PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGAZYVA®

Obinutuzumab for injection

25 mg/mL Concentrate for Solution for Infusion

Professed Standard

Antineoplastic

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	07/2022
4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution	02/2021
7 WARNINGS AND PRECAUTIONS	05/2022
7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	02/2021
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

GAZYVA (obinutuzumab) is indicated for:

- **Chronic Lymphocytic Leukaemia (CLL)**
  - GAZYVA (obinutuzumab) in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) (see 14 CLINICAL TRIALS).

- **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 a response, is indicated for the treatment of patients with previously untreated stage II bulky (>7cm), III or IV follicular lymphoma (FL) (see 14 CLINICAL TRIALS).

1.1 Pediatrics

The safety and efficacy of GAZYVA in children below 18 years of age have not been established. Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

- Geriatrics (≥65 years of age): No significant differences in efficacy were observed between patients ≥ 65 years of age and younger patients (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations and 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

- GAZYVA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Infusion Related Reactions (IRRs)

GAZYVA can cause severe and life-threatening infusion related reactions. Monitor patients closely during infusions. Modify infusion of GAZYVA according to the Grade of reaction (see 7 WARNINGS AND PRECAUTIONS: Infusion Related Reactions and 4 DOSAGE AND ADMINISTRATION).

Hepatitis B Virus (HBV) Reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA (see 7 WARNINGS AND PRECAUTIONS: Hepatitis B Virus Reactivation).

Progressive Multifocal Leukoencephalopathy (PML)
PML can occur in patients receiving GAZYVA. Put GAZYVA treatment on hold in case of PML suspicion, until the diagnosis can be clearly established. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML (see 7 WARNINGS AND PRECAUTIONS: Progressive Multifocal Leukoencephalopathy).

Tumour Lysis Syndrome (TLS)
Serious TLS, including acute renal failure, has been reported in patients receiving GAZYVA [see 7 WARNINGS AND PRECAUTIONS: Tumour Lysis Syndrome (TLS)].

Cardiovascular
Serious cardiac events, including worsening of existing underlying cardiac disease and fatal cases, such as fatal myocardial infarctions, have been reported with GAZYVA therapy (see 7 WARNINGS AND PRECAUTIONS: Cardiovascular).

Infections
Serious and life-threatening infections, some of which resulted in death, have occurred in patients treated with GAZYVA.

Thrombocytopenia
Severe and life threatening thrombocytopenia has been observed during treatment of GAZYVA in combination with chemotherapy. Fatal haemorrhagic events have been reported in patients treated with GAZYVA in combination with chemotherapy. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. (see 7 WARNINGS AND PRECAUTIONS: Thrombocytopenia)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations
GAZYVA should be administered as an intravenous infusion through a dedicated line in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced physician. GAZYVA infusions should not be administered as an intravenous push or bolus. Isotonic 0.9% sodium chloride solution should be used as the infusion vehicle (see 4 DOSAGE AND ADMINISTRATION: 4.3 Reconstitution).

Prophylaxis and Premedication for Tumour Lysis Syndrome (TLS)
Patients with a high tumour burden and/or a high circulating lymphocyte count (>25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. *allopurinol*) or suitable alternative such as urate oxidase (e.g. *rasburicase*) prior to start of GAZYVA infusion as per standard practice (see 7 WARNINGS AND PRECAUTIONS). Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

Prophylaxis and Premedication for Infusion Related Reactions (IRRs)
Premedication to reduce the risk of infusion related reactions (see 7 WARNINGS AND PRECAUTIONS) is outlined in Table 1. Corticosteroid premedication is recommended for FL patients and mandatory for CLL patients for the first infusion. Premedication for subsequent infusions and other premedication should be administered as described below.

Hypotension, as a symptom of IR, may occur during GAZYVA intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration (see 7 WARNINGS AND PRECAUTIONS).

Table 1 Premedication to be administered before GAZYVA Infusion to reduce the risk of Infusion Related Reactions

<table>
<tr><th>Day of Treatment Cycle</th><th>Patients requiring premedication</th><th>Premedication</th><th>Administration</th></tr>
<tr><td rowspan="3">Cycle 1:

CLL
Day 1
Day 2

FL
Day 1</td><td rowspan="3">All patients</td><td>Intravenous corticosteroid[1, 2]</td><td>Completed at least 1 hour prior to GAZYVA infusion.</td></tr>
<tr><td>Oral analgesic/anti-pyretic[3]</td><td rowspan="2">At least 30 minutes before GAZYVA infusion.</td></tr>
<tr><td>Anti-histaminic drug[4]</td></tr>
<tr><td rowspan="5">All subsequent infusions: CLL and FL</td><td>Patients with no IR during the previous infusion</td><td>Oral analgesic/anti-pyretic[3]</td><td>At least 30 minutes before GAZYVA infusion.</td></tr>
<tr><td rowspan="2">Patients with an IR (Grade 1 or 2) with the previous infusion</td><td>Oral analgesic/anti-pyretic[3]</td><td rowspan="2">At least 30 minutes before GAZYVA infusion.</td></tr>
<tr><td>Anti-histaminic drug[4]</td></tr>
<tr><td rowspan="3">Patients with a Grade 3 IR with the previous infusion

OR

Patients with lymphocyte counts >25 x 10^9/L prior to next treatment</td><td>Intravenous corticosteroid[1]</td><td>Completed at least 1 hour prior to GAZYVA infusion.</td></tr>
<tr><td>Oral analgesic/anti-pyretic[3]</td><td rowspan="2">At least 30 minutes before GAZYVA infusion.</td></tr>
<tr><td>Anti-histaminic drug[3]</td></tr>
</table>

[1] 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IR.
[2] If a corticosteroid-containing chemotherapy regimen is administered on the same day as GAZYVA, the corticosteroid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional IV corticosteroid as premedication is not required.

[3] e.g. 1000 mg acetaminophen/paracetamol
[4] e.g. 50 mg diphenhydramine

Premedication for anti-microbial prophylaxis
Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be also considered. Granulocyte colony stimulating factors should be considered in patients with neutropenia if necessary.

4.2 Recommended Dose and Dosage Adjustment

Chronic Lymphocytic Leukaemia (in combination with chlorambucil[1])

Cycle 1
The recommended dosage of GAZYVA is 1000 mg administered over Day 1 and Day 2, and on Day 8 and Day 15 of the first 28 day treatment cycle as shown in Table 2.

Two infusion bags should be prepared for the first dose 100 mg for first infusion (Day 1) and 900 mg for the second infusion (Day 2). If the 100 mg dose is completed without modifications of the infusion rate or interruptions, the 900 mg dose can be administered on the same day (without dose delay) provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg, the 900 mg infusion must be administered the following day (see Table 2).

Cycle 2-6
The recommended dosage of GAZYVA is 1000 mg administered on Day 1 for each 28 day treatment cycle as shown in Table 2.

Table 2 Dose and Infusion Rate of GAZYVA for Patients with CLL

Day of Treatment Cycle		**Dose of GAZYVA**	**Rate of infusion** For management of infusion related reactions that occur during infusion, refer to Table 4.
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 1 (continued) or Day 2	900 mg	If no infusion related reaction 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 the patient experienced an infusion related reaction during the previous infusion, start administration 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.

[1] See CLINICAL TRIALS for information on chlorambucil dose.

Day of Treatment Cycle		Dose of GAZYVA	Rate of infusion For management of infusion related reactions that occur during infusion, refer to Table 4.
	Day 8	1000 mg	If no infusion related reaction occurred during the previous infusion where the final infusion rate was ≥100 mg/hr, 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. If the patient experienced an IRR 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.
	Day 15	1000 mg	
Cycles 2 – 6	Day 1	1000 mg	

Follicular Lymphoma

The recommended dosage of GAZYVA is 1000 mg administered intravenously according to Table 3.

Relapsed/Refractory Follicular Lymphoma
For patients with follicular lymphoma who have relapsed after or who are refractory to rituximab or a rituximab-containing regimen, GAZYVA should be administered in six 28 day cycles in combination with bendamustine[2]. Relapsed/Refractory patients who achieve complete or partial response or have stable disease should continue to receive GAZYVA 1000 mg monotherapy once every 2 months until disease progression or for up to 2 years.

Previously Untreated Follicular Lymphoma
For patients with previously untreated follicular lymphoma, GAZYVA should be administered with chemotherapy as follows:

- Six 28 day cycles in combination with bendamustine[3] or,
- Six 21 day cycles in combination with CHOP, followed by 2 additional cycles of GAZYVA alone or,
- Eight 21 day cycles in combination with CVP.

Previously untreated patients who achieve a complete or partial response to GAZYVA plus chemotherapy should continue to receive GAZYVA (1000 mg) alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

GAZYVA should be administered at the standard infusion rate in Cycle 1 (see Table 3). In patients who do not experience Grade ≥3 infusion related reactions (IRRs) during Cycle 1, GAZYVA may be administered as a short (approximately 90 minutes) duration infusion (SDI) from Cycle 2 onwards (see Table 4).

[2] See CLINICAL TRIALS for information on bendamustine dose.

[3] See CLINICAL TRIALS for information on bendamustine dose.

Table 3 Dose and Infusion Rate of GAZYVA for Patients with FL

Day of treatment cycle		**Dose of GAZYVA**	**Rate of infusion** For management of infusion related reactions that occur during infusion, refer to Table 5.
Cycle 1	Day 1	1000 mg	Administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 8	1000 mg	If no infusion related reaction or an infusion related reaction of Grade 1 occurred during the previous infusion, where the final infusion rate was ≥100 mg/hr, 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. If the patient experienced an infusion related reaction of Grade 2 or higher during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycles 2–6 or 2–8	Day 1	1000 mg	
Monotherapy	Every two months until progression or up to two years	1000 mg	

Table 4 Short duration infusion. Dose and infusion rate of GAZYVA for patients with FL

Day of treatment cycle		**Dose of GAZYVA**	**Rate of infusion** For management of IRRs that occur during infusion, refer to Table 5.
Cycles 2–6 or 2-8	Day 1	1000 mg	If no IRR of Grade ≥3 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 IRR occurred during the previous SDI infusion, administer obinutuzumab at the standard infusion rate (see Table 3).
Maintenance	Every 2 months until progression or up to 2 years	1000 mg	

Dosage modifications during treatment (all indications)
No dose reductions of GAZYVA are recommended.

For management of symptomatic adverse events during infusion (infusion related reactions), see Table 5 below and 7 WARNINGS AND PRECAUTIONS.

Table 5 Infusion Rate Modification Guidelines for Infusion Related Reactions (IRRs) - All Indications

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	• Temporarily interrupt infusion and treat symptoms. ○ For patients who experience Grade 3 IRRs during standard infusion upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion related reaction occurred). ○ If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 2 and Table 3). ○ For FL patients who experience Grade 3 IRRs during SDI, 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. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion must be given at the standard rate. • For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. • If the patient experiences a second occurrence of a Grade 3 infusion related reaction, stop the infusion and permanently discontinue therapy.
Grade 1-2 (mild and moderate)	• Reduce infusion rate and treat symptoms. • Upon resolution of symptoms, continue infusion. • If the patient does not experience any infusion related reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 2, Table 3 and Table 4). ○ For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Pediatrics

The safety and efficacy of GAZYVA in children below 18 years of age have not been established. Health Canada has not authorized an indication for pediatric use.

Geriatrics

No dose adjustment is required in elderly patients (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. GAZYVA has not been studied in patients with a CrCl <30 mL/min (see 7 WARNINGS AND PRECAUTIONS: 7.1 Special Populations and 10 CLINICAL PHARMACOLOGY).

Hepatic Impairment
The safety and efficacy of GAZYVA in patients with hepatic impairment have not been established.

4.3 Reconstitution
Parenteral Products:

Instructions for dilution

GAZYVA should be prepared by a health professional using aseptic technique. Use a sterile needle and syringe to prepare GAZYVA.

For CLL cycles 2 – 6 and all FL cycles
Withdraw 40 mL of GAZYVA liquid concentrate from the vial and dilute in PVC or non-PVC polyolefin infusion bags containing sterile, non-pyrogenic 0.9% aqueous sodium chloride solution.

For preparation of infusion bags for CLL only Cycle 1, Day 1 dose administered over 2 days
To ensure differentiation of the two infusion bags for the initial 1000 mg dose, the recommendation is to use bags of different sizes to distinguish between the 100 mg dose for Cycle 1 Day 1 and the 900 mg dose for Cycle 1 Day 1 (continued) or Day 2. To prepare the 2 infusion bags, withdraw 40 mL of GAZYVA liquid concentrate from vial and dilute 4 mL into a 100 mL infusion bag and the remaining 36 mL in a 250 mL PVC or non-PVC polyolefin infusion bags containing sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Clearly label each infusion bag.

Table 6 Reconstitution

Dose of GAZYVA to be Administered	Required Amount of GAZYVA Liquid Concentrate	Size of PVC or non-PVC polyolefin infusion bag
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
1000 mg	40 mL	250 mL

Vial size: 50 mL
Available volume: 40 mL
Concentration: 25 mg/mL

Do not use other diluents such as Dextrose (5%) solution (see Incompatibilities).

The bag should be gently inverted to mix the solution in order to avoid excessive foaming.

Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

Incompatibilities
There are no incompatibilities between GAZYVA and the following compounds, as they have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of GAZYVA with 0.9% sodium chloride:

- polyvinyl chloride, polyethylene, polypropylene or polyolefin bags
- polyvinyl chloride (PVC), polyurethane (PUR) or polyethylene (PE) infusion sets
- optional inline filters with product contact surfaces of polyethersulfon (PES)
- a 3-way stopcock infusion aid made from polycarbonate (PC)
- catheters made from polyetherurethane (PEU)

Diluted product should not be shaken or frozen.

Do not use other diluents such as Dextrose (5%) solution to dilute GAZYVA since its use has not been tested.

Storage
Store vials in a refrigerator at 2 - 8°C. Chemical and physical in-use stability has been demonstrated for 24 hours at 2 - 8°C followed by 24 hours at ambient temperature (≤ 30°C) followed by an infusion taking no longer than 24 hours (see **Error! Reference source not found.** STORAGE, STABILITY AND DISPOSAL).

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions (see **Error! Reference source not found.** STORAGE, STABILITY AND DISPOSAL).

4.4 Administration
Therapy with GAZYVA should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

4.5 Missed Dose

Delayed or missed doses
Chronic Lymphocytic Leukaemia
If a planned dose of GAZYVA is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for GAZYVA should be maintained between doses.

Follicular Lymphoma
If a planned dose of GAZYVA is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose.

If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, requiring delay of treatment, these doses should be given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1.

During monotherapy, maintain the original dosing schedule for subsequent doses.

5 OVERDOSAGE

No experience with overdosage is available from human clinical trials. In clinical trials with GAZYVA (obinutuzumab), doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 7 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Concentrate for solution for infusion 1000 mg obinutuzumab / 40 mL (25 mg.mL)	L-histidine, L-histidine hydrochloride, poloxamer 188, trehalose, water for injection.

GAZYVA is a clear, colourless to slightly brownish liquid supplied as a single 1000 mg dose in a sterile, preservative free, non-pyrogenic 50 mL glass vial containing 40 mL of liquid concentrate (25 mg/mL).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Therapy with GAZYVA should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Cardiovascular

Serious cardiovascular events including fatal myocardial infarction, dysrhythmias, tachycardia, heart failure, acute coronary syndrome, angina pectoris, and cerebrovascular accident have occurred more frequently in patients treated with GAZYVA as compared to those treated in control arm (see 8 ADVERSE REACTIONS). These events may occur as part of an infusion related reaction, may be fatal, and occur in patients who have existing cardiovascular diseases. Patients with a history of cardiac

disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload (see 8 ADVERSE REACTIONS).

Driving and Operating Machinery

No studies on the effects of GAZYVA on the ability to drive and to use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

Endocrine and Metabolism

Tumour Lysis Syndrome (TLS)

Acute renal failure, hyperkalaemia, hypocalcaemia, hyperuricemia, and/or hyperphosphatemia consistent with Tumour Lysis Syndrome can occur within 12-24 hours after the first infusion of GAZYVA. Patients with higher tumour burden and/or high circulating lymphocyte count (>25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are at greater risk for TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g., allopurinol) or a suitable alternative such as a urate oxidate (e.g. *rasburicase*) starting 12-24 hours prior to the infusion of GAZYVA as per standard practice (see 4 DOSAGE AND ADMINISTRATION). All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Gastrointestinal

Serious cases of gastro-intestinal perforation have been reported in patients receiving GAZYVA, mainly in patients with Non-Hodgkin lymphoma (NHL) (see 8 ADVERSE REACTIONS).

Hematologic

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) has been reported in patients receiving GAZYVA for treatment of chronic lymphocytic leukemia and follicular lymphoma. In the majority of cases, the events have involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion. In some cases, the events were associated with IRRs and/or TLS. Serious and/or fatal coagulation abnormalities including DIC have occurred during treatment with GAZYVA. (see 8 ADVERSE REACTIONS).

Neutropenia

Severe and life-threatening (Grade 3 or 4) neutropenia occurred in more than one third of patients receiving GAZYVA (with normal neutrophils at baseline). Febrile neutropenia, worsening existing neutropenia and prolonged (lasting more than 28 days) or late onset neutropenia (occurring 28 days or later after completion of treatment) were also observed.

Blood cell counts should be closely monitored with regular laboratory tests until resolution in patients receiving GAZYVA. Granulocyte colony stimulating factors should be considered in patients with neutropenia if necessary. Dose delays in the case of Grade 3 or 4 neutropenia should be considered. Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis (as appropriate). Antiviral and antifungal prophylaxis should be considered as well.

Thrombocytopenia
Severe and life-threatening thrombocytopenia can occur during treatment with GAZYVA in combination with chemotherapy. Fatal haemorrhagic events have been reported in patients with NHL and CLL treated with GAZYVA in combination with chemotherapy, including during Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

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

B-cell Depletion
Due to the mechanism of action of GAZYVA, anti-CD20 antibody induced B-cell depletion with GAZYVA is expected. The majority of CLL and NHL patients with their B-cell assessed (40/44 in CLL and 732/743 in NHL) had peripheral B-cell depletion at the last dose of GAZYVA.

Immune
Anti-obinutuzumab Antibodies
Patients treated with GAZYVA may develop anti-obinutuzumab antibodies. No clinical or pharmacokinetic consequences of these antibodies have been identified.

Hepatitis B Virus (HBV) 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. Patients with active hepatitis B disease should not be treated with GAZYVA. Patients with positive hepatitis B serology (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), should consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

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

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

Hypersensitivity Reactions
Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with GAZYVA. If a hypersensitivity reaction is suspected during or after an infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. Patients with known hypersensitivity to GAZYVA must not be treated (see 2 CONTRAINDICATIONS). Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

Immunization
The safety of immunization with live or attenuated viral vaccines, following GAZYVA therapy has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery. Treatment with GAZYVA following vaccination should only commence once protective antibody titres have been reached.

Exposure in utero to GAZYVA and vaccination of infants with live virus vaccines:
Due to the potential depletion of B cells in infants of mothers who have been exposed to GAZYVA during pregnancy, the safety and timing of vaccinations with live virus vaccines should be discussed with the child's healthcare provider. Postpone vaccination with live vaccines for infants born to mothers who have been exposed to GAZYVA during pregnancy until the infants' B cell levels are within normal ranges (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women).

Infections
Serious and fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of GAZYVA therapy. When GAZYVA is administered in combination with chemotherapy followed by GAZYVA monotherapy, there is a high risk of infections, especially during the GAZYVA monotherapy phase and after treatment. In FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. A higher incidence of severe, life-threatening and fatal (Grade 3-5) infections was observed in patients treated with GAZYVA and bendamustine, as compared to GAZYVA plus CHOP or CVP, including during the monotherapy phase and after completion of treatment. GAZYVA should not be administered in the presence of an active infection and caution should be exercised when considering the use of GAZYVA in patients with a history of recurring or chronic infections.

Infusion Related **Reactions (IRRs)**
GAZYVA can cause severe and life-threatening infusion related reactions, including anaphylaxis. Infusion related reactions are the most frequently observed adverse drug reactions (ADRs) in patients receiving GAZYVA. GAZYVA-associated infusion related reactions occurred predominantly during infusion of the first 1000 mg. The most frequently reported symptoms of infusion related reaction include nausea, fatigue, chest discomfort, dyspnoea, dizziness, vomiting, diarrhoea, constipation, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills (see 8 ADVERSE DRUG REACTIONS). Severe infusion related reactions including respiratory and cardiac symptoms such as, bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema, atrial fibrillation, and anaphylactic reactions

have been reported in patients treated with GAZYVA. If the symptoms occur, they should be treated as appropriate and infusion should be stopped or the rate of the infusion should be decreased (see Table 2, Table 3, Table 4 and Table 5 in 4 DOSAGE AND ADMINISTRATION).

Patients with a high tumour burden (i.e. high circulating lymphocyte count in CLL (> 25 x 10^9/L)) may be at increased risk of severe infusion related reactions. Splitting the first treatment over two days and premedication may attenuate infusion related reactions. In patients who received the combined measures for prevention of infusion related reactions (corticosteroids, oral analgesic/anti-histamine, omission of antihypertensive medication in the morning of the first infusion, infusion of the first 100 mg at 25 mg/hr, and the Cycle 1, Day 1 dose administered over 2 days, as described in 4 DOSAGE AND ADMINISTRATION), decreased incidence of all Grades IRRs was observed. The rates of Grade 3 to 4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. Mitigation measures to reduce IRRs (see 4 DOSAGE AND ADMINISTRATION: Table 2, Table 3, Table 4 and Table 5) should be followed. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with no Grade 3 to 5 IRRs reported and most patients having no IRRs during subsequent administrations of GAZYVA (see 8 ADVERSE REACTIONS).

For Grade 3 infusion related reactions, the infusion of GAZYVA should be interrupted or permanently discontinued and for Grade 4 infusion related reactions, the infusion of GAZYVA must be permanently discontinued (see 4 DOSAGE AND ADMINISTRATION: Table 5). GAZYVA infusion should be permanently discontinued if patients experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e. life threatening) infusion related reaction or,
- a second occurrence of a Grade 3 (prolonged/recurrent) infusion related reaction (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period (see 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION). Hypotension may occur during GAZYVA intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Progressive Multifocal Leukoencephalopathy (PML)
PML has been observed in patients treated with GAZYVA. JC virus infection resulting in PML, which can be fatal, was observed in patients treated with GAZYVA. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are non-specific and can vary. Common symptoms include muscular weakness, paralysis, sensory abnormalities, cerebellar symptoms, and visual field defects. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (CSF testing for JC viral DNA). Therapy with GAZYVA should be withheld during the investigation of potential PML. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Reproductive Health: Female and Male Potential

Women of child bearing potential should use effective contraception while receiving GAZYVA and for 18 months following treatment with GAZYVA (see 7.1.1 Pregnant Women and 10 CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics).

- **Fertility**

No specific studies in animals have been performed to evaluate the effect of obinutuzumab on fertility. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in cynomolgus monkeys.

- **Teratogenic Risk**

An enhanced pre- and postnatal development (ePPND) toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received weekly intravenous obinutuzumab doses during gestation (organogenesis period; post-coitum days 20 through delivery). Exposed offspring did not exhibit any teratogenic effects but B-cells were completely depleted on day 28 postpartum. Offspring exposures on day 28 postpartum suggest that obinutuzumab can cross the blood-placenta-barrier. Concentrations in infant serum on day 28 postpartum, were in the range of concentrations in maternal serum, whereas concentrations in milk on the same day were very low (less than 0.5% of the corresponding maternal serum levels) suggesting that exposure of infants must have occurred in utero. B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

7.1 Special Populations

7.1.1 Pregnant Women

GAZYVA has not been studied in pregnant women. A reproduction study in cynomolgus monkeys showed no evidence of embryofoetal toxicity or teratogenic effects but resulted in a complete depletion of B-lymphocytes in offspring. B-cell counts returned to normal levels in the offspring, and B-cell counts and immunologic function were restored within 6 months of birth (see 16 NON-CLINICAL TOXICOLOGY). Furthermore, the serum concentrations of GAZYVA in offspring were similar to those in the mothers on day 28 post-partum, whereas concentrations in milk on the same day were very low, suggesting that GAZYVA crosses the placenta.

GAZYVA should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of child bearing potential should use effective contraception while receiving GAZYVA and for 18 months following treatment with GAZYVA (see 10 CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics).

Due to the potential depletion of B cells in newborns following exposure to GAZYVA during pregnancy, newborns should be monitored for B cell depletion. Postpone vaccination with live virus vaccines until the infants' B cell levels are within normal ranges (see 7 WARNINGS AND PRECAUTIONS, Immunization).

7.1.2 Breast-feeding

Since human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during GAZYVA therapy and for 18 months after the last dose of GAZYVA (see 10 CLINICAL PHARMACOLOGY: 10.3 Pharmacokinetics). Animal studies have shown excretion of GAZYVA in breast milk (see 16 NON-CLINICAL TOXICOLOGY).

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Chronic Lymphocytic Leukaemia
In study BO21004 in previously untreated CLL, 79% (526 out of 663) of patients were ≥ 65 years; 46% (156 out of 336) of patients with chronic lymphocytic leukaemia treated with GAZYVA plus chlorambucil were 75 years old or older (median age was 74 years). Patients ≥ 75 years of age experienced more serious adverse events (46% vs. 33%) and adverse events leading to death (7% vs. 2%) than those of patients < 75 years of age. No significant differences in efficacy were observed between patients ≥ 75 years of age and those < 75 years of age (see 14 CLINICAL TRIALS).

Non-Hodgkin Lymphoma
In study GAO4753g in relapsed/refractory indolent Non-Hodgkin Lymphoma (iNHL), 43% (87 out of 204) of patients treated with GAZYVA plus bendamustine were 65 years of age or older. The patients over 65 years and older experienced higher incidence of SAEs (55% vs 30%), AE leading to death (10% vs 5%) and AE leading to withdrawal (26% vs 12%) than in the younger patients treated with GAZYVA plus bendamustine.

A final analysis was performed after a median follow-up of 24.1 months. Forty-four percent (89 out of 204) of patients treated with GAZYVA plus bendamustine were 65 years of age or older. The patients over 65 years and older experienced higher incidence of SAEs (55% vs 37%), AEs with fatal outcome (14% vs 7%) and AEs leading to withdrawal from any study treatment (28% vs 14%) than in the younger patients (age <65 years) treated with GAZYVA plus bendamustine.

The most common SAEs in patients aged ≥65 years were neutropenia, febrile neutropenia, pyrexia, pneumonia, sepsis, and infusion related reactions. The efficacy results had no clinically meaningful difference between the age groups in study GAO4753g.

