout treatment and follow-up, the most common adverse reactions (incidence  $\geq 20\%$ ) observed at least 2% more in the GAZYVA arm included infusion-related reactions, neutropenia, upper respiratory tract infections, constipation and diarrhea (Table 9). Neutropenia, infusion-related reactions, febrile neutropenia and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence  $\geq 5\%$ ) observed more frequently in the GAZYVA arm.

**Table 9 Adverse Reactions (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)**

Body System Adverse Reactions <sup>a, b</sup>	GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion-Related Reaction <sup>c</sup>	72	12	60	8
<b>Blood and Lymphatic System Disorders</b>				
Neutropenia <sup>d</sup>	53	49	47	41
Thrombocytopenia <sup>d</sup>	14	7	8	3
<b>Infections and Infestations</b>				
Upper Respiratory Tract Infection	50	3	43	1
Herpesvirus Infection	18	3	14	1
Pneumonia	14	7	12	6
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	35	< 1	28	< 1
<b>Gastrointestinal Disorders</b>				
Constipation	32	< 1	29	< 1
Diarrhea	30	3	26	2
<b>Nervous System Disorders</b>				
Headache	18	< 1	15	< 1
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Arthralgia	16	0	14	< 1
<b>Psychiatric Disorders</b>				
Insomnia	15	< 1	12	< 1
<b>Metabolism and Nutrition Disorders</b>				
Decreased Appetite	14	< 1	12	< 1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Pruritus	11	< 1	9	0

<sup>a</sup> Includes adverse reactions reported throughout study treatment and follow-up.

<sup>b</sup> Includes grouped terms.

<sup>c</sup> Except where noted, individual events that meet the definition of “infusion-related reaction” are excluded from Table 9 above, as they are already included in the grouped term “Infusion-Related Reaction”. The most common individual terms within the grouped term “Infusion-Related Reaction” in decreasing order of frequency are nausea, chills, pyrexia and vomiting.

<sup>d</sup> Includes adverse reactions reported as infusion-related reactions.

**Infusion-related reactions** are defined as any related adverse reaction that occurred during or within 24 hours of infusion.

**Neutropenia** includes neutropenia, agranulocytosis, granulocytopenia, and neutrophil count decreased.

**Febrile neutropenia** includes febrile neutropenia, neutropenic infection, neutropenic sepsis, and febrile bone marrow aplasia.

**Thrombocytopenia** includes thrombocytopenia and platelet count decreased.

**Upper respiratory tract infection** includes upper respiratory tract congestion, upper respiratory tract inflammation, upper respiratory tract infection, rhinovirus infection, and all terms containing: laryngitis, nasopharyngitis, pharyngitis, rhinitis, tonsillitis, and sinusitis with the exception of sinobronchitis.

**Herpesvirus infection** includes all terms containing “herpes” or “varicella.”

**Pneumonia** includes all terms containing “pneumonia,” bacterial, pneumonia haemophilus, pneumonia pneumococcal, pneumonia fungal, pneumocystis jirovecii infection, lung infection, and lung infiltration.

**Diarrhea** includes diarrhea, defecation urgency, frequent bowel movement, and all terms containing “gastroenteritis”.

**Headache** includes all terms containing “headache” and migraine.

**Insomnia** includes all terms containing “insomnia” and sleep disorder.

**Pruritus** includes pruritus and pruritus generalized.

During the monotherapy period, the common adverse reactions (incidence  $\geq 10\%$ ) observed at least 2% more with GAZYVA were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%), and herpesvirus infection (13%).

Table 10 summarizes treatment-emergent laboratory abnormalities during treatment and follow-up. The Grade 3 to 4 abnormalities reported at least 2% more in the GAZYVA arm were lymphopenia, leukopenia, neutropenia, thrombocytopenia, and hyperuricemia. Patients in the GAZYVA arm, as compared to the rituximab product arm, had higher incidences of Grade 4 neutropenia (38% vs. 30%, respectively), Grade 4 lymphopenia (33% vs. 22%), and Grade 4 leukopenia (17% vs. 12%).

**Table 10 New or Worsening Laboratory Abnormalities (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)**

Laboratory Abnormalities <sup>a</sup>	GAZYVA+ chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Lymphopenia	97	83	95	67
Leukopenia	92	49	89	39
Neutropenia	84	59	76	50
Thrombocytopenia	68	11	50	4
<b>Chemistry</b>				
ALT increased	50	3	43	2
AST increased	44	1	41	1
Hypophosphatemia	36	5	33	5
Hypoalbuminemia	33	1	25	1
Hypoproteinemia	32	0	30	0
Hypocalcemia	32	1	26	1
Hyperuricemia	28	28	22	22
Hyponatremia	26	4	20	3
Hyperkalemia	23	1	17	1
Hypernatremia	16	< 1	13	0

<sup>a</sup> Includes lab abnormalities, reported throughout treatment and follow-up, that were new or worsening, or worsening from baseline unknown.

In the monotherapy phase, new-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the GAZYVA arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%).

## GAZELLE

GAZELLE (NCT03817853) is a single-arm study designed to characterize the safety of GAZYVA administered as a shortened-duration infusion (approximately 90 minutes) in patients with previously untreated FL. All patients received GAZYVA at the standard infusion rate with premedication during Cycle 1. If no Grade 3 or higher IRR occurred with any infusion during Cycle 1, GAZYVA was administered over approximately 90 minutes in Cycle 2 and subsequent cycles. The primary safety

measure was the proportion of patients who experienced Grade 3 or higher IRRs with the 90-minute infusion at Cycle 2. GAZYVA was administered in combination with CHOP, CVP or bendamustine for 6 to 8 cycles (induction), followed by monotherapy for up to 2 years.

Of the 113 patients treated with GAZYVA, 99 (88%) received the 90-minute infusion starting in Cycle 2. In total, 97% of patients who received GAZYVA at either a standard or shorter infusion duration received premedication in Cycle 2. IRRs were observed in 63% of patients throughout induction (including IRRs observed after standard-duration infusion). In cycle 1, 58% of patients developed IRRs with the standard infusion rate (Grade  $\geq 3$  IRR, 5%). Of the patients who received the 90-minute infusion, 10% had IRRs of any grade in Cycle 2, with 8% and 2% of patients having a Grade 1 IRR or Grade 2 IRR, respectively. Following Cycle 2, one (1%) patient experienced a Grade 3 IRR, which occurred after the 90-minute infusion at Cycle 5.

### Infusion-Related Reactions

#### *Chronic Lymphocytic Leukemia*

The incidence of IRRs in the CLL11 study was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 IRRs was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1,000 mg and < 1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1,000 mg infused.

Of the first 53 patients receiving GAZYVA in CLL11, 47 (89%) experienced an IRR. 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 1,000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and < 3% thereafter [see *Dosage and Administration (2.2)*].

#### *Non-Hodgkin Lymphoma*

Overall, 67% of patients in the GADOLIN study experienced an IRR (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3 to 4 IRRs in GADOLIN was 11%. In Cycle 1, the incidence of IRRs (all grades) was 53% in patients receiving GAZYVA in combination with bendamustine of which 34 (9%) were Grade 3 to 4 in severity. In patients receiving GAZYVA in combination with bendamustine, the incidence of IRRs was highest on Day 1 (37%), and gradually decreased on Days 2, 8 and 15 (23%, 6% and 4%, respectively).

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

During GAZYVA monotherapy in GADOLIN, IRRs (all grades) were observed in 8% of patients. One Grade 3 and no Grade 4 IRRs were reported during GAZYVA monotherapy.

Overall, 2% of patients in GADOLIN experienced an IRR leading to discontinuation of GAZYVA.

In GALLIUM, 72% of patients in the GAZYVA treated arm experienced an IRR (all grades). The incidence of Grade 3 to 4 IRRs for these patients was 12%. In Cycle 1, the incidence of IRRs (all grades) was 62% in the GAZYVA treated arm with Grade 3 to 4 IRRs reported in 10%. The incidence of IRRs (all grades) was highest on Day 1 (60%) and decreased on Days 8 and 15 (9% and 6%, respectively).

During Cycle 2, the incidence of IRRs (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles.

During GAZYVA monotherapy treatment in GALLIUM, IRRs (all grades) were observed in 9% of patients.

Overall, 1% of patients in GALLIUM experienced an IRR leading to discontinuation of GAZYVA.

In GAZELLE, 10% of patients with FL experienced IRRs of any grade at Cycle 2 when GAZYVA was administered over approximately 90 minutes.

## Neutropenia

### *Chronic Lymphocytic Leukemia*

The incidence of neutropenia reported as an adverse reaction in CLL11 was 38% in the GAZYVA treated arm and 32% in the rituximab product treated arm, with the incidence of serious adverse reactions being 1% and < 1%, respectively (Table 5). 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 product treated arm.

### *Non-Hodgkin Lymphoma*

The incidence of neutropenia in GADOLIN was higher in the GAZYVA plus bendamustine arm (37%) compared to the arm treated with bendamustine alone (30%). Cases of prolonged neutropenia (3%) and late onset neutropenia (8%) were also reported in the GAZYVA plus bendamustine arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (30%) compared to the GAZYVA monotherapy treatment phase (13%).

The incidence of neutropenia in GALLIUM was higher in the GAZYVA treated arm (53%) compared to the rituximab product treated arm (47%). Cases of prolonged neutropenia (1%) and late onset neutropenia (4%) were also reported in the GAZYVA treated arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with chemotherapy (45%) compared to the GAZYVA monotherapy treatment phase (20%).

## Infection

### *Chronic Lymphocytic Leukemia*

The incidence of infections was similar between GAZYVA and rituximab product treated arms. Thirty-eight percent of patients in the GAZYVA treated arm and 37% in the rituximab product treated arm experienced an infection, with Grade 3 to 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 in GADOLIN was 68% in the GAZYVA plus bendamustine arm and 59% in the bendamustine arm, with Grade 3 to 4 events reported in 20% and 16%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm.

The incidence of infections in GALLIUM was 82% in the GAZYVA treated arm and 73% in the rituximab product treated arm, with Grade 3 to 4 events reported in 21% and 17%, respectively. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm.

The incidence of Grade 3 to 4 infections in the GAZYVA and rituximab product treated arms was lower in patients receiving GCSF prophylaxis (14%; 16%) compared with patients not receiving GCSF prophylaxis (24%; 18%). The incidence of fatal infections in patients receiving GCSF prophylaxis in the GAZYVA and rituximab product treated arms was 2% and 0%, respectively, and was 2% and < 1% in patients not receiving GCSF prophylaxis.

## 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 product treated arm (7%), with the incidence

of Grade 3 to 4 events being 10% and 3%, respectively (Table 5). 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 was 11% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 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 product 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 in GADOLIN was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (25%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 12% and 11%, respectively. Grade 3 to 4 hemorrhagic events were similar in both treatment arms (4% in the GAZYVA plus bendamustine arm and 2% in the bendamustine arm).

In GALLIUM, thrombocytopenia was reported as an adverse reaction in 14% of the GAZYVA treated arm and 8% of the rituximab product treated arm, with the incidence of Grade 3 to 4 events being 7% and 3%, respectively. 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 was 9% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 5% and 1%, respectively. In GALLIUM, both treatment arms had a 12% overall incidence of hemorrhagic events and a < 1% incidence of fatal hemorrhagic events.

#### Disseminated Intravascular Coagulation

In GALLIUM, DIC was reported as an adverse reaction in 0.3% of the GAZYVA treated patients. All events occurred within 1-2 days after the first infusion.

#### Tumor Lysis Syndrome

The incidence of Grade 3 or 4 tumor lysis syndrome in GAZYVA treated patients was 2% in CLL11, 0.5% in GADOLIN and 0.9% in GALLIUM.

#### Musculoskeletal Disorders

##### *Chronic Lymphocytic Leukemia*

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

##### *Non-Hodgkin Lymphoma*

In GADOLIN, adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (44% vs. 30%).

In GALLIUM, musculoskeletal disorders were reported in 54% of patients in the GAZYVA treated arm and 49% of patients in the rituximab product treated arm.

#### 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 IRRs or tumor lysis syndrome. In the CLL11 study, there was no clinically

meaningful difference in overall hepatotoxicity adverse reactions between all arms (4% of patients in the GAZYVA treated arm). Medications commonly used to prevent IRRs (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.

### Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

### Worsening of Pre-existing Cardiac Conditions

Fatal cardiac events have been reported in patients treated with GAZYVA.

## **6.2 Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Seven percent (18/271) of patients with CLL tested positive for anti-GAZYVA antibodies at one or more time points in CLL11. No patients developed anti-GAZYVA antibodies during or following GAZYVA treatment in GADOLIN, while 1 patient (1/564, 0.2%) developed anti-GAZYVA antibodies in GALLIUM. Neutralizing activity of anti-GAZYVA antibodies has not been assessed.

## **6.3 Postmarketing Experience**

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

- *Immune/Autoimmune Events*: Serum sickness

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on findings from animal studies and its mechanism of action, GAZYVA can cause fetal B-cell depletion [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 1,000 mg monthly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys (*see Data*). Advise pregnant women of the potential risk to the fetus.

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 (5.11) 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 child, 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. Because of the potential of serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose.

## **8.3 Females and Males of Reproductive Potential**

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

### Contraception

#### *Females*

Advise females of reproductive potential to use effective contraception during treatment with GAZYVA and for 6 months after the last dose.

## **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 reactions and 7% experienced adverse reactions leading to death. Of the patients younger than 75, 33% experienced a serious adverse reaction and 2% an

adverse reaction leading to death. No significant differences in efficacy were observed between younger and older patients [see *Clinical Studies (14.1)*].

### Non-Hodgkin Lymphoma

Of 204 patients in GADOLIN with relapsed or refractory NHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 55% of patients experienced serious adverse reactions and 28% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 37% and 14% experienced serious adverse reactions and adverse reactions leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GADOLIN.

Of the 691 patients in GALLIUM treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 and over, while 7% were 75 and over. Of patients 65 and over, 63% experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse reactions and 13% had an adverse reaction leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GALLIUM.

## **10 OVERDOSAGE**

There has been no experience with overdose in human clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of GAZYVA and supportive therapy.

## **11 DESCRIPTION**

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 (obinutuzumab) injection 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 use. GAZYVA is supplied at a concentration of 25 mg/mL in 1,000 mg single-dose 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 patients with CLL, GAZYVA caused CD19 B-cell depletion (defined as CD19 B cell counts  $< 0.07 \times 10^9/L$ ). 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 pharmacokinetic parameters of obinutuzumab after 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1,000 mg on day 8 and 15 of Cycle 1, and 1,000 mg on day 1 of Cycles 2–6 for CLL and after 1,000 mg on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years for NHL are provided in Table 11. The dosing regimen is within the linear pharmacokinetic behavior of obinutuzumab.

**Table 11 Obinutuzumab Measures of Exposure**

PK Measure	CLL <sup>a</sup>	Relapsed or refractory FL <sup>a</sup>	First line FL in combination with chemotherapy	
			GAZYVA + Bendamustine <sup>a</sup>	GAZYVA + CHOP or CVP <sup>b</sup>
C <sub>max</sub> , µg/mL	466.3 (35)	553.5 (32)	513.4 (28)	676.4 (30)
C <sub>trough</sub> , µg/mL	192.5 (78)	295 (56)	255 (46)	395 (44)
AUC, µg/mL*day	8701 (51)	11362 (41)	10088 (35)	10723 (37)

Results are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> Induction Cycle 6 of a 28-day cycle;

<sup>b</sup> Induction Cycle 8 of a 21-day cycle.

### Distribution and Elimination

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. The pharmacokinetic properties of obinutuzumab in patients with CLL and NHL are provided in Table 12.

**Table 12 Pharmacokinetic Parameters of Obinutuzumab**

	CLL	NHL
<b>Distribution</b>		
Volume of Distribution <sup>a</sup> , L	4.1 (20)	4.3 (21)
<b>Elimination</b>		
Terminal Half-life, days	25.5 (48)	35.3 (35)
Clearance, L/day	0.11 (53)	0.08 (41)

Parameters are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> At steady state.

## Specific Populations

Age (median [range]: 63 [22, 89] years) and baseline creatinine clearance (CLcr) (median [range] 84 [22, > 120] mL/min) did not affect the pharmacokinetics of GAZYVA. In patients with CLcr  $\leq$  30 mL/min, the pharmacokinetics of GAZYVA was unaffected. GAZYVA has not been studied in patients with hepatic impairment.

The volume of distribution and steady-state clearance increased with body weight; however, the expected change in exposure does not warrant a dose modification.

## **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**

The efficacy of GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (CLL11; NCT01010061) in 781 patients with previously untreated CD20+ CLL requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CLcr) < 70 mL/min. Patients with CLcr < 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 product 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 1,000 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 (2.2)*], 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 CLL11, the median age was 73 years, 62% were male, and 95% were White. Sixty-five percent had a CLcr < 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 CLcr 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 product treated arm and 67% in the chlorambucil alone arm.

In the Stage 1 analysis of CLL11, 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 CLL11, the median PFS was 26.7 months in the GAZYVA arm and 14.9 months in the rituximab product 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 product arm), 18 patients (19%) had negative MRD in the bone marrow in the GAZYVA arm compared to 2 patients (6%) in the rituximab product arm. Out of the patients who achieved CR and CRi, 39 patients (41%) in the GAZYVA arm, and 4 patients (12%) in the rituximab product arm were MRD negative in peripheral blood samples collected at least 3 months after the end of treatment.

Efficacy results are shown in Table 13 and Figures 1 and 2.

**Table 13 Efficacy Results from CLL11**

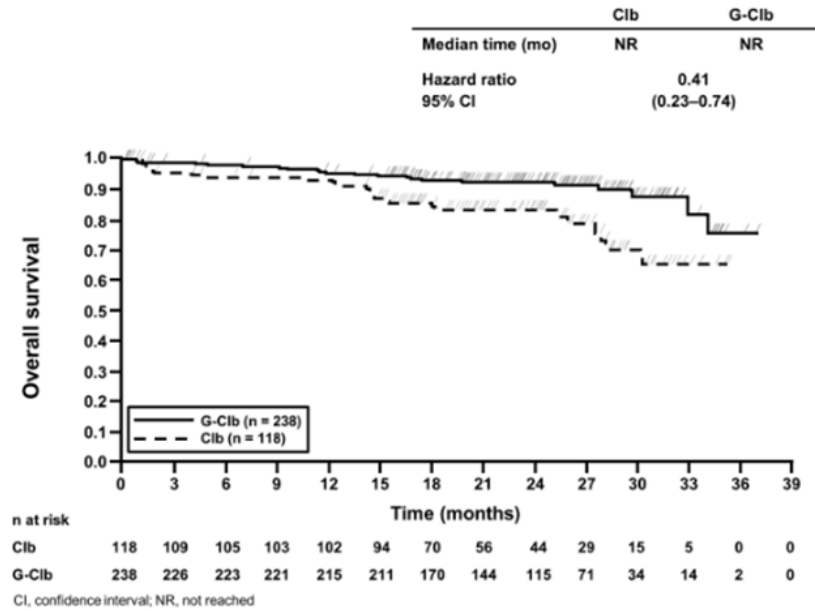
Endpoint	Stage 1 of CLL11		Stage 2 of CLL11	
	GAZYVA + Chlorambucil* n = 238	Chlorambucil n = 118	GAZYVA + Chlorambucil* n = 333	Rituximab product + Chlorambucil n = 330
Median Progression-Free Survival <sup>a</sup>	27.2 months (HR 0.19 [0.14; 0.27], p-value < 0.0001 stratified log-rank test)	11.2 months	26.7 months (HR 0.42 [0.33; 0.54], p-value < 0.0001 stratified log-rank test)	14.9 months
Overall Response Rate <sup>b</sup>	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	

<sup>a</sup> As defined by independent review. Investigator-assessed PFS was consistent with data from independent review.

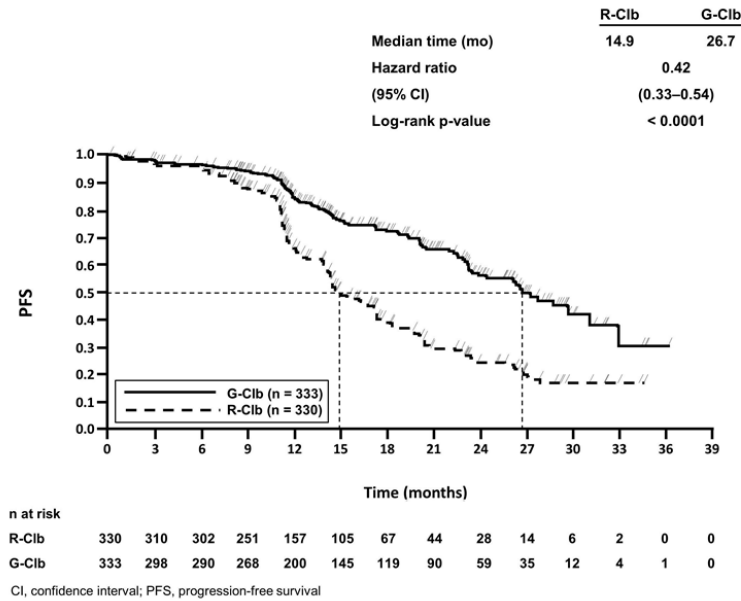
<sup>b</sup> Defined as best overall response rate (ORR = CR + CRi + PR + nPR).

\*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 CLL11 (Stage 1)**



**Figure 2**  
**Kaplan-Meier Curve of Progression-Free Survival in Patients with CLL in CLL11 (Stage 2)**



## 14.2 Follicular Lymphoma

### *GADOLIN*

The efficacy of GAZYVA was evaluated in GADOLIN (NCT01059630), an open-label, multicenter, randomized study that included 335 patients with follicular lymphoma (FL) who had no response to or have progressed during or within 6 months of rituximab product or a rituximab product-containing regimen. These patients were randomized to receive either bendamustine alone (n = 171) or GAZYVA in combination with bendamustine (n = 164) 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 the type of refractoriness to rituximab product (refractory to rituximab product monotherapy versus rituximab product in combination with chemotherapy), the number of prior therapies ( $\leq 2$  versus  $> 2$ ), and geographic region.

GAZYVA was given by intravenous infusion as a flat dose of 1,000 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<sup>2</sup>/day when given in combination with GAZYVA or 120 mg/m<sup>2</sup>/day when given alone.

The primary analysis included 321 FL patients, including 166 patients randomized to bendamustine alone and 155 patients randomized to GAZYVA in combination with bendamustine. In the primary analysis, patients had a median age of 63 years, 88% were White 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 product monotherapy, 37% of patients were refractory to prior rituximab product plus chemotherapy induction treatment, and 41% of patients were refractory to rituximab product maintenance treatment received following rituximab product plus chemotherapy induction. Seventy-nine percent of patients were refractory to both rituximab product and an alkylating agent during any prior regimen (double refractory).

The major efficacy outcome measure was PFS as determined by an independent review committee (IRC). At the time of the primary analysis, 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 14. The Kaplan-Meier curve for IRC-PFS is shown in Figure 3.