Of the 698 iNHL patients in study BO21223 treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 years and over, while 7% were 75 years and over. In patients 65 years and over, 63% of patients experienced serious adverse events, 10% experienced AE leading to death and 27% experienced adverse events leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse events, 3% experienced AE leading to death and 13% had an adverse event leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients in study BO21223.

7.1.5 Renal Impairment

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 27% (90 out of 336) of patients treated with GAZYVA plus chlorambucil had moderate renal impairment (creatinine clearance (CrCl) < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those associated with CrCl ≥ 50 mL/min. The frequencies of serious adverse events and adverse events leading to death were 49% and 7% respectively in patients with moderate renal impairment (creatinine clearance < 50 mL/min) and 35% and 4% respectively in patients with creatinine clearance ≥ 50 mL/min (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY). No significant differences in efficacy were observed between patients with CrCl < 50 mL/min and those with CrCl ≥ 50 mL/min. Patients with CrCl <30 mL/min were excluded from the study (see 14 CLINICAL TRIALS).

Non-Hodgkin Lymphoma

In the pivotal studies in iNHL, 8% patients (GAO4753g: 14 out of 204) and 5% patients (BO21223: 35 out of 698) had moderate renal impairment (CrCl <50 mL/min). These patients experienced more serious adverse events, Grade 3 to 5 adverse events and adverse events leading to treatment withdrawal (patients in Study BO21223 only) than patients with CrCl ≥50 mL/min (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY). Patients with CrCl <40 mL/min were excluded from the study (see 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Chronic Lymphocytic Leukaemia

The most common (≥ 10%) treatment-related adverse drug reactions in clinical trial BO21004/CLL11 (stage 2) during treatment were as follows: infusion related reactions (IR), neutropenia, thrombocytopenia, and diarrhoea. The most frequently observed serious adverse event (≥ 5%) that occurred in patients treated with GAZYVA plus chlorambucil in clinical trial BO21004/CLL11 (stage 2) were IRRs. There were no fatal IRRs reported in study BO21004/CLL11.

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

The safety data presented for relapsed/refractory iNHL comes from the primary analysis of study GAO4753g, in which GAZYVA was given in combination with bendamustine as induction therapy followed by GAZYVA monotherapy. The most common adverse drug reactions (incidence ≥ 10%) observed in patients with iNHL in study GAO4753g were infusion related reactions, neutropenia, cough, constipation, pyrexia, upper respiratory tract infection, arthralgia, sinusitis and asthenia. The most frequently observed serious adverse events (≥ 2%) that occurred in patients treated with GAZYVA plus bendamustine in study GAO4753g were febrile neutropenia, neutropenia, sepsis, IRR, pyrexia, pneumonia and thrombocytopenia.

In the final analysis of study GAO4753g, the most common adverse drug reactions (incidence ≥ 10%) observed in patients with iNHL, in addition to those noted from the primary analysis, were thrombocytopenia, anemia, nausea, diarrhea, vomiting, fatigue, chills, bronchitis, urinary tract infection, nasopharyngitis, decreased appetite, pain in extremity, insomnia, headache, dyspnea, rash,

pruritus, and hypotension. The most frequently observed serious adverse events (≥ 2%) that occurred in patients treated with GAZYVA plus bendamustine in study GAO4753g were the same as those noted in the primary analysis.

Previously Untreated Indolent Non-Hodgkin Lymphoma

The safety data presented for previously untreated iNHL comes from study BO21223, in which patients were treated with either GAZYVA or rituximab in combination with chemotherapy followed by GAZYVA or rituximab monotherapy in responding patients every two months until disease progression or for a maximum of two years. The most common related adverse drug reactions (incidence ≥ 10%) observed in the GAZYVA-containing arm of study BO21223 were infusion related reactions, neutropenia, nausea, fatigue, pyrexia, constipation, vomiting, chills, alopecia, diarrhoea, dyspnoea, leukopenia, thrombocytopenia, and headache. The most frequently observed serious adverse events (≥ 2%) that occurred in patients treated with GAZYVA plus chemotherapy in study BO21223 were neutropenia, febrile neutropenia, pyrexia, pneumonia, sepsis, and infusion related reactions.

For information on important ADRs see 8 ADVERSE REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Chronic Lymphocytic Leukaemia

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up from the pivotal clinical trial, BO21004/CLL11, in which GAZYVA was given in combination with chlorambucil compared to chlorambucil alone (stage 1a) or compared to rituximab plus chlorambucil (stage 2).

The adverse events that occurred in ≥ 1% of patients receiving GAZYVA plus chlorambucil are summarized in Table 8 (Study BO21004/CLL11 Stage 1a) and Table 9 (Study BO21004/CLL11 Stage 2).

Table 8 Summary of Adverse Events occurring in ≥1% of Patients receiving GAZYVA plus Chlorambucil (Study BO21004/CLL11 Stage 1a)[1]

Adverse Event (MedDRA) System Organ Class	All Grades n (%)[2]		Grades 3-5 n (%)[2]	
	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241
Blood and lymphatic system disorders				

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241
Neutropenia	21 (18)	98 (41)	18 (16)	84 (35)
Thrombocytopenia	9 (8)	37 (15)	5 (4)	27 (11)
Anaemia	12 (10)	30 (12)	5 (4)	11 (5)
Leukopenia	–	17 (7)	–	13 (5)
Febrile neutropenia	5 (4)	6 (2)	5 (4)	4 (2)
Haematotoxicity	–	3 (1)	–	3 (1)
Lymphopenia	–	3 (1)	–	–
Pancytopenia	–	3 (1)	–	–
Cardiac disorders				
Cardiac failure	3 (3)	4 (2)	2 (2)	3 (1)
Myocardial infarction	2 (2)	4 (2)	2 (2)	3 (1)
Atrial fibrillation	–	5 (2)	–	–
Cardiac failure congestive	–	3 (1)	–	–
Ear and labyrinth disorders				
Vertigo	3 (3)	3 (1)	–	–
Gastrointestinal Disorders				
Nausea	29 (25)	32 (13)	–	–
Diarrhoea	13 (11)	25 (10)	1 (<1)	6 (2)
Constipation	12 (10)	17 (7)	–	–
Vomiting	14 (12)	13 (5)	–	–
Abdominal pain	6 (5)	11 (5)	–	–
Abdominal pain upper	5 (4)	8 (3)	–	–
Dyspepsia	4 (3)	6 (2)	–	–
Stomatitis	2 (2)	5 (2)	–	–
Dry mouth	–	4 (2)	–	–
Haemorrhoids	1 (<1)	3 (1)	–	–
General disorders and administration site conditions				
Pyrexia	8 (7)	25 (10)	–	–
Fatigue	12 (10)	17 (7)	–	3 (1)
Asthenia	8 (7)	18 (7)	–	–
Oedema peripheral	4 (3)	7 (3)	–	–
Chest pain	2 (2)	7 (3)	–	–
Chills	–	4 (2)	–	–
Oedema peripheral	4 (3)	7 (3)	–	–
Chest pain	2 (2)	7 (3)	–	–
Chills	–	4 (2)	–	–
Infections and infestations				
Nasopharyngitis	8 (7)	17 (7)	–	–
Urinary tract infection	3 (3)	15 (6)	1 (<1)	4 (2)
Pneumonia	4 (3)	12 (5)	4 (3)	8 (3)
Bronchitis	8 (7)	11 (5)	–	–
Oral herpes	1 (<1)	9 (4)	–	–
Respiratory tract infection	4 (3)	8 (3)	–	–

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241
Upper respiratory tract infection	5 (4)	5 (2)	–	–
Rhinitis	1 (<1)	5 (2)	–	–
Pharyngitis	–	5 (2)	–	–
Herpes simplex	3 (3)	4 (2)	–	–
Herpes zoster	1 (<1)	4 (2)	–	–
Lower respiratory tract infection	1 (<1)	4 (2)	–	–
Cystitis	1 (<1)	3 (1)	–	–
Neutropenic sepsis	–	3 (1)	–	3 (1)
Injury, Poisoning and Procedural Complications				
Infusion related reactions	–	166 (69)	–	51 (21)
Excoriation	–	3 (1)	–	–
Investigations				
White blood cell count decreased	1 (<1)	5 (2)	–	5 (2)
Neutrophil count decreased	–	5 (2)	–	5 (2)
Weight increased	–	5 (2)	–	–
Alanine aminotransferase increased	1 (<1)	3 (1)	–	–
Weight decreased	3 (3)	3 (1)	–	–
Platelet count decreased	2 (2)	3 (1)	–	–
Metabolism and nutrition disorders				
Tumour lysis syndrome	1 (<1)	10 (4)	–	4 (2)
Decreased appetite	9 (8)	8 (3)	–	–
Hyperuricaemia	–	8 (3)	–	–
Hyperkalaemia	2 (2)	5 (2)	–	–
Hyperglycaemia	–	4 (2)	–	4 (2)
Dehydration	–	3 (1)	–	–
Hypocalcaemia	–	3 (1)	–	–
Musculoskeletal and connective tissue disorders				
Back pain	2 (2)	12 (5)	–	–
Arthralgia	3 (3)	11 (5)	–	–
Pain in extremity	3 (3)	7 (3)	–	–
Musculoskeletal pain	2 (2)	6 (2)	–	–
Musculoskeletal chest pain	–	6 (2)	–	–
Bone pain	–	4 (2)	–	–
Muscle spasms	2 (2)	3 (1)	–	–
Neoplasms benign, malignant & unspecified (incl cysts & polyps)				

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241	Chlorambucil n = 116	GAZYVA + Chlorambucil n = 241
Squamous cell carcinoma of skin	–	5 (2)	-	3 (1)
Basal cell carcinoma	–	3 (1)	–	–
Nervous system disorders				
Headache	8 (7)	18 (7)	–	–
Dizziness	5 (4)	10 (4)	–	–
Dysgeusia	3 (3)	6 (2)	–	–
Paraesthesia	2 (2)	3 (1)	–	–
Cerebrovascular accident	–	3 (1)	–	3(1)
Psychiatric disorders				
Insomnia	5 (4)	9 (4)	–	–
Anxiety	–	3 (1)	–	–
Restlessness	–	3 (1)	–	–
Respiratory, thoracic and mediastinal disorders				
Cough	8 (7)	23 (10)	–	–
Epistaxis	2 (2)	6 (2)	–	–
Dyspnoea	8 (7)	5 (2)	–	–
Bronchitis chronic	1 (<1)	4 (2)	–	–
Oropharyngeal pain	4 (3)	3 (1)	–	–
Dysphonia	1 (<1)	3 (1)	–	–
Pleural effusion	–	3 (1)	–	–
Renal and urinary disorders				
Dysuria	1 (<1)	3 (1)	–	–
Skin and subcutaneous tissue disorders				
Pruritus	5 (4)	9 (4)	–	–
Rash	3 (3)	8 (3)	–	–
Alopecia	–	5 (2)	–	–
Dry skin	1 (<1)	3 (1)	–	–
Vascular disorders				
Hypertension	2 (2)	9 (4)	2 (2)	4 (2)
Hypotension	–	3 (1)	–	–

[1] In all grades or Grade 3-5.

[2] NCI-CTCAE version 4.0

Table 9 Summary of Adverse Events occurring in ≥1% of Patients receiving GAZYVA plus Chlorambucil (Study BO21004/CLL11 Stage 2)[1]

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336
Blood and lymphatic system disorders				
Neutropenia	103 (32)	128 (38)	91 (28)	111 (33)
Thrombocytopenia	21 (7)	48 (14)	10 (3)	35 (10)
Anaemia	35 (11)	37 (11)	12 (4)	14 (4)
Leukopenia	6 (2)	21 (6)	3 (<1)	15 (4)
Febrile neutropenia	4 (1)	10 (3)	4 (1)	8 (2)
Haematotoxicity	1 (<1)	5 (1)	-	5 (1)
Cardiac disorders				
Cardiac failure	3 (<1)	5 (1)	-	-
Atrial fibrillation	2 (<1)	5 (1)	-	-
Tachycardia	2 (<1)	4 (1)	-	-
Myocardial infarction	-	4 (1)	-	-
Ear and labyrinth disorders				
Vertigo	7 (2)	5 (1)	-	-
Gastrointestinal disorders				
Nausea	42 (13)	40 (12)	-	-
Diarrhoea	24 (7)	34 (10)	1 (<1)	7 (2)
Constipation	16 (5)	28 (8)	-	-
Vomiting	22 (7)	19 (6)	-	-
Abdominal pain	10 (3)	14 (4)	-	-
Abdominal pain upper	6 (2)	9 (3)	-	-
Dyspepsia	8 (2)	7 (2)	-	-
Stomatitis	7 (2)	6 (2)	-	-
Haemorrhoids	2 (<1)	5 (1)	-	-
Dry mouth	–	5 (1)	-	-
General disorders and administration site conditions				
Pyrexia	24 (7)	29 (9)	-	-
Fatigue	30 (9)	27 (8)	-	-
Asthenia	25 (8)	23 (7)	-	-
Oedema peripheral	17 (5)	11 (3)	-	-
Chest pain	9 (3)	8 (2)	-	-
Chills	5 (2)	5 (1)	-	-
Pain	3 (<1)	4 (1)	-	-
Infections and infestations				
Nasopharyngitis	10 (3)	19 (6)	-	-
Urinary tract infection	5 (2)	18 (5)	2 (<1)	5 (1)
Pneumonia	20 (6)	17 (5)	17 (5)	13 (4)
Bronchitis	16 (5)	12 (4)	-	-
Oral herpes	5 (2)	11 (3)	-	-