**Table 14 Primary Analysis Efficacy Results from GADOLIN<sup>a, b</sup>**

Endpoint	GADOLIN	
	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 155	Bendamustine n = 166
Median Progression-Free Survival (months)	Not Reached (HR = 0.48 [0.34; 0.68], p-value < 0.0001 by stratified log-rank test)	13.8
Best Overall Response <sup>c</sup>	78.7%	74.7%
Complete Response	15.5%	18.7%
Partial Response	63.2%	56.0%
Median duration of response (months)	Not Reached	11.6

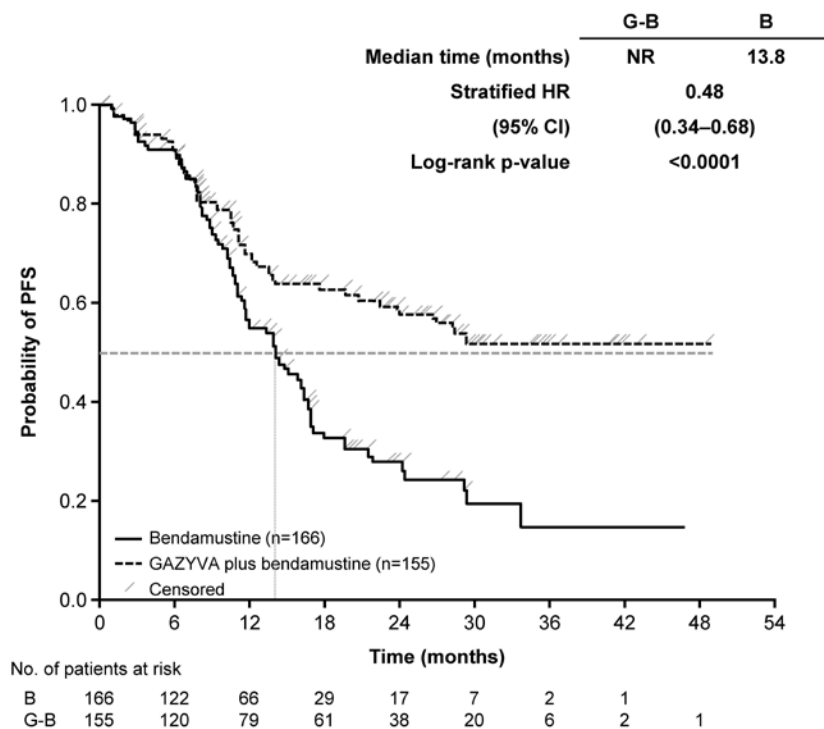
<sup>a</sup> Based on FL population.

<sup>b</sup> As defined by independent review.

<sup>c</sup> Best response of PR or CR within 12 months of study start.

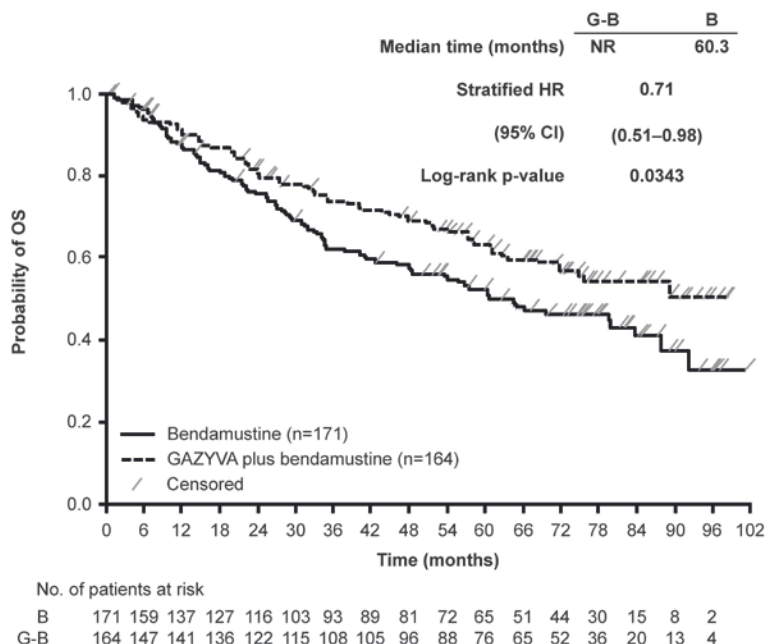
**Figure 3**

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



The final analysis included a total of 335 patients with 171 randomized to bendamustine alone and 164 to GAZYVA in combination with bendamustine. With an overall median observation time of 52.2 months (range: 0-100.9 months), there were 66 deaths (40.2%) in the GAZYVA arm and 85 deaths (51.3%) in the bendamustine-alone arm (OS HR = 0.71, 95% CI: 0.51, 0.98). The Kaplan-Meier curve for OS is presented in Figure 4.

**Figure 4**  
**Kaplan-Meier Curve of Overall Survival in Patients with FL**



### GALLIUM

The efficacy of GAZYVA was evaluated in GALLIUM (NCT01332968), a multicenter, open-label, randomized study that included 1202 patients with previously untreated, stage II bulky, III or IV FL. Patients were randomized 1:1 to receive either GAZYVA (n = 601) or rituximab product (n = 601) in combination with chemotherapy (CHOP, CVP, or bendamustine) for 6–8 cycles. Patients were stratified by chemotherapy (selected by each site; all patients at that site received the chosen chemotherapy regimen), FLIPI (Follicular Lymphoma International Prognostic Index) risk group and geographic region. Patients with at least PR to combination therapy received monotherapy with GAZYVA (1,000 mg) or rituximab product every two months until disease progression or for a maximum of two years. The study excluded patients with follicular lymphoma grade 3b or transformed disease; patients having an ANC < 1500 /  $\mu$ L, platelets < 75,000 /  $\mu$ L, or CLcr < 40 mL/min; and patients with hepatic transaminases > 2.5 x upper limit of normal unless attributable to lymphoma.

GAZYVA was given by intravenous infusion as a flat dose of 1,000 mg on Days 1, 8 and 15 of Cycle 1 and Day 1 of subsequent treatment cycles.

GAZYVA and bendamustine were given in six 28-day cycles. Bendamustine was administered at 90 mg/m<sup>2</sup>/day on Days 1 and 2 of each cycle, with prednisone 100 mg orally or equivalent on Day 1 of Cycle 1.

GAZYVA and CHOP were given in six 21-day cycles. Subsequently, two additional cycles of GAZYVA were given for a total of 8 GAZYVA cycles. CHOP consisted of cyclophosphamide 750 mg/m<sup>2</sup> intravenously, doxorubicin 50 mg/m<sup>2</sup>, and vincristine 1.4 mg/m<sup>2</sup> (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

GAZYVA and CVP were given in eight 21-day cycles. CVP consisted of cyclophosphamide 750 mg/m<sup>2</sup> intravenously and vincristine 1.4 mg/m<sup>2</sup> (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

Patients had a median age of 59 years, 81% were White and 53% were female; 7% had Stage II, 35% had Stage III, and 56% had Stage IV disease, with 44% having bulky disease ( $\geq 7$  cm) overall; 79% had a FLIPI score of  $> 2$ ; and 97% had an ECOG performance status of 0–1. The chemotherapy was bendamustine in 57%, CHOP in 33%, and CVP in 10% of patients.

Efficacy was based on PFS per IRC, with a median observation time of 38 months. Upon interim analysis, the risk of progression or death was significantly reduced in the GAZYVA containing arm compared to the rituximab product containing arm (Table 15). Kaplan-Meier curves for PFS are shown in Figure 5. Overall response and complete remission rates were similar.

**Table 15 Efficacy in Previously Untreated Follicular Lymphoma (GALLIUM)**

<b>Endpoint per IRC</b>	<b>GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 601</b>	<b>Rituximab product + chemotherapy followed by rituximab product monotherapy n = 601</b>
Progression-Free Survival <sup>a</sup> Number of events (%)	108 (18%) HR = 0.72 [95% CI: 0.56, 0.93], p-value = 0.0118 <sup>b</sup>	141 (23%)
Overall Response Rate <sup>c</sup>	91%	88%
Complete Remission Rate <sup>c</sup>	28%	27%

<sup>a</sup> Investigator-assessed PFS was consistent with data from independent review.

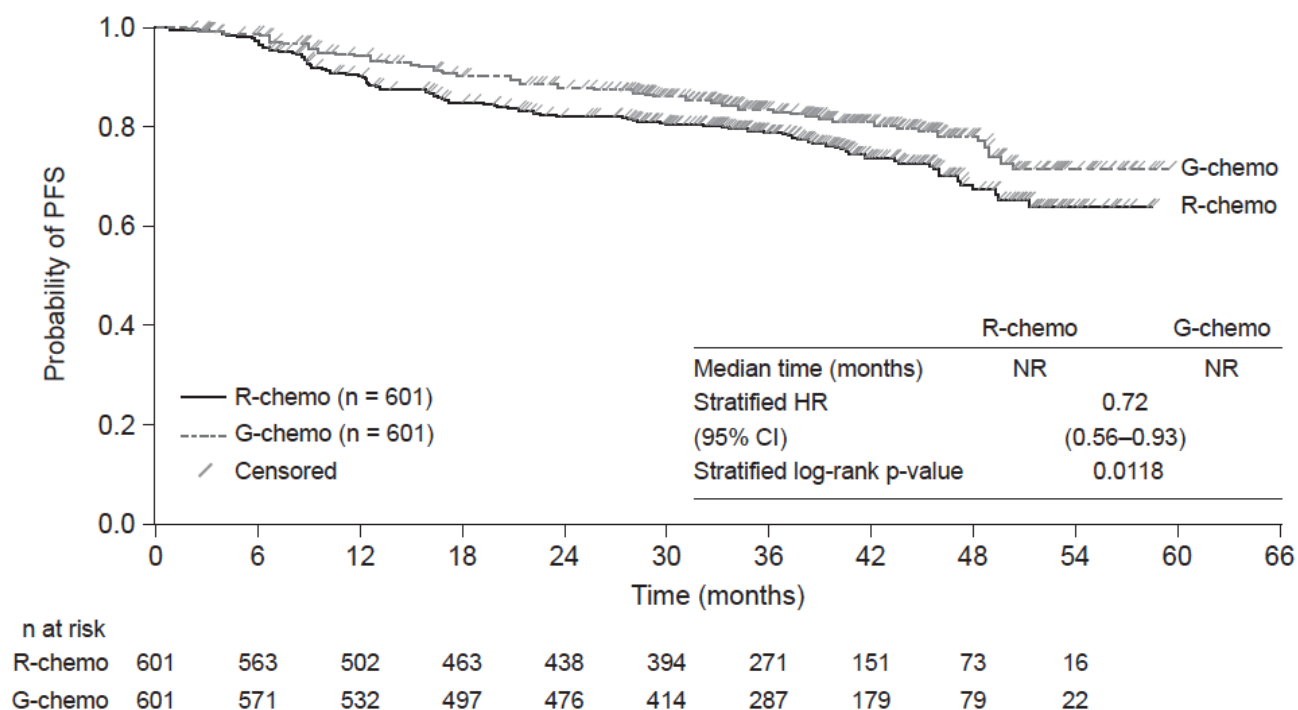
<sup>b</sup> Stratified log-rank test.

<sup>c</sup> After completion of combination therapy. Assessed by CT without positron emission tomography.



**Figure 5**

**Kaplan-Meier Curves of Progression Free Survival in Patients with Previously Untreated FL**



CI, confidence interval; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; NR, not reached; PFS, progression-free survival; R-chemo, rituximab plus chemotherapy

**16 HOW SUPPLIED/STORAGE AND HANDLING**

GAZYVA is a clear, colorless to slightly brown, preservative-free solution for intravenous use supplied as 1,000 mg/40 mL (25 mg/mL) in single-dose vials (NDC 50242-070-01).

Store at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. Protect from light. DO NOT FREEZE. DO NOT SHAKE.

**17 PATIENT COUNSELING INFORMATION**

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

- Signs and symptoms of infusion-related 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 (5.5) and Adverse Reactions (6.1)].
- Signs of infections including fever and cough [see Warnings and Precautions (5.6) 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)].
- Signs and symptoms of bleeding or thrombosis [see Warnings and Precautions (5.8 and 5.9)].

Advise patients of the need for:

- Periodic monitoring of blood counts [*see Warnings and Precautions (5.7, 5.8 and 5.9) and Adverse Reactions (6.1)*].
- Avoid vaccinations with live viral vaccines [*see Warnings and Precautions (5.10)*].
- 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. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.11), Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with GAZYVA and for 6 months after the last dose [*see Use in Specific Populations (8.3)*].

Advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose [*see Use in Specific Populations (8.2)*].

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**GAZYVA® (obinutuzumab)**

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

South San Francisco, CA 94080-4990

U.S. License No. 1048

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**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 use  
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**

Dosage and Administration, Recommended Dosage for Follicular Lymphoma (2.3) 2/2022  
Dosage Modifications for Adverse Reactions (2.5) 2/2022  
Dosage and Administration, Preparation and Administration (2.6) 2/2022  
Warnings and Precautions, Thrombocytopenia (5.8) and Disseminated Intravascular Coagulation (5.9) 7/2022

**INDICATIONS AND USAGE**

GAZYVA is a CD20-directed cytolytic antibody 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 who relapsed after, or are refractory to, a rituximab-containing regimen. (1, 14)
- in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma. (1, 14)

**DOSAGE AND ADMINISTRATION**

- Premedicate for infusion-related reactions and tumor lysis syndrome. (2.1, 5.3, 5.4)
- Administer only as intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
- The recommended dosage for chronic lymphocytic leukemia is 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1,000 mg on day 8 and 15 of Cycle 1, and 1,000 mg on day 1 of Cycles 2–6. (2.2)
- The recommended dosage for follicular lymphoma is 1,000 mg on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years. (2.3)

**DOSAGE FORMS AND STRENGTHS**

Injection: 1,000 mg/40 mL (25 mg/mL) single-dose vial. (3)

**CONTRAINDICATIONS**

GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use. (4)

**WARNINGS AND PRECAUTIONS**

- **Infusion-Related Reactions:** Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt, reduce rate, or discontinue for infusion-related reactions based on severity. (2.1, 5.3)
- **Hypersensitivity Reactions Including Serum Sickness:** Discontinue GAZYVA permanently. (5.4)
- **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. (5.5)
- **Infections:** 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:** In patients with Grade 3 to 4 neutropenia, monitor laboratory tests until resolution and for infection. Consider dose delays and infection prophylaxis, as appropriate. (5.7)
- **Thrombocytopenia:** Monitor for decreased platelet counts and bleeding. Transfusion may be necessary. (5.8)
- **Disseminated Intravascular Coagulation:** Evaluate cause and monitor for bleeding, thrombosis, and need for supportive care. (5.9)
- **Immunization:** Avoid administration of live virus vaccines during GAZYVA treatment and until B-cell recovery. (5.10)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception. (5.11)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence  $\geq 20\%$  and  $\geq 2\%$  greater in the GAZYVA treated arm) were:

- **Previously untreated CLL:** infusion-related reactions and neutropenia. (6)
- **Relapsed or refractory NHL:** infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain. (6)
- **Previously untreated NHL:** infusion-related reactions, neutropenia, upper respiratory tract infections, cough, constipation, and diarrhea. (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](http://www.fda.gov/medwatch).**

**USE IN SPECIFIC POPULATIONS**

- **Lactation:** Advise not to breastfeed. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 7/2022**

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## 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 (CLL)**

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia.

### **1.2 Follicular Lymphoma (FL)**

GAZYVA, in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosing Information**

- Premedicate before each infusion [see *Dosage and Administration* (2.4)].
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk of tumor lysis syndrome [see *Dosage and Administration* (2.4) and *Warnings and Precautions* (5.4)].
- Administer only as an intravenous infusion through a dedicated line [see *Dosage and Administration* (2.6)].
- 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-related reactions that can be fatal if they occur [see *Warnings and Precautions* (5.3)].

### **2.2 Recommended Dosage for Chronic Lymphocytic Leukemia**

Each dose of GAZYVA is 1,000 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) according to Table 1.

**Table 1 Dose of GAZYVA to be Administered During Six 28-Day Treatment Cycles for Patients with CLL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
<b>Cycle 1 (loading doses)</b>	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	If no infusion-related reaction (IRR) occurred during the previous infusion, 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. If an IRR occurred during the previous infusion, administer at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1,000 mg	If no IRR 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	1,000 mg	
<b>Cycles 2–6</b>	Day 1	1,000 mg	If an infusion-related reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

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

### 2.3 Recommended Dosage for Follicular Lymphoma

Each dose of GAZYVA is 1,000 mg administered intravenously according to Table 2.

For patients with relapsed or refractory FL, administer GAZYVA in combination with bendamustine in six 28-day cycles. Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles should continue on GAZYVA 1,000 mg as monotherapy for up to two years.

For patients with previously untreated FL, administer GAZYVA with one of the following chemotherapy regimens:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by 2 additional 21-day cycles of GAZYVA alone
- Eight 21-day cycles in combination with CVP

Patients with previously untreated FL who achieve a complete response or partial response to the initial 6 or 8 cycles should continue on GAZYVA 1,000 mg as monotherapy for up to two years.

GAZYVA should be administered at the standard infusion rate in Cycle 1 (see Table 2). In patients with FL who do not experience a Grade 3 or higher IRR during Cycle 1, GAZYVA may be administered as a shorter, approximately 90-minute infusion from Cycle 2 onwards (see Table 3) with continued premedication.

**Table 2 Dose and Standard Infusion Rate of GAZYVA to be Administered During 6–8 Treatment Cycles, Followed by GAZYVA Monotherapy for Patients with FL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
<b>Cycle 1 (loading doses)</b>	Day 1	1,000 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	1,000 mg	If no infusion-related reaction or an infusion-related reaction of Grade 1 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	1,000 mg	
<b>Cycles 2–6 or 2–8</b>	Day 1	1,000 mg	If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
<b>Monotherapy</b>	Every two months for up to two years	1,000 mg	

**Table 3 Dose and Infusion Rate of a GAZYVA 90-Minute Infusion for Patients with FL**

Day of treatment cycle		Dose of GAZYVA	Rate of infusion
<b>Cycle 1</b>	Days 1, 8, 15	1,000 mg	See Table 2
<b>Cycles 2–6* or 2-8*</b>	Day 1	1,000 mg	If no Grade 3 or higher IRR occurred during Cycle 1: 100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes.  If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 or higher IRR occurred during the previous approximately 90-minute infusion, administer all subsequent GAZYVA infusions at the standard infusion rate (see Table 2).
<b>Monotherapy*</b>	Every two months for up to two years	1,000 mg	

\* Consider an approximately 90-minute infusion in patients with FL who do not experience a Grade 3 or higher infusion-related reaction to GAZYVA in Cycle 1 and subsequent cycles.

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible. During GAZYVA and chemotherapy treatment, adjust the dosing schedule accordingly to maintain the time interval between chemotherapy cycles. During monotherapy, maintain the original dosing schedule for subsequent doses. Initiate monotherapy approximately two months after the last dose of GAZYVA administered during the induction phase.

## 2.4 Recommended Premedication and Prophylactic Medications

### Infusion-Related Reactions

Premedication to reduce the risk of IRRs is outlined in Table 4 [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)*].

**Table 4 Premedication for GAZYVA Infusion to Reduce Infusion-Related Reactions**

Day of Treatment Cycle	Patients requiring premedication	Premedication	Administration
<b>Cycle 1:</b>  <b>CLL</b> <b>Day 1,</b> <b>Day 2</b>  <b>FL</b> <b>Day 1</b>	All patients	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone <sup>1,2</sup>	Completed at least 1 hour prior to GAZYVA infusion.
		650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	
<b>All subsequent infusions, CLL or FL</b>	All patients	650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
	Patients with an IRR (Grade 1-2) with the previous infusion	650–1,000 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 x 10 <sup>9</sup> /L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone <sup>1</sup>	Completed at least 1 hour prior to GAZYVA infusion.
		650–1,000 mg acetaminophen	At least 30 minutes before GAZYVA infusion.
		anti-histamine (e.g., 50 mg diphenhydramine)	

Premedication applies to both standard and approximately 90-minute infusions.

<sup>1</sup> Hydrocortisone is not recommended as it has not been effective in reducing the rate of IRRs.

<sup>2</sup> If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

### Tumor Lysis Syndrome Prophylaxis

Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10<sup>9</sup>/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)*].

### 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. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (> 1 week) neutropenia.

## **2.5 Dosage Modifications for Adverse Reactions**

### Infusion-Related Reactions

If a patient experiences an IRR, adjust the infusion as follows [see *Warnings and Precautions (5.3)*]:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue GAZYVA.
- Grade 3 (severe): Interrupt infusion and manage symptoms.
  - For patients who experience Grade 3 IRRs during standard infusion, 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 IRR reaction occurred), and if patient does not experience any further IRR 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 or higher IRR at rechallenge.
  - For patients with FL who experience Grade 3 IRRs during the approximately 90-minute infusion, upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than 400 mg/hr. Administer subsequent infusions at the standard rate. Permanently discontinue treatment if patients experience a Grade 3 or higher IRR 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 manage symptoms. Upon resolution of symptoms, continue or resume GAZYVA infusion, and if patient does not experience any further IRR 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.

### Other Adverse Reactions

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

## **2.6 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.
- Use a sterile needle and syringe to prepare GAZYVA.
- Dilute into a 0.9% Sodium Chloride Injection, USP PVC or non-PVC polyolefin infusion bag.

*Chronic Lymphocytic Leukemia*

- Preparation of solution for infusion on day 1 (100 mg) and day 2 (900 mg) of Cycle 1:
  - Prepare day 1 (100 mg) and day 2 (900 mg) infusion bags at the same time using one vial (1,000 mg/40 mL) on day 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 Injection, USP infusion bag for immediate administration.
  - Dilute the remaining 36 mL (900 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP 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 of Cycles 2–6:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag.

#### *Follicular Lymphoma*

- Preparation of solution for infusion:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag.
- Mix diluted solution by gentle inversion. Do not shake or freeze.
- For microbiological stability, immediately use diluted GAZYVA infusion solution. If not used immediately, store 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.

#### Storage

Use the diluted solution immediately. If not used immediately, store for up to 24 hours at 2°C to 8°C. Discard after 24 hours.

#### Administration

- 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.

### **3 DOSAGE FORMS AND STRENGTHS**

Injection: 1,000 mg/40 mL (25 mg/mL) clear, colorless to slightly brown solution in single-dose vial.

## 4 CONTRAINDICATIONS

GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use [*see Warnings and Precautions (5.4)*].

## 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 healthcare providers 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 healthcare providers 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

John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, occurred 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-Related Reactions

GAZYVA can cause severe and life-threatening infusion-related reactions (IRRs). Sixty-five percent of patients with CLL experienced a reaction to the first 1,000 mg of GAZYVA infused. Thirty-seven percent of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of GAZYVA infusion. IRRs have occurred within 24 hours of receiving GAZYVA. IRRs 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). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills [*see Adverse Reactions (6.1)*].

Premedicate patients with acetaminophen, anti-histamine, and a glucocorticoid [see *Dosage and Administration* (2.4)]. Closely monitor patients during the entire infusion. Reduce infusion rate, interrupt infusion or permanently discontinue GAZYVA for IRRs based on severity [see *Dosage and Administration* (2.5)]. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed.

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 IRR to GAZYVA. 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 Hypersensitivity Reactions Including Serum Sickness**

Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from IRRs. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure.

If a hypersensitivity reaction is suspected during or after an infusion, stop the infusion and permanently discontinue treatment. GAZYVA is contraindicated in patients with known hypersensitivity reactions to GAZYVA, including serum sickness with prior GAZYVA use [see *Contraindications* (4)].

#### **5.5 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.

Administer appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA for patients at risk for TLS [see *Dosage and Administration* (2.4)]. 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.

#### **5.6 Infections**

Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by GAZYVA monotherapy as in the GALLIUM study, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment [see *Adverse Reactions* (6.1)].

In GALLIUM, more Grade 3 to 5 infections were reported in the recipients of GAZYVA and bendamustine (117/410 patients, 29%) as compared to GAZYVA plus CHOP or CVP (43/281 patients, 15%). More fatal infections were reported in patients treated with GAZYVA and bendamustine (3%), as compared to GAZYVA plus CHOP or CVP ( $< 1\%$ ), including during the monotherapy phase and after completion of treatment.

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.