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336
Respiratory tract infection	7 (2)	9 (3)	-	-
Upper respiratory tract infection	15 (5)	8 (2)	-	-
Rhinitis	5 (2)	6 (2)	-	-
Herpes simplex	3 (<1)	7 (2)	-	-
Herpes zoster	5 (2)	4 (1)	-	-
Infection	4 (1)	4 (1)	-	-
Lower respiratory tract infection	3 (<1)	5 (1)	-	-
Pharyngitis	3 (<1)	5 (1)	-	-
Injury, poisoning and procedural complications				
Infusion related reactions	121 (38)	221 (66)	12 (4)	67 (20)
Fall	5 (2)	6 (2)	-	-
Excoriation	-	4 (1)	-	-
Investigations				
Neutrophil count decreased	2 (<1)	5 (1)	2 (<1)	5 (1)
White blood cell count decreased	1 (<1)	5 (1)	1 (<1)	5 (1)
Weight increased	-	5 (1)	-	-
Weight decreased	6 (2)	4 (1)	-	-
Alanine aminotransferase increased	2 (<1)	4 (1)	-	-
Platelet count decreased	1 (<1)	4 (1)	-	-
Metabolism and nutrition disorders				
Decreased appetite	9 (3)	10 (3)	-	-
Hyperuricaemia	2 (<1)	8 (2)	-	-
Hyperkalaemia	3 (<1)	6 (2)	-	-
Hyperglycaemia	3 (<1)	5 (1)	2 (<1)	4 (1)
Hypocalcaemia	-	5 (1)	-	-
Dehydration	-	4 (1)	-	-
Musculoskeletal and connective tissue disorders				
Back pain	9 (3)	16 (5)	-	-
Arthralgia	8 (2)	16 (5)	-	-
Pain in extremity	7 (2)	7 (2)	-	-
Musculoskeletal pain	3 (<1)	7 (2)	-	-
Musculoskeletal chest pain	1 (<1)	7 (2)	-	-
Bone pain	5 (2)	5 (1)	-	-
Nervous system disorders				
Headache	18 (6)	21 (6)	-	-
Dizziness	8 (2)	12 (4)	-	-
Dysgeusia	2 (<1)	6 (2)	-	-
Paraesthesia	1 (<1)	5 (1)	-	-

Adverse Event (MedDRA) System Organ Class	All Grades n (%) [2]		Grades 3-5 n (%) [2]	
	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336	rituximab + Chlorambucil n = 321	GAZYVA + Chlorambucil n = 336
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Squamous cell carcinoma of skin	3 (<1)	5 (1)	-	-
Basal cell carcinoma	1 (<1)	4 (1)	-	-
Psychiatric disorders				
Insomnia	9 (3)	12 (4)	-	-
Anxiety	4 (1)	4 (1)	-	-
Renal and urinary disorders			-	-
Pollakiuria	1 (<1)	4 (1)	-	-
Respiratory, thoracic and mediastinal disorders				
Cough	19 (6)	25 (7)	-	-
Dyspnoea	13 (4)	9 (3)	-	-
Epistaxis	5 (2)	8 (2)	-	-
Bronchitis chronic	-	4 (1)	-	-
Skin and subcutaneous tissue disorders				
Pruritus	11 (3)	11 (3)	-	-
Rash	19 (6)	8 (2)	-	-
Alopecia	1 (<1)	6 (2)	-	-
Vascular disorders				
Hypertension	6 (2)	9 (3)	3 (<1)	4 (1)
Hypotension	6 (2)	4 (1)	-	-

[1]In all Grades or Grade 3-5.

[2] NCI-CTCAE version 4.0

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

The adverse drug reactions (ADRs) described in this section is based on a safety population of 392 patients with iNHL (of whom 81% had FL) from the primary analysis (cut-off date 01 September 2014) of the pivotal open-label multicentre, randomized trial, GAO4753g. GAZYVA was given in combination with bendamustine during induction and as GAZYVA monotherapy, and compared to bendamustine during induction alone. The safety data from study GAO4753g were collected during induction, monotherapy and follow-up in patients who had received at least one dose of treatment.

In the subgroup of patients with FL, the profile of adverse reactions was consistent with the overall iNHL population.

In patients treated with GAZYVA plus bendamustine, 79% received all 6 treatment cycles of GAZYVA and 76% received all 6 cycles of bendamustine compared to 67% of patients in the bendamustine-only arm in the induction phase. One hundred and forty-three patients in the GAZYVA plus bendamustine

arm continued with GAZYVA monotherapy of which 97% (139 patients) received ≥90% of planned GAYZVA during the monotherapy phase.

A final analysis of the pivotal open-label multicentre, randomized trial, GAO4753g was performed after a median follow-up of 24.1 months. At the final analysis (cut-off date 30 November 2018), the safety population consisted of 407 patients with iNHL (of whom 81% has FL). In patients treated with GAZYVA plus bendamustine, 82% received all 6 treatment cycles of GAZYVA and 78% received all 6 cycles of bendamustine compared to 72% of patients in the bendamustine-only arm in the induction phase. One hundred and fifty-eight patients in the GAZYVA plus bendamustine arm continued with GAZYVA monotherapy of which 98% (155 patients) received ≥90% of planned GAYZVA during the monotherapy phase.

Table 10 summarises the adverse events that occurred in ≥ 1% of patients receiving GAZYVA plus bendamustine.

Table 10 Summary of Adverse Events occurring in ≥ 1% of Patients receiving GAZYVA plus Bendamustine (Study GAO4753g) (cut-off date: 01 September 2014)

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Blood & Lymphatic system disorders				
Neutropenia	56 (28)	68 (35)	52 (26)	64 (33)
Thrombocytopenia	47 (24)	28 (14)	32 (16)	20 (10)
Anaemia	29 (15)	22 (11)	19 (10)	14 (7)
Febrile neutropenia	7 (4)	9 (5)	7 (3)	9 (5)
Lymph node pain	-	4 (2)	-	-
Leukopenia	4 (2)	3 (2)	3 (2)	2 (1)
Pancytopenia	-	2 (1)	-	-
Cardiac disorders				
Atrial fibrillation	1 (<1)	4 (2)	-	2 (1)
Cardiac failure	-	4 (2)	-	2 (1)
Tachycardia	1 (<1)	2 (1)	-	-
Ear & labyrinth disorders				
Vertigo	5 (3)	4 (2)	-	-
Deafness	-	3 (2)	-	-
Ear pain	2 (1)	2 (1)	-	-
Hearing impaired	-	2 (1)	-	-
Eye disorders				
Vision blurred	3 (2)	6 (3)	-	-
Dry eye	2 (1)	4 (2)	-	-
Ocular hyperaemia	-	4 (2)	-	-
Visual impairment	1 (<1)	2 (1)	-	-
Gastrointestinal disorders				
Diarrhoea	53 (27)	45 (23)	5 (3)	2 (1)
Constipation	31 (16)	36 (19)		

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Vomiting	41 (21)	26 (13)	2 (1)	4 (2)
Abdominal pain	15 (8)	12 (6)	1 (<1)	2 (1)
Dyspepsia	5 (3)	10 (5)	-	-
Stomatitis	8 (4)	8 (4)	-	-
Abdominal distension	9 (5)	7 (4)	1 (<1)	-
Dry mouth	7 (4)	7 (4)	-	-
Abdominal pain upper	12 (6)	6 (3)	1 (<1)	1 (<1)
Gastrooesophageal reflux disease	3 (2)	6 (3)	-	-
Mouth ulceration	2 (1)	4 (2)	-	1 (<1)
Colitis	-	4 (2)	-	2 (1)
Haemorrhoids	-	4 (2)	-	-
Rectal haemorrhage	-	3 (2)	-	2 (1)
Flatulence	2 (1)	3 (2)	-	-
Dysphagia	3 (2)	3 (2)	-	-
Toothache	2 (1)	3 (2)	-	-
Abdominal pain lower	3 (2)	2 (1)	-	-
Gastrointestinal pain	2 (1)	2 (1)	-	-
Gastrointestinal disorder	-	2 (1)	-	-
Gastrointestinal haemorrhage	-	2 (1)	-	2 (1)
Nausea	-	-	3 (2)	2 (1)
Proctalgia	-	2 (1)	-	-
Upper gastrointestinal haemorrhage	-	2 (1)	-	2 (1)
General disorders & administration site conditions				
Fatigue	55 (28)	57 (29)	5 (3)	3 (2)
Pyrexia	27 (14)	35 (18)	-	2 (1)
Asthenia	16 (8)	22 (11)	-	2 (1)
Oedema peripheral	12 (6)	11 (6)	-	-
Influenza like illness	8 (4)	10 (5)	-	-
Chest pain	4 (2)	9 (5)	1 (<1)	-
Mucosal inflammation	8 (4)	8 (4)	-	2 (1)
Chills	10 (5)	6 (3)	-	-
Pain	10 (5)	4 (2)	1 (<1)	-
Peripheral swelling	6 (3)	4 (2)	-	-
Catheter site pain	1 (<1)	3 (2)	-	-
Oedema	1 (<1)	3 (2)	-	-
Malaise	-	3 (2)	-	1 (<1)
General physical health deterioration	-	2 (1)	-	2 (1)
Swelling	-	2 (1)	-	-
Immune system disorders				
Hypogammaglobulinaemia	1 (<1)	2 (1)	-	-

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Injury, Poisoning and Procedural Complications				
Infusion related reactions[‡]	125 (63)	133 (69)	11(6)	21 (11%)
Fall	2 (1)	4 (2)	-	-
Wrist fracture	-	3 (2)	-	1 (<1)
Femur fracture	-	2 (1)	-	2 (1)
Laceration	-	2 (1)	-	-
Ligament sprain	-	2 (1)	-	-
Limb injury	-	2 (1)	-	-
Muscle rupture	-	2 (1)	-	-
Wound	-	2 (1)	-	-
Infections & infestations				
Upper respiratory tract infection	16 (8)	25 (13)	1 (<1)	4 (2)
Sinusitis	10 (5)	23 (12)	-	2 (1)
Urinary tract infection	11 (6)	19 (10)	-	6 (3)
Bronchitis	19 (10)	18 (9)	2 (1)	-
Nasopharyngitis	8 (4)	17 (9)	-	-
Pneumonia	13 (7)	10 (5)	11 (6)	5 (3)
Oral herpes	8 (4)	8 (4)	-	-
Pharyngitis	1 (<1)	8 (4)	-	-
Herpes zoster	15 (8)	7 (4)	3 (2)	1 (<1)
Sepsis	7 (4)	6 (3)	7 (4)	6 (3)
Rhinitis	6 (3)	6 (3)	-	-
Lung infection	2 (1)	6 (3)	1 (<1)	2 (1)
Influenza	-	6 (3)	-	-
Conjunctivitis	7 (4)	5 (3)	-	-
Respiratory tract infection	3 (2)	4 (2)	-	-
Lower respiratory tract infection	7 (4)	4 (2)	2 (1)	3 (2)
Otitis media	2 (1)	4 (2)	-	-
Oral candidiasis	4 (2)	3 (2)	-	-
Cellulitis	3 (2)	3 (2)	1 (<1)	-
Folliculitis	2 (1)	3 (2)	1 (<1)	-
Respiratory tract infection viral	2 (1)	3 (2)	-	-
Gastroenteritis	4 (2)	2 (1)	-	1 (<1)
Tooth infection	3 (2)	2 (1)	1 (<1)	-
Skin infection	2 (1)	2 (1)	-	-
Bronchopneumonia	1 (<1)	2 (1)	-	1 (<1)
Oral fungal infection	1 (<1)	2 (1)	-	-
Bacteraemia	-	2 (1)	-	-
Device related infection	-	2 (1)	-	1 (<1)
Ear infection	-	2 (1)	-	-

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Escherichia sepsis	-	2 (1)	-	2 (1)
Fungal skin infection	-	2 (1)	-	-
Rash pustular	-	2 (1)	-	-
Vaginal infection	-	2 (1)	-	-
Viral sinusitis	-	2 (1)	-	-
Investigations		- -		
Weight decreased	16 (8)	9 (5)	-	-
Blood bilirubin increased	-	3 (2)	-	-
Weight increased	-	3 (2)	-	-
C-reactive protein increased	-	2 (1)	-	1 (<1)
Cardiac murmur	-	2 (1)	-	-
Metabolism & nutrition disorders				
Decreased appetite	28 (14)	28 (14)	2 (1)	3 (2)
Hypokalaemia	13 (7)	14 (7)	5 (3)	2 (1)
Hypomagnesaemia	4 (2)	5 (3)	-	1 (<1)
Hypophosphataemia	1 (<1)	4 (2)	1 (<1)	1 (<1)
Hyperuricaemia	5 (3)	3 (2)	-	-
Fluid retention	2 (1)	2 (1)	-	-
Hyponatraemia	2 (1)	2 (1)	2 (1)	2 (1)
Hyperglycaemia	1 (<1)	2 (1)	-	2 (1)
Diabetes mellitus	-	2 (1)	-	1 (<1)
Increased appetite	-	2 (1)	-	-
Musculoskeletal & connective tissue disorders				
Arthralgia	9 (5)	23 (12)		
Pain in extremity	7 (4)	17 (9)	-	2 (1)
Back pain	18 (9)	12 (6)	-	1 (<1)
Myalgia	13 (7)	10 (5)	-	-
Muscle spasms	8 (4)	7 (4)	-	-
Bone pain	2 (1)	7 (4)	-	-
Neck pain	5 (3)	5 (3)	-	-
Musculoskeletal chest pain	2 (1)	4 (2)	-	-
Groin pain	2 (1)	3 (2)	-	-
Joint swelling	2 (1)	3 (2)	-	-
Musculoskeletal pain	1 (<1)	3 (2)	-	-
Pain in jaw	2 (1)	2 (1)	-	-
Osteoarthritis	1 (<1)	2 (1)	-	1 (<1)
Neoplasms benign, malignant & unspecified (incl. cysts & polyps)				
Basal cell carcinoma	1 (<1)	3 (2)	1 (<1)	-
Squamous cell carcinoma	2 (1)	2 (1)	1 (<1)	-

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Myelodysplastic syndrome	1 (<1)	2 (1)	1 (<1)	2 (1)
Squamous cell carcinoma of skin	1 (<1)	2 (1)	-	-
Nervous system disorders				
Headache	23 (12)	18 (9)	1 (<1)	-
Dizziness	12 (6)	10 (5)	-	-
Dysgeusia	10 (5)	7 (7)	-	-
Paraesthesia	2 (1)	5 (3)	-	-
Migraine	-	3 (2)	-	1 (<1)
Hypoaesthesia	3 (2)	3 (2)	-	-
Neuropathy peripheral	1 (<1)	3 (2)	-	-
Cognitive disorder	1 (<1)	2 (1)	-	-
Syncope	5 (3)	2 (1)	4 (2)	2 (1)
Presyncope	1 (<1)	2 (1)	-	2 (1)
Disturbance in attention	-	2 (1)	-	-
Psychiatric disorders				
Insomnia	19 (10)	18 (9)	-	-
Depression	3 (2)	7 (4)	-	-
Anxiety	8 (4)	5 (3)	1 (<1)	-
Confusional state	1 (<1)	3 (2)	-	1 (<1)
Depressed mood	1 (<1)	2 (1)	-	-
Renal & Urinary disorders				
Pollakiuria	8 (4)	6 (3)	-	1 (<1)
Dysuria	1 (<1)	5 (3)	-	1 (<1)
Urinary incontinence	-	5 (3)	-	1 (<1)
Nocturia	2 (1)	2 (1)	-	-
Reproductive system & Breast disorders				
Benign prostatic hyperplasia	2 (1)	2 (1)	-	-
Erectile dysfunction	1 (<1)	2 (1)	-	-
Respiratory, Thoracic & Mediastinal disorders				
Cough	33 (17)	51 (26)	-	-
Nasal congestion	3 (2)	14 (7)	-	-
Dyspnoea	19 (10)	12 (6)	1 (<1)	1 (<1)
Oropharyngeal pain	6 (3)	9 (5)	-	1 (<1)
Rhinorrhoea	2 (1)	8 (4)	-	-
Productive cough	5 (3)	4 (2)	-	1 (<1)
Epistaxis	5 (3)	3 (2)	-	-
Dyspnoea exertional	7 (4)	3 (2)	-	-
Pleural effusion	4 (2)	2 (1)	1 (<1)	1 (<1)
Lung disorder	-	2 (1)	-	-
Respiratory tract congestion	-	2 (1)	-	-

Adverse Event (MedDRA[a]) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194	Bendamustine n = 198	GAZYVA + Bendamustine* n = 194
Skin & Subcutaneous Tissue disorders				
Rash	21 (11)	18 (9)	-	-
Pruritus	11 (6)	17 (9)	-	-
Night sweats	4 (2)	8 (4)	-	-
Alopecia	3 (2)	5 (3)	-	-
Eczema	1 (<1)	5 (3)	-	-
Dry skin	9 (5)	3 (2)	-	-
Hyperhidrosis	4 (2)	3 (2)	-	-
Urticaria	1 (<1)	3 (2)	-	-
Pruritus generalised	1 (<1)	2 (1)	-	-
Rash pruritic	2 (1)	2 (1)	-	1 (<1)
Dermatitis acneiform	-	2 (1)	-	-
Ecchymosis	-	2 (1)	-	-
Vascular disorders				
Phlebitis	10 (5)	8 (4)	-	-
Hypertension	6 (3)	8 (4)	1 (<1)	2 (1)
Hypotension	3 (2)	5 (3)	2 (1)	2 (1)

*followed by GAZYVA monotherapy

[a]MedDRA coded adverse reactions as reported by investigators (excluding adverse events considered infusion related reactions)

‡ defined as any related adverse event that occurred during or within 24 hours of infusion

Patients in the bendamustine arm received 6 cycles of induction treatment only, whereas after the induction period, patients in the GAZYVA plus bendamustine arm continued on with GAZYVA monotherapy. During GAZYVA monotherapy, the most common adverse reactions were cough (15%), upper respiratory tract infections (12%), neutropenia (10.5%), sinusitis (10%), diarrhoea (8%), infusion related reactions (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), nasopharyngitis (6%), urinary tract infections (6%) and pyrexia (6%). The most common Grade 3-5 adverse reactions were neutropenia (10%), and anaemia, febrile neutropenia, thrombocytopenia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1.4%).

A the final analysis (cut-off date 30 November 2018), the most common adverse reactions during GAZYVA monotherapy, in addition to those noted in the primary analysis, were rash (6%), vomiting (6%), pneumonia (5%), dyspnoea (5%), and pain in the extremity (5%). Grade 3-5 adverse reactions, in addition to those noted in the primary analysis, were pneumonia.

Previously Untreated Indolent Non-Hodgkin Lymphoma

The safety of GAZYVA in study BO21223 was evaluated based on a safety population of 1390 patients with previously untreated iNHL (of whom 86% had FL). In the population of patients with FL, the profile of adverse reactions was consistent with the overall iNHL population. The study excluded patients having an absolute neutrophil count (ANC) < 1500/µL, platelets < 75,000/µL, or CrCl < 40 mL/min; and patients with hepatic transaminases > 2.5 x upper limit of normal unless attributable to lymphoma.

During combination therapy with chemotherapy, 93% of patients received all treatment cycles of GAZYVA and 92% of patients received all treatment cycles of rituximab. Of the responding patients who commenced monotherapy with GAZYVA or rituximab, 77% and 73% (respectively) completed the full course.

Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab 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 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 arm.

Table 11 summarises the adverse events that occurred in ≥ 1% of patients receiving GAZYVA plus chemotherapy in study BO21223.

Table 11 Summary of adverse events occurring in ≥1% of safety-evaluable patients receiving GAZYVA plus chemotherapy for the entire study period (Study BO21223)

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Blood and Lymphatic System Disorders				
Neutropenia	312 (45)	353 (51)	275 (40)	326 (47)
Thrombocytopenia	53 (8)	93 (13)	20 (3)	48 (7)
Leukopenia	85 (12)	88 (13)	63 (9)	61 (9)
Anaemia	72 (10)	73 (11)	17 (3)	32 (5)
Febrile neutropenia	38 (6)	51 (7)	37 (5)	48 (7)
Lymphopenia	12 (2)	8 (1)	8 (1)	5 (<1)
Bone marrow failure	5 (<1)	8 (1)	5 (<1)	8 (1)
Cardiac Disorders				
Tachycardia	12 (2)	22 (3)	1 (<1)	1 (<1)
Palpitations	20 (3)	18 (3)	1 (<1)	1 (<1)
Atrial Fibrillation	11 (2)	18 (3)	4 (<1)	8 (1)
Sinus Tachycardia	3 (<1)	9 (1)	-	2 (<1)
Bradycardia	2 (<1)	9 (1)	-	1 (<1)
Sinus Bradycardia	-	7 (1)	-	3 (<1)
Ear and Labyrinth Disorders				
Vertigo	25 (4)	20 (3)	-	-
Tinnitus	6 (<1)	15 (2)	-	-
Ear Pain	14 (2)	12 (2)	1 (<1)	-
Hypoacusis	6 (<1)	8 (1)	-	1 (<1)
Eye Disorders				
Dry Eye	12 (2)	18 (3)	-	-
Vision Blurred	9 (1)	11 (2)	1 (<1)	-
Cataract	5 (<1)	9 (1)	2 (<1)	1 (<1)
Eye pain	8 (1)	8 (1)	-	-
Ocular Hyperaemia	4 (<1)	7 (1)	-	-
Gastrointestinal Disorders				
Nausea	333 (48)	351 (50)	11 (2)	9 (1)
Constipation	216 (31)	251 (36)	3 (<1)	3 (<1)
Diarrhoea	167 (24)	214 (31)	11 (2)	13 (2)
Vomiting	151 (22)	181 (26)	11 (2)	9 (1)
Abdominal Pain	80 (12)	73 (11)	7 (1)	8 (1)
Dyspepsia	48 (7)	63 (9)	-	-
Abdominal Pain Upper	54 (8)	56 (8)	2 (<1)	1 (<1)
Stomatitis	53 (8)	54 (8)	2 (<1)	1 (<1)
Dry Mouth	23 (3)	32 (5)	-	-
Gastrooesophageal Reflux Disease	25 (4)	30 (4)	-	-
Abdominal Distension	18 (3)	22 (3)	-	1 (<1)
Abdominal Discomfort	18 (3)	20 (3)	-	-
Oral Pain	16 (2)	19 (3)	-	-

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Toothache	21 (3)	16 (2)	2 (<1)	-
Haemorrhoids	7 (1)	16 (2)	-	1 (<1)
Gastritis	15 (2)	14 (2)	1 (<1)	-
Flatulence	9 (1)	12 (2)	-	-
Gingival Pain	7 (1)	9 (1)	-	-
Colitis	6 (<1)	9 (1)	3 (<1)	2 (<1)
Dental Caries	6 (<1)	9 (1)	1 (<1)	-
Dysphagia	12 (2)	8 (1)	1 (<1)	1 (<1)
Abdominal Pain Lower	11 (2)	7 (1)	-	-
General Disorders and Administration Site Conditions				
Fatigue	271 (39)	273 (39)	6 (<1)	9 (1)
Pyrexia	161 (23)	218 (31)	8 (1)	20 (3)
Chills	76 (11)	130 (19)	4 (<1)	4 (<1)
Asthenia	41 (6)	46 (7)	1 (<1)	1 (<1)
Oedema Peripheral	38 (6)	47 (7)	1 (<1)	2 (<1)
Chest Discomfort	36 (5)	46 (7)	1 (<1)	2 (<1)
Mucosal Inflammation	44 (6)	37 (5)	1 (<1)	3 (<1)
Influenza Like Illness	34 (5)	33 (5)	-	-
Chest Pain	33 (5)	29 (4)	3 (<1)	3 (<1)
Malaise	25 (4)	28 (4)	-	-
Pain	36 (5)	24 (3)	3 (<1)	-
Peripheral Swelling	23 (3)	22 (3)	-	-
Feeling Hot	10 (1)	17 (2)	1 (<1)	3 (<1)
Oedema	8 (1)	15 (2)	-	-
Infusion Site Extravasation	9 (1)	10 (1)	-	-
Non-Cardiac Chest Pain	8 (1)	10 (1)	-	2 (<1)
Feeling Cold	4 (<1)	9 (1)	-	-
Extravasation	1 (<1)	8 (1)	-	-
Face Oedema	6 (<1)	7 (1)	-	-
Infusion Site Pain	2 (<1)	7 (1)	-	-
Immune System Disorders				
Hypogammaglobulinaemia	13 (2)	15 (2)	2 (<1)	2 (<1)
Hypersensitivity	18 (3)	14 (2)	3 (<1)	-
Seasonal Allergy	17 (3)	10 (1)	-	-
Infections and Infestations				
Upper Respiratory Tract Infection	133 (19)	155 (22)	6 (<1)	7 (1)
Viral Upper Respiratory Tract Infection	140 (20)	133 (19)	-	1 (<1)
Herpes Zoster	48 (7)	77 (11)	6 (<1)	11 (2)
Urinary Tract Infection	71 (10)	76 (11)	10 (1)	13 (2)
Pneumonia	57 (8)	76 (11)	32 (5)	38 (5)
Sinusitis	48 (7)	68 (10)	3 (<1)	3 (<1)