## 5.7 Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider dose delays for Grade 3 or 4 neutropenia. Consider administration of granulocyte colony-stimulating factors (GCSF) 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). 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. Consider antiviral and antifungal prophylaxis.

## 5.8 Thrombocytopenia

Severe and life-threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL and CLL treated with GAZYVA in combination with chemotherapy, including during Cycle 1.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle and if clinically indicated, evaluate laboratory coagulation parameters [*see Warnings and Precautions (5.9)*]. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider 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 that may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

## 5.9 Disseminated Intravascular Coagulation (DIC)

Fatal and severe DIC has been reported in patients receiving GAZYVA for treatment of follicular lymphoma and chronic lymphocytic leukemia. The majority of DIC cases have involved changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, DIC was associated with IRRs, TLS, or both [*see Adverse Reactions (6.1)*]. In patients with suspected DIC, evaluate potential causes, and monitor coagulation parameters, platelet counts, and for signs and symptoms of bleeding or thrombosis. Manage according to standard guidelines for DIC. Supportive care, including transfusion of blood products and other medical management, may be necessary.

## 5.10 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.

## 5.11 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, GAZYVA can cause B-cell depletion in infants exposed to obinutuzumab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving GAZYVA and for 6 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:

- Hepatitis B virus reactivation [*see Warnings and Precautions (5.1)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.2)*]
- Infusion-related reactions [*see Warnings and Precautions (5.3)*]

- Hypersensitivity reactions including serum sickness [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Neutropenia [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
- Disseminated intravascular coagulation [see Warnings and Precautions (5.9)]

## 6.1 Clinical Trials Experience

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

### Chronic Lymphocytic Leukemia

The data below are based on a safety population of 773 previously untreated patients with CLL in the CLL11 study. Patients were treated with chlorambucil alone, GAZYVA in combination with chlorambucil, or rituximab product 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 product 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 GAZYVA treated patients. The incidence of Grade 3 to 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 GAZYVA with similar incidences of Grade 3 to 4 abnormalities between the two arms.

Patients received three 1,000 mg doses of GAZYVA on the first cycle and a single dose of 1,000 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 (2.2)]. In total, 81% of patients received all 6 cycles (of 28 days each) of GAZYVA-based therapy.

Adverse reactions in  $\geq 10\%$  of patients in the GAZYVA containing arm were infusion-related reactions, neutropenia, thrombocytopenia, and diarrhea. The most common Grade 3 to 4 adverse reactions (incidence  $\geq 10\%$ ) in the GAZYVA containing arm were neutropenia, infusion-related reactions, and thrombocytopenia.

**Table 5 Adverse Reactions (Incidence  $\geq 5\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with CLL (Stage 2)**

Body System Adverse Reactions	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion-Related Reaction	66	20	38	4
<b>Blood and Lymphatic System Disorders<sup>a</sup></b>				
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
<b>Gastrointestinal Disorders</b>				
Diarrhea	10	2	8	< 1

Body System Adverse Reactions	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Constipation	8	0	5	0
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	9	< 1	7	< 1
<b>Infections and Infestations</b>				
Nasopharyngitis	6	< 1	3	0
Urinary Tract Infection	5	1	2	< 1

<sup>a</sup> Adverse reactions reported under “Blood and lymphatic system disorders” reflect those reported by investigator as clinically significant.

**Table 6 Post-Baseline Laboratory Abnormalities (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with CLL (Stage 2)**

Laboratory Abnormalities	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Leukopenia	84	35	62	16
Lymphopenia	80	39	50	16
Neutropenia	76	46	69	41
Thrombocytopenia	48	13	40	8
Anemia	39	10	37	10
<b>Chemistry</b>				
Hypocalcemia	37	3	32	< 1
ALT increased	28	2	21	1
AST increased	27	2	21	< 1
Hyponatremia	26	7	18	2
Hypoalbuminemia	23	< 1	16	< 1
Hypokalemia	14	1	10	< 1

## Non-Hodgkin Lymphoma

### *GADOLIN*

The GADOLIN study evaluated safety in 407 patients with relapsed or refractory NHL, including FL (81%), small lymphocytic lymphoma and marginal zone lymphoma (a disease for which GAZYVA is not indicated), who did not respond to or progressed within 6 months of treatment with rituximab product or a rituximab product-containing regimen. In the population of patients with FL, the profile of adverse reactions was consistent with the overall NHL population. Patients received either GAZYVA in combination with bendamustine (204 patients), followed by GAZYVA monotherapy in patients that had not progressed, or bendamustine alone (203 patients).

Patients randomized to the GAZYVA + bendamustine arm received three weekly 1,000 mg doses of GAZYVA in the first cycle and a single dose of 1,000 mg once every 28 days for 5 additional cycles, in combination with bendamustine 90 mg/m<sup>2</sup> intravenously on Days 1 and 2 in all 6 cycles. Patients who did not progress on the combination received a single 1,000 mg dose of GAZYVA monotherapy every two months until progression or for a maximum of two years. The control arm received bendamustine 120 mg/m<sup>2</sup> on Days 1 and 2 of each cycle for 6 cycles, with a cycle length of 28 days. In the GAZYVA arm, 78% of patients received 6 cycles of bendamustine and 82% received their full 6 cycles of GAZYVA; 72 (46%) of the 158 patients who began GAZYVA monotherapy received all planned doses. In the control arm, 72% of patients received 6 cycles of bendamustine.

Serious adverse reactions occurred in 45% of the GAZYVA arm and 37% of the bendamustine-only arm. Fatal adverse reactions within 90 days of treatment occurred in 3.4% and 2.5%, respectively. During treatment and follow-up combined, fatal adverse reactions occurred in 10% of GAZYVA

recipients and in 7.4% of recipients of bendamustine alone, with infection and second primary malignancies being the leading causes.

Dose modification due to adverse reactions occurred in 50% of the GAZYVA arm and 42% of the control arm, and discontinuation of any study drug due to adverse reactions occurred in 20% and 17%, respectively.

Table 7 presents selected adverse reactions in GADOLIN. The most common adverse reactions (incidence  $\geq 20\%$ ) in GAZYVA recipients included infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain.

**Table 7 Adverse Reactions (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Relapsed or Refractory NHL (GADOLIN)**

Body System Adverse Reactions <sup>a, b</sup>	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 204		Bendamustine n = 203	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
<b>Procedural Complications</b>				
Infusion-Related Reaction <sup>c</sup>	67	11	63	5
<b>General Disorders</b>				
Fatigue	40	3	36	3
Pyrexia	19	1	15	1
<b>Blood and Lymphatic System Disorders</b>				
Neutropenia	37	35 <sup>d</sup>	29	27
<b>Infections and Infestations</b>				
Upper Respiratory Tract Infection	36	3	23	1
Respiratory Tract Infection, Unspecified	14	1	8	0
Urinary Tract Infection	13	3	7	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	31	<1	21	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal Pain	28	1	20	0
Arthralgia	12	<1	5	0
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	17	<1	14	<1
Pruritus	11	0	6	0

<sup>a</sup> Includes adverse reactions reported throughout study treatment and follow-up.

<sup>b</sup> Includes grouped terms.

<sup>c</sup> Except where noted, individual events that meet the definition of “infusion-related reaction” are excluded from Table 7 above, as they are included in the grouped term “Infusion-Related Reaction”.

<sup>d</sup> Includes 1 fatal event.

**Infusion-related reactions** are defined as any related adverse reaction that occurred during or within 24 hours of infusion.

**Fatigue** includes fatigue, lethargy, asthenia.

**Pyrexia** includes pyrexia, hyperthermia, body temperature increased.

**Cough** includes cough, productive cough, upper-airway cough syndrome.

**Neutropenia** includes neutropenia, agranulocytosis, granulocytopenia, neutrophil count decreased.

**Upper respiratory tract infection** includes upper respiratory tract congestion, upper respiratory tract inflammation, upper respiratory fungal infection, rhinovirus infection, and all terms containing: upper respiratory tract infection, laryngitis, nasopharyngitis, pharyngitis, rhinitis, tonsillitis, and sinusitis with the exception of sinobronchitis.

**Respiratory tract infection unspecified** includes respiratory tract infection, respiratory tract infection viral, influenza, influenza-like illness, sinobronchitis, respiratory syncytial virus infection.

**Urinary tract infection** includes all terms containing: urinary tract infection, cystitis, pyelonephritis.

**Musculoskeletal pain** includes non-cardiac chest pain, bone pain, spinal pain, myalgia, back pain, neck pain, musculoskeletal discomfort, pain in extremity, and all terms containing “musculoskeletal pain”.

**Rash** includes drug eruption, skin reaction, all terms containing “rash”, urticaria, and selected terms containing “dermatitis”.

**Pruritus** includes pruritus, pruritus generalized.



Other clinically relevant adverse reactions (incidence < 10% and ≥ 2% greater in the GAZYVA arm) included:

- *Blood and lymphatic system disorders:* febrile neutropenia (6%)
- *Infection:* sepsis (7%)

During GAZYVA monotherapy (158 patients), adverse reactions in ≥ 10% of patients included upper and lower respiratory tract infections, cough, neutropenia, musculoskeletal pain, fatigue, diarrhea, rash, and urinary tract infection.

Table 8 presents selected new or worsening laboratory abnormalities in the GADOLIN trial.

**Table 8 New or Worsening Laboratory Abnormalities (Incidence ≥ 10% and ≥ 2% Greater in the GAZYVA Arm<sup>a</sup>) in Patients with Relapsed or Refractory NHL (GADOLIN)**

Laboratory Abnormalities	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 204		Bendamustine n = 203	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Lymphopenia	97	92	96	84
Leukopenia	84	47	87	34
Neutropenia	76	53	75	42
<b>Chemistry</b>				
Hypophosphatemia	41	8	38	7
Hypocalcemia	39	3	24	1
ALT/SGPT increased	36	2	31	3
Alkaline phosphatase increased	27	0	23	0
Hyperbilirubinemia	21	2	17	2
Hyperkalemia	20	3	18	0

<sup>a</sup> Two percent difference in either any-grade or Grade 3 to 4 laboratory abnormalities.

In the GAZYVA monotherapy phase, new or worsening grade 3 or 4 abnormalities included neutropenia in 25% of patients (Grade 4, 10%) and lymphopenia in 23% (Grade 4, 5%).

### GALLIUM

A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%). Patients received chemotherapy (bendamustine, CHOP, or CVP) combined with either GAZYVA (691 patients) or rituximab product (694 patients), followed in responding patients by GAZYVA or rituximab product monotherapy every two months until disease progression or for a maximum of two years. The study excluded patients having an absolute neutrophil count (ANC) < 1500 / μL, platelets < 75,000 / μL, CLcr < 40 mL/min and, unless attributable to lymphoma, hepatic transaminases > 2.5 x upper limit of normal.

The median age was 60 (range: 23-88), 47% were male, 82% were white, and 97% had an ECOG performance status of 0 or 1. The chemotherapy was bendamustine in 59%, CHOP in 31% and CVP in 10% of patients. Following combination therapy, 624 patients (90%) in the GAZYVA arm and 612 patients (88%) in the rituximab product arm received monotherapy.

Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab product arm, most often from infections in the GAZYVA arm. During treatment and follow-up combined, fatal adverse reactions were reported in 5% of the GAZYVA arm and 4% of the rituximab product arm, with infections and second malignancies being leading causes. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to < 1% in the rituximab product arm.

During combination therapy, 93% of patients received all treatment cycles in the GAZYVA arm, and 92% received all treatment cycles in the rituximab product arm. Of the responding patients who began monotherapy with GAZYVA or rituximab product, 76% and 73%, respectively, completed the full course. Dose modification due to adverse reactions occurred in 74% of the GAZYVA arm and 63% of the rituximab product arm throughout study treatment, and discontinuation of any study drug due to adverse reactions occurred in 18% and 15%, respectively.

Throughout treatment and follow-up, the most common adverse reactions (incidence  $\geq 20\%$ ) observed at least 2% more in the GAZYVA arm included infusion-related reactions, neutropenia, upper respiratory tract infections, constipation and diarrhea (Table 9). Neutropenia, infusion-related reactions, febrile neutropenia and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence  $\geq 5\%$ ) observed more frequently in the GAZYVA arm.