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Lower Respiratory Tract Infection	74 (11)	65 (9)	8 (1)	16 (2)
Rhinitis	35 (5)	57 (6)	-	2 (<1)
Bronchitis	43 (6)	51 (7)	3 (<1)	10 (1)
Oral Herpes	41 (6)	46 (7)	1 (<1)	2 (<1)
Respiratory Tract Infection	37 (5)	43 (6)	7 (1)	8 (1)
Influenza	23 (3)	36 (5)	-	2 (<1)
Conjunctivitis	26 (4)	35 (5)	1 (<1)	-
Pharyngitis	15 (2)	30 (4)	-	-
Cystitis	18 (3)	25 (4)	-	1 (<1)
Chronic Sinusitis	11 (2)	25 (4)	1 (<1)	3 (<1)
Infection	24 (4)	23 (3)	10 (1)	7 (1)
Oral Candidiasis	18 (3)	21 (3)	-	-
Lung Infection	20 (3)	18 (3)	9 (1)	10 (1)
Cellulitis	11 (2)	17 (2)	3 (<1)	5 (<1)
Sepsis	10 (1)	16 (2)	9 (1)	14 (2)
Gastroenteritis	19 (3)	15 (2)	1 (<1)	6 (<1)
Ear Infection	12 (2)	15 (2)	-	-
Viral Infection	12 (2)	12 (2)	2 (<1)	1 (<1)
Hordeolum	3 (<1)	12 (2)	-	-
Gingivitis	9 (1)	11 (2)	-	-
Folliculitis	17 (3)	10 (1)	-	-
Vulvovaginal Candidiasis	6 (<1)	10 (1)	-	-
Otitis Media	6 (<1)	9 (1)	-	-
Tooth Infection	6 (<1)	9 (1)	-	3 (<1)
Eye Infection	1 (<1)	9 (1)	-	-
Periodontitis	5 (<1)	8 (1)	-	1 (<1)
Tooth Abscess	5 (<1)	8 (1)	1 (<1)	-
Vaginal Infection	5 (<1)	8 (1)	1 (<1)	-
Lip Infection	4 (<1)	7 (1)	-	-
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	353 (51)	439 (63)	35 (5)	48 (7)
Contusion	14 (2)	18 (3)	1 (<1)	-
Fall	15 (2)	17 (2)	3 (<1)	-
Laceration	7 (1)	8 (1)	-	-
Procedural Pain	5 (<1)	8 (1)	-	-
Investigations				
Weight Decreased	42 (6)	35 (5)	3 (<1)	3 (<1)
Alanine Aminotransferase Increased	19 (3)	32 (5)	1 (<1)	5 (<1)
Aspartate Aminotransferase Increased	12 (2)	21 (3)	-	1 (<1)
Blood Creatinine Increased	10 (1)	16 (2)	-	1 (<1)

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Blood Lactate Dehydrogenase Increased	8 (1)	15 (2)	-	1 (<1)
C-Reactive Protein Increased	4 (<1)	11 (2)	-	2 (<1)
Body Temperature Increased	1 (<1)	9 (1)	-	-
Blood Alkaline Phosphatase Increased	6 (<1)	8 (1)	-	2 (<1)
Weight Increased	14 (2)	7 (1)	-	-
Blood Bilirubin Increased	5 (<1)	7 (1)	1 (<1)	1 (<1)
Blood Pressure Increased	5 (<1)	7 (1)	3 (<1)	1 (<1)
Metabolism and Nutrition Disorders				
Decreased Appetite	88 (13)	98 (14)	2 (<1)	2 (<1)
Hypokalaemia	28 (4)	46 (7)	6 (<1)	5 (<1)
Hyperuricaemia	17 (3)	26 (4)	-	1 (<1)
Hyperglycaemia	17 (3)	16 (2)	7 (1)	5 (<1)
Dehydration	9 (1)	14 (2)	4 (<1)	4 (<1)
Hyperkalaemia	6 (<1)	13 (2)	2 (<1)	2 (<1)
Diabetes Mellitus	11 (2)	12 (2)	1 (<1)	2 (<1)
Hypophosphataemia	9 (1)	9 (1)	2 (<1)	3 (<1)
Gout	7 (1)	9 (1)	-	-
Hyponatraemia	3 (<1)	9 (1)	2 (<1)	6 (<1)
Hypomagnesaemia	8 (1)	8 (1)	1 (<1)	-
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	96 (14)	117 (17)	3 (<1)	-
Back Pain	116 (17)	100 (14)	4 (<1)	4 (<1)
Pain In Extremity	64 (9)	66 (10)	4 (<1)	-
Myalgia	36 (5)	52 (7)	1 (<1)	-
Bone Pain	43 (6)	39 (6)	3 (<1)	1 (<1)
Muscle Spasms	39 (6)	39 (6)	-	-
Musculoskeletal Pain	39 (6)	35 (5)	-	-
Neck Pain	18 (3)	23 (3)	-	1 (<1)
Joint Swelling	15 (2)	16 (2)	-	-
Musculoskeletal Chest Pain	13 (2)	13 (2)	-	-
Groin Pain	22 (3)	11 (2)	-	-
Flank Pain	11 (2)	11 (2)	-	-
Muscular Weakness	11 (2)	10 (1)	1 (<1)	-
Osteoarthritis	11 (2)	10 (1)	2 (<1)	2 (<1)
Pain In Jaw	7 (1)	10 (1)	-	-
Musculoskeletal Stiffness	4 (<1)	9 (1)	-	1 (<1)
Arthritis	7 (1)	8 (1)	1 (<1)	-
Spinal Pain	4 (<1)	9 (1)	-	1 (<1)

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)				
Basal Cell Carcinoma	11 (2)	17 (2)	2 (<1)	4 (<1)
Nervous System Disorders				
Headache	120 (17)	151 (22)	1 (<1)	2 (<1)
Dizziness	58 (8)	71 (10)	1 (<1)	2 (<1)
Dysgeusia	57 (8)	61 (9)	-	-
Paraesthesia	50 (7)	60 (9)	2 (<1)	1 (<1)
Peripheral Sensory Neuropathy	47 (7)	58 (8)	1 (<1)	3 (<1)
Neuropathy Peripheral	51 (7)	51 (7)	2 (<1)	-
Hypoaesthesia	27 (4)	30 (4)	-	-
Lethargy	28 (4)	28 (4)	-	1 (<1)
Polyneuropathy	19 (3)	21 (3)	1 (<1)	3 (<1)
Syncope	16 (2)	19 (3)	7 (<1)	11 (2)
Tremor	11 (2)	12 (2)	1 (<1)	-
Migraine	10 (1)	8 (1)	-	-
Disturbance In Attention	7 (1)	8 (1)	-	-
Presyncope	7 (1)	8 (1)	4 (<1)	2 (<1)
Restless Legs Syndrome	3 (<1)	7 (1)	-	-
Psychiatric Disorders				
Insomnia	86 (12)	108 (16)	2 (<1)	3 (<1)
Anxiety	28 (4)	44 (6)	1 (<1)	1 (<1)
Depression	34 (5)	33 (5)	3 (<1)	5 (<1)
Renal and Urinary Disorders				
Pollakiuria	11 (2)	25 (4)	-	-
Dysuria	18 (3)	20 (3)	-	-
Nocturia	6 (<1)	10 (1)	-	-
Urinary Incontinence	6 (<1)	8 (1)	-	-
Haematuria	8 (1)	7 (1)	-	-
Reproductive System and Breast Disorders				
Vaginal Discharge	3 (<1)	8 (1)	-	-
Respiratory, Thoracic and Mediastinal Disorders				
Cough	180 (26)	219 (31)	1 (<1)	2 (<1)
Dyspnoea	92 (13)	120 (17)	12 (2)	23 (3)
Oropharyngeal Pain	72 (10)	82 (12)	2 (<1)	1 (<1)
Productive Cough	33 (5)	41 (6)	1 (<1)	-
Throat Irritation	37 (5)	26 (4)	-	-
Rhinorrhoea	14 (2)	26 (4)	-	-
Nasal Congestion	11 (2)	19 (3)	-	-
Dyspnoea Exertional	26 (4)	14 (2)	-	-
Pulmonary Embolism	4 (<1)	14 (2)	3 (<1)	13 (2)

Adverse Event (MedDRA) System Organ Class	All Grades n (%)		Grades 3-5 n (%)	
	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698	RITUXAN + chemotherapy n = 692	GAZYVA + chemotherapy n = 698
Hypoxia	5 (<1)	14 (2)	-	5 (<1)
Pleural Effusion	12 (2)	13 (2)	4 (<1)	5 (<1)
Chronic Obstructive Pulmonary Disease	4 (<1)	10 (1)	2 (<1)	1 (<1)
Asthma	9 (1)	9 (1)	2 (<1)	1 (<1)
Dysphonia	9 (1)	9 (1)	-	-
Upper-Airway Cough Syndrome	4 (<1)	9 (1)	-	-
Sinus Congestion	8 (1)	8 (1)	-	-
Rhinitis Allergic	6 (<1)	8 (1)	-	-
Wheezing	5 (<1)	7 (1)	-	-
Skin and Subcutaneous Tissue Disorders				
Rash	130 (19)	125 (18)	10 (1)	7 (1)
Pruritus	92 (13)	97 (14)	1 (<1)	2 (<1)
Alopecia	76 (11)	90 (13)	1 (<1)	-
Dry Skin	35 (5)	39 (6)	-	-
Erythema	34 (5)	37 (5)	-	3 (<1)
Night Sweats	36 (5)	31 (4)	1 (<1)	1 (<1)
Hyperhidrosis	28 (4)	29 (4)	-	1 (<1)
Urticaria	26 (4)	22 (3)	4 (<1)	1 (<1)
Eczema	12 (1)	15 (2)	-	-
Rash Maculo-Papular	18 (3)	13 (2)	3 (<1)	2 (<1)
Rash Pruritic	6 (<1)	11 (2)	1 (<1)	-
Skin Exfoliation	3 (<1)	10 (1)	-	-
Dermatitis	7 (1)	9 (1)	-	-
Dermatitis Acneiform	6 (<1)	9 (1)	-	-
Rash Macular	6 (<1)	7 (1)	-	1 (<1)
Vascular Disorders				
Hypertension	49 (7)	62 (9)	13 (2)	17 (2)
Hypotension	29 (4)	49 (7)	3 (<1)	11 (2)
Flushing	40 (6)	46 (7)	-	1 (<1)
Hot Flush	24 (4)	37 (5)	-	1 (<1)
Phlebitis	24 (4)	20 (3)	-	-
Thrombophlebitis	16 (2)	12 (2)	-	-
Vein Disorder	6 (<1)	10 (1)	-	-
Vasculitis	4 (<1)	7 (1)	-	-

During the monotherapy period with GAZYVA, the most common adverse events (incidence ≥ 5%) in patients with previously untreated iNHL were cough (21%), neutropenia (19%), upper respiratory tract infection (15%), viral upper respiratory tract infection (15%), diarrhea (13%), arthralgia (10%), fatigue (9%), sinusitis (9%), infusion related reactions (8%), pneumonia (8%), herpes zoster (8%), lower respiratory tract infection (7%), pyrexia (7%), back pain (6%), headache (6%), urinary tract infection (6%), nausea (6%), bronchitis (5%) and vomiting (5%). The most common Grade 3–4 adverse events

(incidence ≥ 1%) during the monotherapy period were neutropenia (17%), pneumonia (3%), with 2 deaths due to pneumonia reported in the GAZYVA treated arm) and febrile neutropenia (2%).

Additional Information on Selected Adverse Reactions

Infusion related reactions (IRRs):
Most frequently reported (≥5%) symptoms associated with an IRR were nausea, fatigue, chest discomfort, dyspnoea, dizziness, vomiting, diarrhoea, constipation, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills. Respiratory symptoms such as, bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and cardiac symptoms such as atrial fibrillation have also been reported (see 7 WARNINGS AND PRECAUTIONS).

Chronic Lymphocytic Leukaemia
The incidence of Infusion Related Reactions (IRRs) (term specifically reported by the investigators) was 65% with the infusion of the first 1000 mg of GAZYVA (20% of patients experiencing a Grade 3-4 IRR, with no fatal (Grade 5) events reported) and 27% with the first infusion of rituximab (3% of patients experiencing a Grade 3-4 IRR, with no fatal (Grade 5) events reported). Overall, 7% of patients experienced an IRR leading to discontinuation of GAZYVA. The incidence of IRR with subsequent GAZYVA infusions was 3% with the second 1000 mg dose and 1% thereafter. The incidence of IRR with subsequent rituximab infusions was 13% in cycle 2, 6% in cycle 3, 2% in cycles 4 and 5, and 1% in cycle 6. No Grade 3-5 IRR were reported beyond the first 1000 mg of GAZYVA infusions of Cycle 1.

In patients who received the recommended measures for prevention of IRRs as described in 4 DOSAGE AND ADMINISTRATION, a decreased incidence of all Grades IRRs was observed. The rates of Grade 3-4 IRRs (which are based on a relatively low number of patients) were similar before and after mitigation measures were implemented.

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
In study GAO4753g, Cycle 1, the overall incidence of Infusion Related Reactions (IRRs) (term specifically reported by the investigators) was higher in patients receiving GAZYVA plus bendamustine (55%) compared to patients receiving bendamustine alone (42%) (with Grade 3-5 IRR reported in 9% and 2%, respectively and no fatal events reported). In patients receiving GAZYVA plus bendamustine the incidence of IRR was highest on Day 1 (38%) and gradually decreased on Days 2, 8 and 15 (25%, 7% and 4%, respectively).

The incidence of IRR in subsequent infusions was comparable in both arms and decreased with each cycle. IRRs were also observed in 8% of patients during GAZYVA monotherapy. Overall, 3% of patients experienced an infusion related reaction leading to discontinuation of GAZYVA.

In the final analysis of study GAO4753g, Cycle 1, the overall incidence of Infusion Related Reactions (term specifically reported by the investigators) was higher in patients receiving GAZYVA plus bendamustine (53%) compared to patients receiving bendamustine alone (42%) (with Grade 3-5 IRR reported in 17% and 3%, respectively and no fatal events reported). In patients receiving GAZYVA plus bendamustine, the incidence of IRR was highest on Day 1 (76/204, 37%) and gradually decreased on Days 2 (46/204), 23%), 8 (12/204, 6%) and 15 (8/204, 4%).

The incidence of IRR in subsequence infusion was comparable in both arms and decreased with each cycle. IRRs were also observed in 8% of patients during GAZYVA monotherapy. Overall, 2% of patients experienced an infusion related reaction leading to discontinuation of GAZYVA and/or bendamustine.

Previously Untreated Indolent Non-Hodgkin Lymphoma

In study BO21223, 72% of patients in the GAZYVA treated arm experienced an infusion related reaction (all grades). The incidence of Grade 3-4 infusion related reactions for these patients was 12%. In Cycle 1, the incidence of infusion related reactions (all grades) was 62% in the GAZYVA treated arm with Grade 3–4 infusion related reactions reported in 10%. The incidence of infusion related reactions (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 infusion related reactions (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles.

During GAZYVA monotherapy treatment in Study BO21223, infusion related reactions (all grades) were observed in 9% of patients.

Overall, 2% of patients in study BO21223 experienced an infusion related reaction leading to discontinuation of GAZYVA.

In the study MO40597 designed to characterize the safety profile of short (approximately 90 minutes) GAZYVA infusions after Cycle 1 in patients with previously untreated FL, the incidence, severity and types of symptoms of IRRs were similar to those observed in patients receiving infusions administered at the standard infusion rate in study BO21223. In study MO40597, during Cycle 2, the incidence of infusion related reactions (all grades) was 11.8% in the Safety-Evaluable Population and 11.3% in patients who received GAZYVA as short duration infusion. The incidence decreased with subsequent cycles. Two patients discontinued study treatment due to infusion related reactions during Cycle 1. No patient discontinued study treatment due to infusion related reactions during Cycle 2 or subsequent cycles with short duration infusion.

Neutropenia:

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the GAZYVA plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte colony-stimulating factors. Cases of prolonged neutropenia (2% in the GAZYVA plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the GAZYVA plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see 7 WARNINGS AND PRECAUTIONS).

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

In study GAO4753g, the incidence of neutropenia was higher in the GAZYVA plus bendamustine arm compared to the arm treated with bendamustine alone. Cases of prolonged neutropenia (3% in the GAZYVA plus bendamustine arm) and late onset neutropenia (7% in the GAZYVA plus bendamustine arm) were also reported (see 7 WARNINGS AND PRECAUTIONS). The incidence of neutropenia was

higher during treatment with GAZYVA in combination with bendamustine (31%) compared to the GAZYVA monotherapy treatment phase (12%).

In the final analysis of study GAO4753g, the incidence of neutropenia during the entire study was higher in the GAZYVA plus bendamustine arm compared to the arm treated with bendamustine alone. Cases of prolonged neutropenia (3% in the GAZYVA plus bendamustine arm) and late onset neutropenia (8% in the GAZYVA plus bendamustine arm) were also reported (see 7 WARNINGS AND PRECAUTIONS). The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (32%) compared to the GAZYVA monotherapy treatment phase (15%).

Previously Untreated Indolent Non-Hodgkin Lymphoma
The incidence of neutropenia in study BO21223 was higher in the GAZYVA-treated arm (53%) compared to the rituximab-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 Leukaemia
The incidence of infection was similar in the GAZYVA plus chlorambucil arm (38%) compared to the rituximab plus chlorambucil arm (37%) (with Grade 3-5 events reported in 12% and 14%, respectively. Fatal infections were reported in 2 patients (1%) in the GAZYVA plus chlorambucil arm and 2 patients (1%) in the rituximab plus chlorambucil arm in study BO21004/CLL11).

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
The incidence of infection in study GAO4753g was 66% in the GAZYVA plus bendamustine arm and 57% in the bendamustine arm (with Grade 3-5 events reported in 18% and 17%, respectively, and fatal events reported in 5 patients [2.5%] and 7 patients [3.5%], respectively).

In the final analysis of study GAO4753g, the incidence of infection during the entire study period was 68% in the GAZYVA plus bendamustine arm and 59% in the bendamustine arm (with Grade 3-5 events reported in 23% and 19%, respectively, and fatal events reported in 6 patients [2.9%] and 7 patients [3.4%], respectively).

Previously Untreated Indolent Non-Hodgkin Lymphoma
The incidence of infection in study BO21223 was 81% in the GAZYVA-treated arm and 73% in the rituximab-treated arm, with Grade 3–4 events reported in 21% and 17%, respectively. Fatal (grade 5) infections were reported for 15 patients (2.1%) in the GAZYVA treated arm and for 4 patients (0.6%) in the rituximab treated arm.

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

Thrombocytopenia:

Chronic Lymphocytic Leukaemia

The overall incidence of thrombocytopenia reported as an adverse reaction in study BO21004 was higher in the GAZYVA plus chlorambucil arm (16%) compared to the rituximab plus chlorambucil arm (7%) with the incidence of Grade 3 or 4 events being 11% 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 11% in the GAZYVA and 3% in the rituximab treated arms, with Grade 3 or 4 rates being 8% and 2%, respectively. Four percent of patients treated with GAZYVA plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the GAZYVA infusion), compared with 1% of patients treated with rituximab plus chlorambucil. The overall incidence of haemorrhagic events and the number of fatal haemorrhagic events were similar between the treatment arms, with 3 in the rituximab and 4 in the GAZYVA treated arms; however, all fatal haemorrhagic events in patients treated with GAZYVA (cerebrovascular accident, alveolar pulmonary haemorrhage, subdural haematoma, haemorrhagic stroke) occurred in Cycle 1 (see 7 WARNINGS AND PRECAUTIONS).

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

The incidence of thrombocytopenia in study GAO4753g was 15% in the GAZYVA plus bendamustine arm and 24% in the bendamustine arm. Thrombocytopenia was reported as serious in 5 patients (2.5%) in the GAZYVA plus bendamustine arm and none in the bendamustine arm. One acute thrombocytopenia was reported in the GAZYVA plus bendamustine arm. The incidence of haemorrhagic events was 11% in both arms. Grade 3-5 haemorrhagic events were 4% in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm. No fatal events were reported (see 7 WARNINGS AND PRECAUTIONS).

In the final analysis of study GAO4753g, the incidence of thrombocytopenia during the entire study period was 15% in the GAZYVA plus bendamustine arm and 25% in the bendamustine arm. Thrombocytopenia was reported as serious in 5 patients (2.5%) in the GAZYVA plus bendamustine arm and none in the bendamustine arm. One acute thrombocytopenia was reported in the GAZYVA plus bendamustine arm. The incidence of haemorrhagic events was 12% in the GAZYVA plus bendamustine arm and 11% in the bendamustine arm. Grade 3-5 haemorrhagic events were 4% in the GAZYVA plus bendamustine arm and 2.5% in the bendamustine arm. No fatal haemorrhagic events were reported (see 7 WARNINGS AND PRECAUTIONS).

Previously Untreated Indolent Non-Hodgkin Lymphoma

The incidence of thrombocytopenia in study BO21223 was 13% in the GAZYVA-treated arm and 8% in the rituximab-treated arm, with the incidence of Grade 3-4 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 were 9% in the GAZYVA- and 3% in the rituximab-treated arms, with Grade 3–4 rates being 5% and 1%, respectively. Acute thrombocytopenia occurred more frequently in the GAZYVA-treated arm (1%) than in the rituximab-treated arm (< 1%). In study BO21223, the overall incidence of haemorrhagic events was 12% in both treatment arms. The number of fatal haemorrhagic events was also identical between the treatment

arms, with 2 fatal events reported in each arm. Both fatal events reported in the GAZYVA arm were due to GI haemorrhage.

Coagulation abnormalities including disseminated intravascular coagulation (DIC):

DIC has been reported in patients receiving GAZYVA for treatment of chronic lymphocytic leukemia and follicular lymphoma. In some cases, the events were associated with IRRs and/or TLS. Three patients were reported with DIC (one serious, two non-serious) among a total of 1135 obinutuzumab-treated patients in the three largest company-sponsored controlled trials in FL and CLL (CLL11/BO21004, GALLIUM/BO21223, GADOLIN/GO01297/GAO4753g). All three events occurred in the GAZYVA treatment groups within 1-2 days after the first infusion; no cases were reported in the comparator groups. All patients continued treatment (see 7 WARNINGS AND PRECAUTIONS).

Cardiac Events:

Chronic Lymphocytic Leukaemia
Higher frequencies of cardiac adverse events in CLL patients have been seen in GAZYVA plus chlorambucil arm as compared to the rituximab plus chlorambucil arm (15% vs 10% respectively). This difference was mainly driven by tachycardias (7% vs 3% respectively) resulting from infusion related reactions. The incidence of serious cardiac events was similar in the GAZYVA plus chlorambucil arm as compared to the rituximab plus chlorambucil arm (6% vs 4%). Two fatal cardiac events were reported in the GClb arm and 5 in the RClb arm.

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
Higher frequencies of cardiac adverse events in NHL patients have been seen in GAZYVA plus bendamustine arm as compared to the bendamustine arm (11% vs 6% respectively). Serious cardiac disorders, 3 (2%) events were observed in the bendamustine arm as compared to 7 (3.4%) in the GAZYVA plus bendamustine arm. One third of the events occurred during or within 24 hours of the infusion.

In the final analysis of study GAO4753g, higher frequencies of cardiac adverse events in NHL patients have been seen in GAZYVA plus bendamustine arm as compared to the bendamustine arm (12% vs 6% respectively). Serious cardiac adverse event in the bendamustine arm were observed at an incidence of 2% as compared to 3% in the GAZYVA plus bendamustine arm. Five out of 25 patients in the GAZYVA plus bendamustine arm and 2 out of 13 patients in the bendamustine arm experienced cardiac events during or within 24 hours of the infusion.

Previously Untreated Indolent Non-Hodgkin Lymphoma
Higher frequencies of cardiac events have been seen in GAZYVA plus chemotherapy arm as compared to the rituximab plus chemotherapy arm (16.0% vs 10.5% respectively). The difference was mainly driven by tachycardia (3.2% vs 1.7% respectively), atrial fibrillation (2.6% vs. 1.6% respectively), bradycardia (1.3% vs 0.3%) and sinus bradycardia (1.0% vs 0.0%, respectively) events, commonly occurring as part of infusion related reactions. Serious cardiac events occurred more frequently in GAZYVA plus chemotherapy arm as compared to rituximab plus chemotherapy arm (5.9% vs 2%, respectively). Fatal cardiac events occurred in two patients in each arm.

Gastro-Intestinal Perforation:
Serious cases of gastro-intestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL. In the study GAO4753g, 2 patients (1%) experienced 3 gastrointestinal perforation events, two Grade 2 and one Grade 3. One of the events was serious.

In study BO21223, 5 patients (0.7%) experienced 5 gastrointestinal perforation events (one Grade 4, two grade 3 and two grade 2) in GAZYVA plus chemotherapy arm and 3 patients (0.4%) experienced 3 gastrointestinal perforation events in rituximab plus chemotherapy arm (all 3 were Grade 2). Three out of the 5 events in GAZYVA plus chemotherapy arm were serious, while none of the gastrointestinal events was serious in rituximab plus chemotherapy arm.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Events (<1%) (Study BO21004/CLL11 Stage 1a and Stage 2) in CLL

Blood and lymphatic system disorders: anaemia haemolytic autoimmune, bone marrow failure, bone marrow toxicity, granulocytopenia, haemolysis, haemolytic anaemia, idiopathic thrombocytopenic purpura, lymphopenia, microcytic anaemia, pancytopenia.

Cardiac disorders: acute coronary syndrome, angina pectoris, atrial flutter, atrial tachycardia, atrial thrombosis, atrioventricular block bradycardia, cardiac failure chronic, cardiac failure congestive, nodal rhythm, pericardial effusion, tachyarrhythmia, tachycardia, ventricular arrhythmia.

Congenital, familial and genetic disorders: hereditary non-polyposis colorectal cancer syndrome.

Ear and labyrinth disorders: ear pain, hearing impaired, hypoacusis, tinnitus.

Eye disorders: cataract, conjunctivitis, dry eye, eye disorder, eye pain, lacrimation increased, ocular hyperaemia, vision blurred, visual acuity reduced, vitreous opacities.

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal symptom, anal fissure, aphthous stomatitis, ascites, buccal polyp, chapped lips, dysphagia, enterocolitis, flatulence, gastritis, gingival pain, haematochezia, inguinal hernia, mouth ulceration, oesophagitis, pancreatitis acute, paraesthesia oral, rectal polyp, tooth disorder, tooth loss, toothache.

General disorders and administration site conditions: chest discomfort, death, feeling cold, feeling hot, general physical health deterioration, impaired healing, influenza like illness, infusion site phlebitis, malaise, mucosal inflammation, oedema, pain, performance status decreased, spinal pain.

Hepatobiliary disorders: bile duct stone, biliary colic, biliary tract disorder, cholecystitis, cholelithiasis, hepatitis, hepatitis toxic, hepatocellular injury, liver disorder.

Immune system disorders: anaphylactic reaction, secondary immunodeficiency.

Infections and infestations: abscess oral, bacterial infection, candidiasis, cystitis, dacryocystitis, device related sepsis, diverticulitis, ear infection, endocarditis, enterocolitis infectious, erysipelas, escherichia infection, escherichia sepsis, eye infection, folliculitis, fungal infection, fungal skin infection, gangrene, gastroenteritis, gastrointestinal infection, herpes virus infection, herpes zoster ophthalmic, infection,

infective exacerbation of bronchiectasis, influenza, laryngitis, liver abscess, localised infection, neutropenic sepsis, oesophageal candidiasis, oral candidiasis, oral fungal infection, osteomyelitis, otitis externa fungal, pneumonia influenza, pulmonary sepsis, pulmonary tuberculosis, pyelonephritis, respiratory tract infection viral, sepsis, septic arthritis staphylococcal, septic shock, sialoadenitis, sinobronchitis, sinusitis, skin infection, streptococcal sepsis, subcutaneous abscess, superinfection bacterial, tooth infection, vaginal infection, vulvovaginal candidiasis, wound infection.