**Table 9 Adverse Reactions (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)**

Body System Adverse Reactions <sup>a, b</sup>	GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion-Related Reaction <sup>c</sup>	72	12	60	8
<b>Blood and Lymphatic System Disorders</b>				
Neutropenia <sup>d</sup>	53	49	47	41
Thrombocytopenia <sup>d</sup>	14	7	8	3
<b>Infections and Infestations</b>				
Upper Respiratory Tract Infection	50	3	43	1
Herpesvirus Infection	18	3	14	1
Pneumonia	14	7	12	6
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	35	< 1	28	< 1
<b>Gastrointestinal Disorders</b>				
Constipation	32	< 1	29	< 1
Diarrhea	30	3	26	2
<b>Nervous System Disorders</b>				
Headache	18	< 1	15	< 1
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Arthralgia	16	0	14	< 1
<b>Psychiatric Disorders</b>				
Insomnia	15	< 1	12	< 1
<b>Metabolism and Nutrition Disorders</b>				
Decreased Appetite	14	< 1	12	< 1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Pruritus	11	< 1	9	0

<sup>a</sup> Includes adverse reactions reported throughout study treatment and follow-up.

<sup>b</sup> Includes grouped terms.

<sup>c</sup> Except where noted, individual events that meet the definition of “infusion-related reaction” are excluded from Table 9 above, as they are already included in the grouped term “Infusion-Related Reaction”. The most common individual terms within the grouped term “Infusion-Related Reaction” in decreasing order of frequency are nausea, chills, pyrexia and vomiting.

<sup>d</sup> Includes adverse reactions reported as infusion-related reactions.

**Infusion-related reactions** are defined as any related adverse reaction that occurred during or within 24 hours of infusion.

**Neutropenia** includes neutropenia, agranulocytosis, granulocytopenia, and neutrophil count decreased.

**Febrile neutropenia** includes febrile neutropenia, neutropenic infection, neutropenic sepsis, and febrile bone marrow aplasia.

**Thrombocytopenia** includes thrombocytopenia and platelet count decreased.

**Upper respiratory tract infection** includes upper respiratory tract congestion, upper respiratory tract inflammation, upper respiratory tract infection, rhinovirus infection, and all terms containing: laryngitis, nasopharyngitis, pharyngitis, rhinitis, tonsillitis, and sinusitis with the exception of sinobronchitis.

**Herpesvirus infection** includes all terms containing “herpes” or “varicella.”

**Pneumonia** includes all terms containing “pneumonia,” bacterial, pneumonia haemophilus, pneumonia pneumococcal, pneumonia fungal, pneumocystis jirovecii infection, lung infection, and lung infiltration.

**Diarrhea** includes diarrhea, defecation urgency, frequent bowel movement, and all terms containing “gastroenteritis”.

**Headache** includes all terms containing “headache” and migraine.

**Insomnia** includes all terms containing “insomnia” and sleep disorder.

**Pruritus** includes pruritus and pruritus generalized.

During the monotherapy period, the common adverse reactions (incidence  $\geq 10\%$ ) observed at least 2% more with GAZYVA were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%), and herpesvirus infection (13%).

Table 10 summarizes treatment-emergent laboratory abnormalities during treatment and follow-up. The Grade 3 to 4 abnormalities reported at least 2% more in the GAZYVA arm were lymphopenia, leukopenia, neutropenia, thrombocytopenia, and hyperuricemia. Patients in the GAZYVA arm, as compared to the rituximab product arm, had higher incidences of Grade 4 neutropenia (38% vs. 30%, respectively), Grade 4 lymphopenia (33% vs. 22%), and Grade 4 leukopenia (17% vs. 12%).

**Table 10 New or Worsening Laboratory Abnormalities (Incidence  $\geq 10\%$  and  $\geq 2\%$  Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)**

Laboratory Abnormalities <sup>a</sup>	GAZYVA+ chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
<b>Hematology</b>				
Lymphopenia	97	83	95	67
Leukopenia	92	49	89	39
Neutropenia	84	59	76	50
Thrombocytopenia	68	11	50	4
<b>Chemistry</b>				
ALT increased	50	3	43	2
AST increased	44	1	41	1
Hypophosphatemia	36	5	33	5
Hypoalbuminemia	33	1	25	1
Hypoproteinemia	32	0	30	0
Hypocalcemia	32	1	26	1
Hyperuricemia	28	28	22	22
Hyponatremia	26	4	20	3
Hyperkalemia	23	1	17	1
Hypernatremia	16	< 1	13	0

<sup>a</sup> Includes lab abnormalities, reported throughout treatment and follow-up, that were new or worsening, or worsening from baseline unknown.

In the monotherapy phase, new-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the GAZYVA arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%).

## GAZELLE

GAZELLE (NCT03817853) is a single-arm study designed to characterize the safety of GAZYVA administered as a shortened-duration infusion (approximately 90 minutes) in patients with previously untreated FL. All patients received GAZYVA at the standard infusion rate with premedication during Cycle 1. If no Grade 3 or higher IRR occurred with any infusion during Cycle 1, GAZYVA was administered over approximately 90 minutes in Cycle 2 and subsequent cycles. The primary safety

measure was the proportion of patients who experienced Grade 3 or higher IRRs with the 90-minute infusion at Cycle 2. GAZYVA was administered in combination with CHOP, CVP or bendamustine for 6 to 8 cycles (induction), followed by monotherapy for up to 2 years.

Of the 113 patients treated with GAZYVA, 99 (88%) received the 90-minute infusion starting in Cycle 2. In total, 97% of patients who received GAZYVA at either a standard or shorter infusion duration received premedication in Cycle 2. IRRs were observed in 63% of patients throughout induction (including IRRs observed after standard-duration infusion). In cycle 1, 58% of patients developed IRRs with the standard infusion rate (Grade  $\geq 3$  IRR, 5%). Of the patients who received the 90-minute infusion, 10% had IRRs of any grade in Cycle 2, with 8% and 2% of patients having a Grade 1 IRR or Grade 2 IRR, respectively. Following Cycle 2, one (1%) patient experienced a Grade 3 IRR, which occurred after the 90-minute infusion at Cycle 5.

### Infusion-Related Reactions

#### *Chronic Lymphocytic Leukemia*

The incidence of IRRs in the CLL11 study was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 IRRs was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1,000 mg and < 1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1,000 mg infused.

Of the first 53 patients receiving GAZYVA in CLL11, 47 (89%) experienced an IRR. 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 1,000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and < 3% thereafter [see *Dosage and Administration (2.2)*].

#### *Non-Hodgkin Lymphoma*

Overall, 67% of patients in the GADOLIN study experienced an IRR (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3 to 4 IRRs in GADOLIN was 11%. In Cycle 1, the incidence of IRRs (all grades) was 53% in patients receiving GAZYVA in combination with bendamustine of which 34 (9%) were Grade 3 to 4 in severity. In patients receiving GAZYVA in combination with bendamustine, the incidence of IRRs was highest on Day 1 (37%), and gradually decreased on Days 2, 8 and 15 (23%, 6% and 4%, respectively).

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

During GAZYVA monotherapy in GADOLIN, IRRs (all grades) were observed in 8% of patients. One Grade 3 and no Grade 4 IRRs were reported during GAZYVA monotherapy.

Overall, 2% of patients in GADOLIN experienced an IRR leading to discontinuation of GAZYVA.

In GALLIUM, 72% of patients in the GAZYVA treated arm experienced an IRR (all grades). The incidence of Grade 3 to 4 IRRs for these patients was 12%. In Cycle 1, the incidence of IRRs (all grades) was 62% in the GAZYVA treated arm with Grade 3 to 4 IRRs reported in 10%. The incidence of IRRs (all grades) was highest on Day 1 (60%) and decreased on Days 8 and 15 (9% and 6%, respectively).

During Cycle 2, the incidence of IRRs (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles.

During GAZYVA monotherapy treatment in GALLIUM, IRRs (all grades) were observed in 9% of patients.

Overall, 1% of patients in GALLIUM experienced an IRR leading to discontinuation of GAZYVA.

In GAZELLE, 10% of patients with FL experienced IRRs of any grade at Cycle 2 when GAZYVA was administered over approximately 90 minutes.

## Neutropenia

### *Chronic Lymphocytic Leukemia*

The incidence of neutropenia reported as an adverse reaction in CLL11 was 38% in the GAZYVA treated arm and 32% in the rituximab product treated arm, with the incidence of serious adverse reactions being 1% and < 1%, respectively (Table 5). 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 product treated arm.

### *Non-Hodgkin Lymphoma*

The incidence of neutropenia in GADOLIN was higher in the GAZYVA plus bendamustine arm (37%) compared to the arm treated with bendamustine alone (30%). Cases of prolonged neutropenia (3%) and late onset neutropenia (8%) were also reported in the GAZYVA plus bendamustine arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (30%) compared to the GAZYVA monotherapy treatment phase (13%).

The incidence of neutropenia in GALLIUM was higher in the GAZYVA treated arm (53%) compared to the rituximab product treated arm (47%). Cases of prolonged neutropenia (1%) and late onset neutropenia (4%) were also reported in the GAZYVA treated arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with chemotherapy (45%) compared to the GAZYVA monotherapy treatment phase (20%).

## Infection

### *Chronic Lymphocytic Leukemia*

The incidence of infections was similar between GAZYVA and rituximab product treated arms. Thirty-eight percent of patients in the GAZYVA treated arm and 37% in the rituximab product treated arm experienced an infection, with Grade 3 to 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 in GADOLIN was 68% in the GAZYVA plus bendamustine arm and 59% in the bendamustine arm, with Grade 3 to 4 events reported in 20% and 16%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm.

The incidence of infections in GALLIUM was 82% in the GAZYVA treated arm and 73% in the rituximab product treated arm, with Grade 3 to 4 events reported in 21% and 17%, respectively. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm.

The incidence of Grade 3 to 4 infections in the GAZYVA and rituximab product treated arms was lower in patients receiving GCSF prophylaxis (14%; 16%) compared with patients not receiving GCSF prophylaxis (24%; 18%). The incidence of fatal infections in patients receiving GCSF prophylaxis in the GAZYVA and rituximab product treated arms was 2% and 0%, respectively, and was 2% and < 1% in patients not receiving GCSF prophylaxis.

## 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 product treated arm (7%), with the incidence

of Grade 3 to 4 events being 10% and 3%, respectively (Table 5). 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 was 11% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 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 product 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 in GADOLIN was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (25%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 12% and 11%, respectively. Grade 3 to 4 hemorrhagic events were similar in both treatment arms (4% in the GAZYVA plus bendamustine arm and 2% in the bendamustine arm).

In GALLIUM, thrombocytopenia was reported as an adverse reaction in 14% of the GAZYVA treated arm and 8% of the rituximab product treated arm, with the incidence of Grade 3 to 4 events being 7% and 3%, respectively. 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 was 9% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 5% and 1%, respectively. In GALLIUM, both treatment arms had a 12% overall incidence of hemorrhagic events and a < 1% incidence of fatal hemorrhagic events.

#### Disseminated Intravascular Coagulation

In GALLIUM, DIC was reported as an adverse reaction in 0.3% of the GAZYVA treated patients. All events occurred within 1-2 days after the first infusion.

#### Tumor Lysis Syndrome

The incidence of Grade 3 or 4 tumor lysis syndrome in GAZYVA treated patients was 2% in CLL11, 0.5% in GADOLIN and 0.9% in GALLIUM.

#### Musculoskeletal Disorders

##### *Chronic Lymphocytic Leukemia*

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

##### *Non-Hodgkin Lymphoma*

In GADOLIN, adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (44% vs. 30%).

In GALLIUM, musculoskeletal disorders were reported in 54% of patients in the GAZYVA treated arm and 49% of patients in the rituximab product treated arm.

#### 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 IRRs or tumor lysis syndrome. In the CLL11 study, there was no clinically

meaningful difference in overall hepatotoxicity adverse reactions between all arms (4% of patients in the GAZYVA treated arm). Medications commonly used to prevent IRRs (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.

### Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

### Worsening of Pre-existing Cardiac Conditions

Fatal cardiac events have been reported in patients treated with GAZYVA.

## **6.2 Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Seven percent (18/271) of patients with CLL tested positive for anti-GAZYVA antibodies at one or more time points in CLL11. No patients developed anti-GAZYVA antibodies during or following GAZYVA treatment in GADOLIN, while 1 patient (1/564, 0.2%) developed anti-GAZYVA antibodies in GALLIUM. Neutralizing activity of anti-GAZYVA antibodies has not been assessed.

## **6.3 Postmarketing Experience**

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

- *Immune/Autoimmune Events*: Serum sickness

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on findings from animal studies and its mechanism of action, GAZYVA can cause fetal B-cell depletion [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 1,000 mg monthly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys (*see Data*). Advise pregnant women of the potential risk to the fetus.

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 (5.11) 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 child, 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. Because of the potential of serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose.

## **8.3 Females and Males of Reproductive Potential**

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

### Contraception

#### *Females*

Advise females of reproductive potential to use effective contraception during treatment with GAZYVA and for 6 months after the last dose.

## **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 reactions and 7% experienced adverse reactions leading to death. Of the patients younger than 75, 33% experienced a serious adverse reaction and 2% an



adverse reaction leading to death. No significant differences in efficacy were observed between younger and older patients [see *Clinical Studies (14.1)*].

### Non-Hodgkin Lymphoma

Of 204 patients in GADOLIN with relapsed or refractory NHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 55% of patients experienced serious adverse reactions and 28% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 37% and 14% experienced serious adverse reactions and adverse reactions leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GADOLIN.

Of the 691 patients in GALLIUM treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 and over, while 7% were 75 and over. Of patients 65 and over, 63% experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse reactions and 13% had an adverse reaction leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GALLIUM.

## **10 OVERDOSAGE**

There has been no experience with overdose in human clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of GAZYVA and supportive therapy.

## **11 DESCRIPTION**

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 (obinutuzumab) injection 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 use. GAZYVA is supplied at a concentration of 25 mg/mL in 1,000 mg single-dose 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 patients with CLL, GAZYVA caused CD19 B-cell depletion (defined as CD19 B cell counts < 0.07 x 10<sup>9</sup>/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 pharmacokinetic parameters of obinutuzumab after 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1,000 mg on day 8 and 15 of Cycle 1, and 1,000 mg on day 1 of Cycles 2–6 for CLL and after 1,000 mg on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years for NHL are provided in Table 11. The dosing regimen is within the linear pharmacokinetic behavior of obinutuzumab.

**Table 11 Obinutuzumab Measures of Exposure**

PK Measure	CLL <sup>a</sup>	Relapsed or refractory FL <sup>a</sup>	First line FL in combination with chemotherapy	
			GAZYVA + Bendamustine <sup>a</sup>	GAZYVA + CHOP or CVP <sup>b</sup>
C <sub>max</sub> , µg/mL	466.3 (35)	553.5 (32)	513.4 (28)	676.4 (30)
C <sub>trough</sub> , µg/mL	192.5 (78)	295 (56)	255 (46)	395 (44)
AUC, µg/mL*day	8701 (51)	11362 (41)	10088 (35)	10723 (37)

Results are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> Induction Cycle 6 of a 28-day cycle;

<sup>b</sup> Induction Cycle 8 of a 21-day cycle.

### Distribution and Elimination

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. The pharmacokinetic properties of obinutuzumab in patients with CLL and NHL are provided in Table 12.

**Table 12 Pharmacokinetic Parameters of Obinutuzumab**

	CLL	NHL
<b>Distribution</b>		
Volume of Distribution <sup>a</sup> , L	4.1 (20)	4.3 (21)
<b>Elimination</b>		
Terminal Half-life, days	25.5 (48)	35.3 (35)
Clearance, L/day	0.11 (53)	0.08 (41)

Parameters are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> At steady state.

## Specific Populations

Age (median [range]: 63 [22, 89] years) and baseline creatinine clearance (CLcr) (median [range] 84 [22, > 120] mL/min) did not affect the pharmacokinetics of GAZYVA. In patients with CLcr  $\leq$  30 mL/min, the pharmacokinetics of GAZYVA was unaffected. GAZYVA has not been studied in patients with hepatic impairment.

The volume of distribution and steady-state clearance increased with body weight; however, the expected change in exposure does not warrant a dose modification.

## **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**

The efficacy of GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (CLL11; NCT01010061) in 781 patients with previously untreated CD20+ CLL requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CLcr)  $<$  70 mL/min. Patients with CLcr  $<$  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 product 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 1,000 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 (2.2)*], 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 CLL11, the median age was 73 years, 62% were male, and 95% were White. Sixty-five percent had a CLcr  $<$  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 CLcr 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 product treated arm and 67% in the chlorambucil alone arm.

In the Stage 1 analysis of CLL11, 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 CLL11, the median PFS was 26.7 months in the GAZYVA arm and 14.9 months in the rituximab product 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 product arm), 18 patients (19%) had negative MRD in the bone marrow in the GAZYVA arm compared to 2 patients (6%) in the rituximab product arm. Out of the patients who achieved CR and CRi, 39 patients (41%) in the GAZYVA arm, and 4 patients (12%) in the rituximab product arm were MRD negative in peripheral blood samples collected at least 3 months after the end of treatment.

Efficacy results are shown in Table 13 and Figures 1 and 2.

**Table 13 Efficacy Results from CLL11**

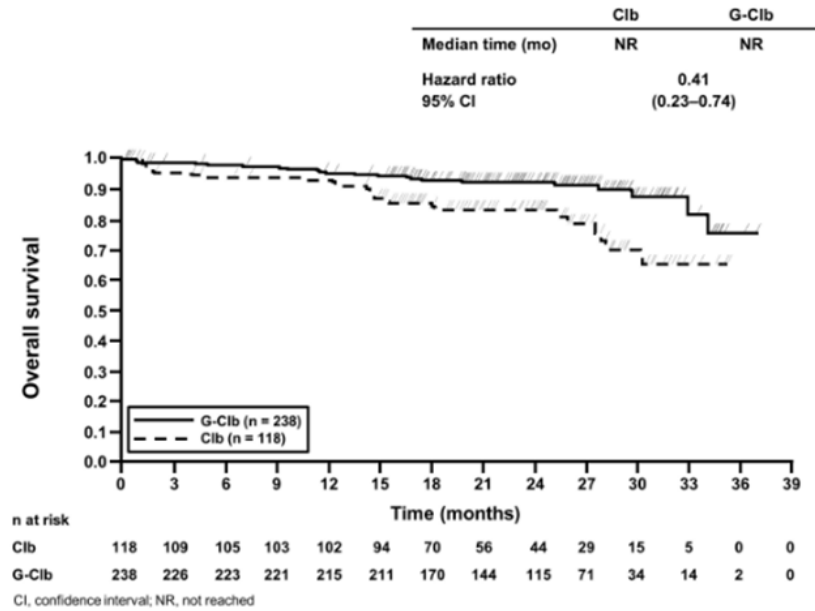
Endpoint	Stage 1 of CLL11		Stage 2 of CLL11	
	GAZYVA + Chlorambucil* n = 238	Chlorambucil n = 118	GAZYVA + Chlorambucil* n = 333	Rituximab product + Chlorambucil n = 330
Median Progression-Free Survival <sup>a</sup>	27.2 months (HR 0.19 [0.14; 0.27], p-value < 0.0001 stratified log-rank test)	11.2 months	26.7 months (HR 0.42 [0.33; 0.54], p-value < 0.0001 stratified log-rank test)	14.9 months
Overall Response Rate <sup>b</sup>	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	

<sup>a</sup> As defined by independent review. Investigator-assessed PFS was consistent with data from independent review.

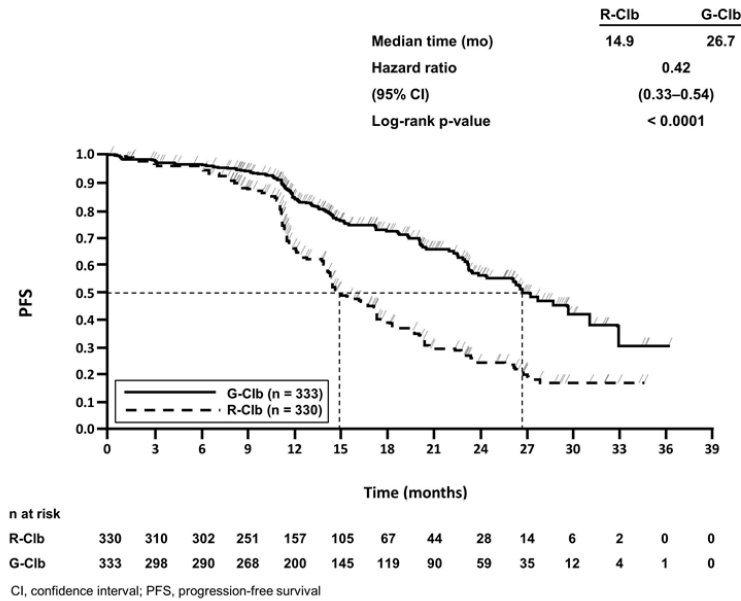
<sup>b</sup> Defined as best overall response rate (ORR = CR + CRi + PR + nPR).

\*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 CLL11 (Stage 1)**



**Figure 2**  
**Kaplan-Meier Curve of Progression-Free Survival in Patients with CLL in CLL11 (Stage 2)**



## 14.2 Follicular Lymphoma

### *GADOLIN*

The efficacy of GAZYVA was evaluated in GADOLIN (NCT01059630), an open-label, multicenter, randomized study that included 335 patients with follicular lymphoma (FL) who had no response to or have progressed during or within 6 months of rituximab product or a rituximab product-containing regimen. These patients were randomized to receive either bendamustine alone (n = 171) or GAZYVA in combination with bendamustine (n = 164) 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 the type of refractoriness to rituximab product (refractory to rituximab product monotherapy versus rituximab product in combination with chemotherapy), the number of prior therapies ( $\leq 2$  versus  $> 2$ ), and geographic region.

GAZYVA was given by intravenous infusion as a flat dose of 1,000 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<sup>2</sup>/day when given in combination with GAZYVA or 120 mg/m<sup>2</sup>/day when given alone.

The primary analysis included 321 FL patients, including 166 patients randomized to bendamustine alone and 155 patients randomized to GAZYVA in combination with bendamustine. In the primary analysis, patients had a median age of 63 years, 88% were White 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 product monotherapy, 37% of patients were refractory to prior rituximab product plus chemotherapy induction treatment, and 41% of patients were refractory to rituximab product maintenance treatment received following rituximab product plus chemotherapy induction. Seventy-nine percent of patients were refractory to both rituximab product and an alkylating agent during any prior regimen (double refractory).

The major efficacy outcome measure was PFS as determined by an independent review committee (IRC). At the time of the primary analysis, 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 14. The Kaplan-Meier curve for IRC-PFS is shown in Figure 3.

**Table 14 Primary Analysis Efficacy Results from GADOLIN<sup>a, b</sup>**

Endpoint	GADOLIN	
	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 155	Bendamustine n = 166
Median Progression-Free Survival (months)	Not Reached (HR = 0.48 [0.34; 0.68], p-value < 0.0001 by stratified log-rank test)	13.8
Best Overall Response <sup>c</sup>	78.7%	74.7%
Complete Response	15.5%	18.7%
Partial Response	63.2%	56.0%
Median duration of response (months)	Not Reached	11.6

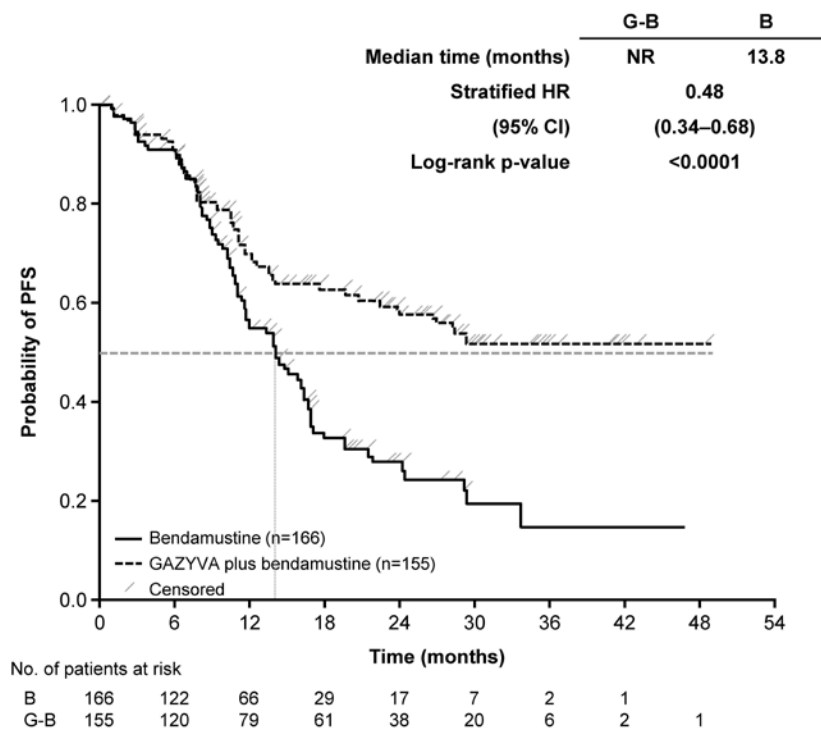
<sup>a</sup> Based on FL population.

<sup>b</sup> As defined by independent review.

<sup>c</sup> Best response of PR or CR within 12 months of study start.

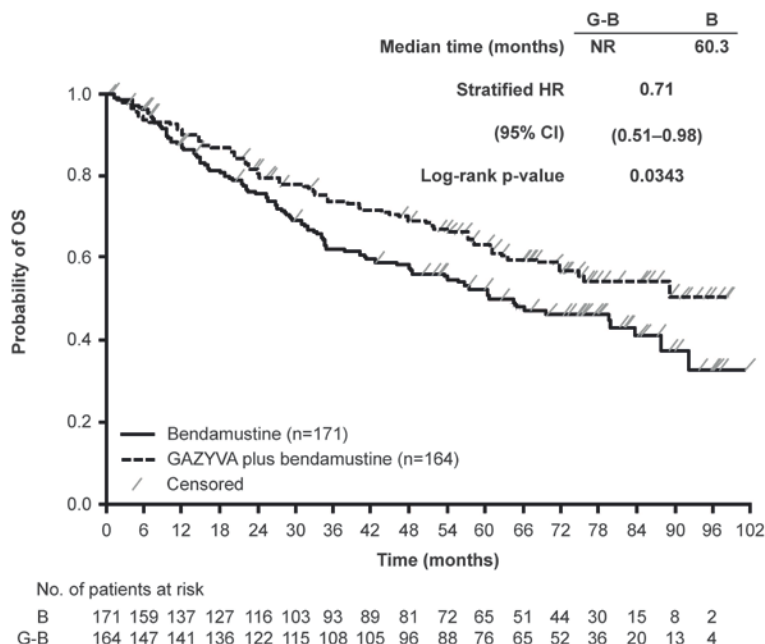
**Figure 3**

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



The final analysis included a total of 335 patients with 171 randomized to bendamustine alone and 164 to GAZYVA in combination with bendamustine. With an overall median observation time of 52.2 months (range: 0-100.9 months), there were 66 deaths (40.2%) in the GAZYVA arm and 85 deaths (51.3%) in the bendamustine-alone arm (OS HR = 0.71, 95% CI: 0.51, 0.98). The Kaplan-Meier curve for OS is presented in Figure 4.

**Figure 4**  
**Kaplan-Meier Curve of Overall Survival in Patients with FL**



### GALLIUM

The efficacy of GAZYVA was evaluated in GALLIUM (NCT01332968), a multicenter, open-label, randomized study that included 1202 patients with previously untreated, stage II bulky, III or IV FL. Patients were randomized 1:1 to receive either GAZYVA (n = 601) or rituximab product (n = 601) in combination with chemotherapy (CHOP, CVP, or bendamustine) for 6–8 cycles. Patients were stratified by chemotherapy (selected by each site; all patients at that site received the chosen chemotherapy regimen), FLIPI (Follicular Lymphoma International Prognostic Index) risk group and geographic region. Patients with at least PR to combination therapy received monotherapy with GAZYVA (1,000 mg) or rituximab product every two months until disease progression or for a maximum of two years. The study excluded patients with follicular lymphoma grade 3b or transformed disease; patients having an ANC < 1500 /  $\mu$ L, platelets < 75,000 /  $\mu$ L, or CLcr < 40 mL/min; and patients with hepatic transaminases > 2.5 x upper limit of normal unless attributable to lymphoma.

GAZYVA was given by intravenous infusion as a flat dose of 1,000 mg on Days 1, 8 and 15 of Cycle 1 and Day 1 of subsequent treatment cycles.

GAZYVA and bendamustine were given in six 28-day cycles. Bendamustine was administered at 90 mg/m<sup>2</sup>/day on Days 1 and 2 of each cycle, with prednisone 100 mg orally or equivalent on Day 1 of Cycle 1.



GAZYVA and CHOP were given in six 21-day cycles. Subsequently, two additional cycles of GAZYVA were given for a total of 8 GAZYVA cycles. CHOP consisted of cyclophosphamide 750 mg/m<sup>2</sup> intravenously, doxorubicin 50 mg/m<sup>2</sup>, and vincristine 1.4 mg/m<sup>2</sup> (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

GAZYVA and CVP were given in eight 21-day cycles. CVP consisted of cyclophosphamide 750 mg/m<sup>2</sup> intravenously and vincristine 1.4 mg/m<sup>2</sup> (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

Patients had a median age of 59 years, 81% were White and 53% were female; 7% had Stage II, 35% had Stage III, and 56% had Stage IV disease, with 44% having bulky disease ( $\geq 7$  cm) overall; 79% had a FLIPI score of  $> 2$ ; and 97% had an ECOG performance status of 0–1. The chemotherapy was bendamustine in 57%, CHOP in 33%, and CVP in 10% of patients.

Efficacy was based on PFS per IRC, with a median observation time of 38 months. Upon interim analysis, the risk of progression or death was significantly reduced in the GAZYVA containing arm compared to the rituximab product containing arm (Table 15). Kaplan-Meier curves for PFS are shown in Figure 5. Overall response and complete remission rates were similar.

**Table 15 Efficacy in Previously Untreated Follicular Lymphoma (GALLIUM)**

<b>Endpoint per IRC</b>	<b>GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 601</b>	<b>Rituximab product + chemotherapy followed by rituximab product monotherapy n = 601</b>
Progression-Free Survival <sup>a</sup> Number of events (%)	108 (18%) HR = 0.72 [95% CI: 0.56, 0.93], p-value = 0.0118 <sup>b</sup>	141 (23%)
Overall Response Rate <sup>c</sup>	91%	88%
Complete Remission Rate <sup>c</sup>	28%	27%

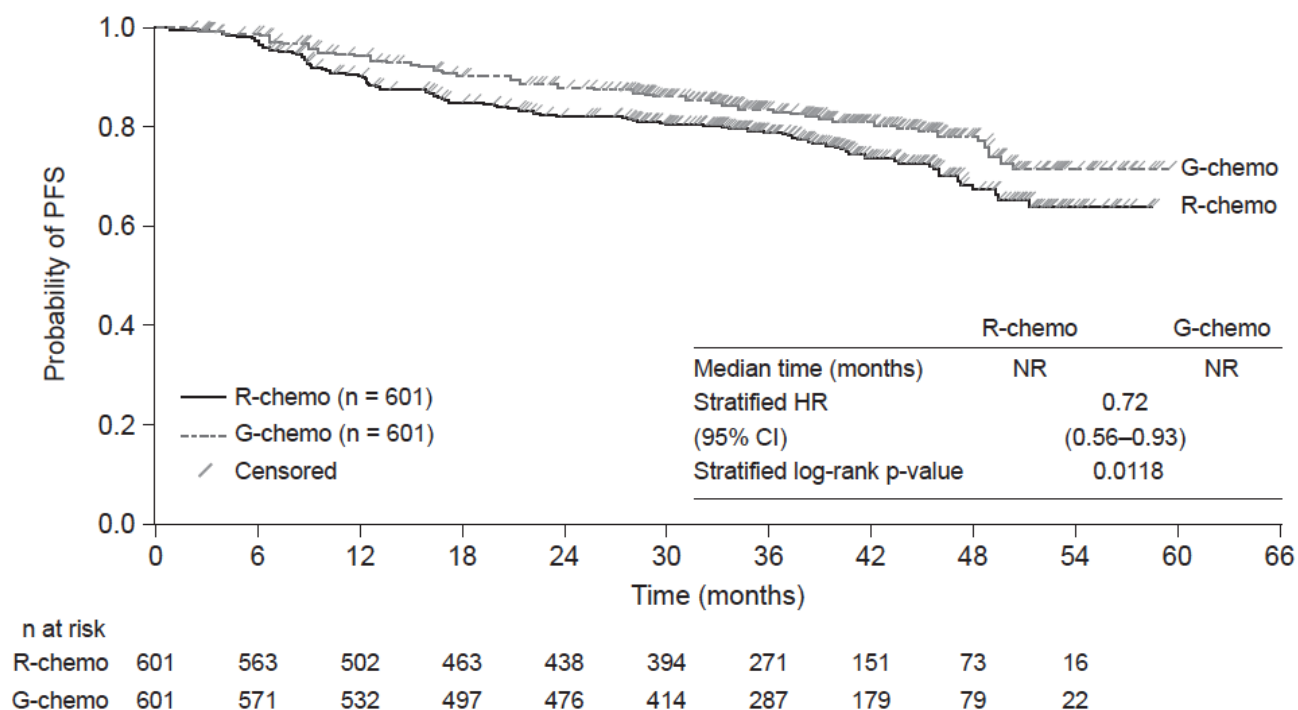
<sup>a</sup> Investigator-assessed PFS was consistent with data from independent review.

<sup>b</sup> Stratified log-rank test.

<sup>c</sup> After completion of combination therapy. Assessed by CT without positron emission tomography.

**Figure 5**

**Kaplan-Meier Curves of Progression Free Survival in Patients with Previously Untreated FL**



CI, confidence interval; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; NR, not reached; PFS, progression-free survival; R-chemo, rituximab plus chemotherapy

**16 HOW SUPPLIED/STORAGE AND HANDLING**

GAZYVA is a clear, colorless to slightly brown, preservative-free solution for intravenous use supplied as 1,000 mg/40 mL (25 mg/mL) in single-dose vials (NDC 50242-070-01).

Store at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. Protect from light. DO NOT FREEZE. DO NOT SHAKE.

**17 PATIENT COUNSELING INFORMATION**

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

- Signs and symptoms of infusion-related 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 (5.5) and Adverse Reactions (6.1)].
- Signs of infections including fever and cough [see Warnings and Precautions (5.6) 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)].
- Signs and symptoms of bleeding or thrombosis [see Warnings and Precautions (5.8 and 5.9)].

Advise patients of the need for:

- Periodic monitoring of blood counts [*see Warnings and Precautions (5.7, 5.8 and 5.9) and Adverse Reactions (6.1)*].
- Avoid vaccinations with live viral vaccines [*see Warnings and Precautions (5.10)*].
- 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. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.11), Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with GAZYVA and for 6 months after the last dose [*see Use in Specific Populations (8.3)*].

Advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose [*see Use in Specific Populations (8.2)*].

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**GAZYVA® (obinutuzumab)**

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

South San Francisco, CA 94080-4990

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