Injury, poisoning and procedural complications: back injury, contusion, epicondylitis, eye injury, femoral neck fracture, forearm fracture, head injury, laceration, limb injury, multiple fractures, muscle rupture, muscle strain, overdose, pubis fracture, radius fracture, shunt thrombosis, soft tissue injury, spinal compression fracture, spinal fracture, subdural haematoma, subdural haemorrhage, tendon rupture, thoracic vertebral fracture, tibia fracture, wrist fracture.

Investigations: aspartate aminotransferase increased, basophil count increased, blood alkaline phosphatase increased, blood creatinine increased, blood glucose increased, blood immunoglobulin g decreased, blood potassium increased, blood pressure increased, blood urea increased, blood uric acid increased, haemoglobin decreased, hepatic enzyme increased, international normalised ratio increased, lymphocyte count decreased, mean cell haemoglobin increased, monocyte count increased, pH urine decreased, serum ferritin decreased, transaminases increased.

Metabolism and nutrition disorders: cell death, diabetes mellitus, gout, hypercalcaemia, hypertriglyceridaemia, hypoglycaemia, hypokalaemia, hyponatraemia, hypophosphataemia, hypoproteinaemia, iron deficiency, iron overload, malnutrition, polydipsia, type 2 diabetes mellitus, vitamin B12 deficiency.

Musculoskeletal and connective tissue disorders: arthritis, bursitis, flank pain, gouty arthritis, groin pain, muscle spasms, muscular weakness, myalgia, neck pain, osteoarthritis, pain in jaw, rotator cuff syndrome, spinal column stenosis, tendonitis.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): adenocarcinoma gastric, adenocarcinoma of colon, colon cancer, fibromatosis, keratoacanthoma, lung adenocarcinoma, myelodysplastic syndrome, plasma cell myeloma, prostate cancer, rectal adenocarcinoma, renal cell carcinoma, schwannoma, seborrhoeic keratosis, squamous cell carcinoma, squamous cell carcinoma oflung.

Nervous system disorders: ageusia, ataxia, balance disorder, cerebral ischaemia, cerebrovascular accident, dysaesthesia, dysarthria, haemorrhage intracranial, haemorrhagic stroke, hypoaesthesia, lethargy, loss of consciousness, metabolic encephalopathy, neuropathy peripheral, orthostatic intolerance, presyncope, restless legs syndrome, sciatica, syncope, tension headache, tremor, trigeminal neuralgia.

Psychiatric disorders: agitation, apathy, confusional state, delirium, depression, disorientation, emotional distress, hallucination, psychiatric symptom, restlessness.

Renal and urinary disorders: acute prerenal failure, bladder pain, dysuria, haematuria, nephrolithiasis, nocturia, pollakiuria, proteinuria, renal failure, renal failure acute, urinary retention.

Reproductive system and breast disorders: epididymitis, testicular hypertrophy, testicular swelling.

Respiratory, thoracic and mediastinal disorders: acute pulmonary oedema, chronic obstructive pulmonary disease, dysphonia, dyspnoea exertional, hiccups, increased upper airway secretion, laryngeal inflammation, nasal congestion, oropharyngeal discomfort, pharyngeal ulceration, pleural effusion, pneumonitis, pneumothorax, productive cough, pulmonary alveolar haemorrhage, pulmonary embolism, pulmonary hypertension, pulmonary oedema, rhinorrhea.

Skin and subcutaneous tissue disorders: acne, actinic keratosis, blister, decubitus ulcer, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, dry skin, ecchymosis, eczema, erythema, hyperhidrosis, night sweats, petechiae, pruritus generalised, psoriasis, rash maculo-papular, rash papular, rash pruritic, seborrhoeic dermatitis, skin disorder, skin fissures, skin lesion, skin reaction, urticaria.

Surgical and medical procedures: knee arthroplasty, tooth extraction.

Vascular disorders: blood pressure fluctuation, capillary leak syndrome, deep vein thrombosis, diabetic macroangiopathy, flushing, haematoma, haemorrhage, hot flush, hypertensive crisis, lymphedema, orthostatic hypotension, peripheral artery thrombosis, peripheral ischaemia, phlebitis superficial, superior vena cava syndrome, thrombophlebitis superficial, thrombosis, varicose ulceration, venous thrombosis.

Less Common Clinical Trial Adverse Events (<1%) (Study GAO4753g) in NHL

Blood and lymphatic system disorders: Agranulocytosis, Hypoglobulinaemia, Lymphadenopathy, Thrombocytopenic purpura

Cardiac disorders: Palpitations, Angina pectoris, Myocardial infarction, Acute coronary syndrome, Atrial flutter, Coronary artery disease, Intracardiac thrombus, Sinus bradycardia

Ear and labyrinth disorders: Hypoacusis, Tinnitus, Cerumen impaction, Deafness unilateral, Ear discomfort

Eye disorders: Chalazion, Cataract, Conjunctival haemorrhage, Eye irritation, Eye pain, Eye pruritus, Eye swelling, Eyelid haematoma, Glaucoma, Periorbital oedema, Uveitis, Visual acuity reduced

Gastrointestinal disorders: Anal ulcer, Aphthous stomatitis, Gastritis, Abdominal discomfort, Haematochezia, Odynophagia, Oral pain, Retching, Abdominal hernia, Anal fissure, Breath odour, Chapped lips, Chronic gastritis, Dental caries, Diarrhoea haemorrhagic, Faeces discoloured, Food poisoning, Gastrointestinal sounds abnormal, Ileus, Inguinal hernia, Intestinal perforation, Mouth swelling, Oral mucosal erythema, Pancreatitis, Parotid gland enlargement, Tongue coated, Tongue ulceration

General disorders and administration site conditions: Axillary pain, Induration, Catheter site erythema, Catheter site haematoma, Catheter site swelling, Drug intolerance, Injection site hypersensitivity, Injection site induration, Sensation of foreign body, Tenderness

Hepatobiliary disorders: Cholecystitis, Cholestasis, Hepatic steatosis, Hepatic failure, Liver disorder

Immune system disorders: Contrast media allergy, Graft versus host disease, Hypersensitivity

Infections and infestations: Infection, Eye infection, Herpes simplex, Pneumocystis jirovecii pneumonia, Atypical pneumonia, Cytomegalovirus chorioretinitis, Diverticulitis, Furuncle, Laryngitis, Lower respiratory tract infection viral, Sinobronchitis, Staphylococcal skin infection, Tooth abscess, Vulvovaginal mycotic infection, Abdominal abscess, Abscess limb, Acarodermatitis, Acute sinusitis, Bacterial infection, Bronchiolitis, Campylobacter infection Candida infection, Chronic sinusitis, Cystitis, Cystitis Escherichia, Erysipelas, Fungal sepsis, Gastroenteritis salmonella, Gastroenteritis viral, Genital herpes, Groin infection, Labyrinthitis, Lip infection, Lower respiratory tract infection bacterial, Lung infection pseudomonal, Lyme disease, Nail bed infection, Nasal abscess, Penile infection, Pseudomonal sepsis, Salmonellosis, Sputum purulent, Staphylococcal sepsis, Tongue abscess, Tonsillitis, Urinary tract infection bacterial, Urosepsis, Wound infection

Injury, poisoning and procedural complications: Contusion, Hand fracture, Arthropod bite, Contrast media reaction, Facial bones fracture, Hip fracture, Nail injury, Radius fracture, Seroma, Skin abrasion, Skin wound, Sunburn, Synovial rupture, Thermal burn, Tooth fracture, Ulna fracture, Vascular pseudoaneurysm

Investigations: Blood creatinine increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, B-lymphocyte count decreased, Blood alkaline phosphatase increased, Blood calcium decreased, Blood glucose increased, Blood immunoglobulin G decreased, Blood iron decreased, Blood thyroid stimulating hormone increased, Body temperature increased, Creatinine renal clearance increased, Immunoglobulins decreased, Platelet count decreased, QRS axis abnormal, Urine output increased, Waist circumference increased

Metabolism and nutrition disorders: Gout, Electrolyte imbalance, Glucose tolerance impaired, Hyperlipidaemia, Hypoalbuminaemia, Hypocalcaemia, Hypoglycaemia, Hypoproteinaemia Type 2 diabetes mellitus

Musculoskeletal and connective tissue disorders: Flank pain, Muscular weakness, Tendon pain, Arthritis, Muscle haemorrhage, Musculoskeletal discomfort, Osteitis, Polymyalgia rheumatic, Rheumatic disorder, Synovial cyst, Tendonitis, Upper extremity mass

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Acute myeloid leukaemia, Malignant melanoma, Acoustic neuroma, Bladder cancer, Bowen's disease, Colorectal cancer, Meningioma, Polycythaemia vera, Renal cancer, Seborrhoeic keratosis, T-cell lymphoma

Nervous system disorders: Lethargy, Memory impairment, Neuralgia, Post herpetic neuralgia, Burning sensation, Carpal tunnel syndrome, Dysaesthesia, Hyperaesthesia, Parosmia, Peripheral motor neuropathy, Restless legs syndrome, Sedation, Sinus headache, Somnolence, Vasogenic cerebral oedema

Psychiatric disorders: Agitation, Delirium, Libido decreased, Mania, Restlessness

Renal and urinary disorders: Renal failure acute, Haematuria, Renal failure chronic, Bladder spasm, Micturition frequency decreased, Nephrolithiasis, Polyuria, Strangury, Ureteric obstruction

Reproductive system and breast disorders: Vaginal haemorrhage, Breast pain, Gynaecomastia, Prostatitis, Uterine inflammation, Vulvovaginal dryness

Respiratory, thoracic and mediastinal disorders: Dysphonia, Hiccups, Asthma, Haemoptysis, Interstitial lung disease, Pleuritic pain, Rhinitis allergic, Sputum discoloured, Bronchitis chronic, Nasal obstruction, Paranasal sinus hypersecretion, Pneumonia aspiration, Pneumothorax, Sinus disorder, Sleep apnoea syndrome

Skin and subcutaneous tissue disorders: Blister, Drug eruption, Dermatitis, Erythrosis, Rash popular, Acne, Dermatitis allergic, Hyperkeratosis, Petechiae, Photosensitivity reaction, Psoriasis, Rash erythematous, Rosacea, Skin exfoliation, Skin mass, Skin reaction, Solar dermatitis, Toxic skin eruption

Social circumstances: Social stay hospitalisation

Vascular disorders: Orthostatic hypotension, Hot flush, Hypertensive crisis, Lymphoedema, Peripheral vascular disorder, Peripheral venous disease, Subclavian vein thrombosis, Thrombophlebitis superficial, Vascular insufficiency, Vascular pain, Vein disorder, Venous stenosis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Chronic Lymphocytic Leukaemia

The post-baseline laboratory abnormalities observed during treatment in study BO21004/CLL11 are presented in Table 12 and Table 13.

Table 12 Post-Baseline Laboratory Abnormalities by NCI CTC AE Grade with ≥5% Incidence and ≥2 % Greater in the GAZYVA Treated Arm in Study BO21004/CLL11 (Stage 1a)

Investigations	Chlorambucil n = 116		GAZYVA + Chlorambucil n = 241	
	All Grades n (%)	Grades3–4 n (%)	All Grades n(%)	Grades 3–4 n (%)
Chemistry				
Hypocalcaemia	38 (33)	2 (2(	91 (38)	7 (3)
Hyperkalaemia	21 (18)	3 (3)	80 (33)	12 (5)
Creatinine increased	23 (20)	2 (2)	72 (30)	1 (<1)
Hyponatremia	14 (12)	3 (3)	72 (30)	20 (8)
AST (SGOT increased)	18 (16)	0 (0)	71 (29)	3 (1)
ALT (SGPT increased)	18 (16)	0 (0)	65 (27)	4 (2)
Hypoalbuminemia	17 (15)	1 (<1)	56 (23)	1 (<1)
Alkaline Phosphatase increased	13 (11)	0 (0)	44 (18)	0 (0)
Hypokalaemia	6 (5)	1 (<1)	35 (15)	3 (1)
Haematology				
Leukopenia	14 (12)	1 (< 1)	202 (84)	89 (37)
Lymphopenia	11 (9)	3 (3)	192 (80)	97 (40)
Neutropenia	62 (53)	31 (27)	189 (78)	115 (48)

Table 13 Post-Baseline Laboratory Abnormalities by NCI CTC AE Grade with ≥5% Incidence and ≥2 % Greater in the GAZYVA Treated Arm in Study BO21004/CLL11 (Stage 2)

Investigations	Rituximab + Chlorambucil n = 321		GAZYVA + Chlorambucil n = 336	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Chemistry				
Hypocalcaemia	102 (32)	3 (<1)	124 (37)	9 (3)
Hyperkalaemia	102 (32)	11 (3)	104 (31)	14 (4)
ALT (SGPT increased)	68 (21)	4 (1)	93 (28)	7 (2)
AST (SGOT increased)	68 (21)	3 (<1)	91 (27)	7 (2)
Hyponatremia	59 (18)	8 (2)	87 (26)	23 (7)
Hypoalbuminemia	52 (16)	1 (<1)	78 (23)	1 (<1)
Haematology				
Leukopenia	200 (62)	50 (16)	281 (84)	117 (35)
Lymphopenia	162 (50)	52 (16)	269 (80)	131 (39)
Neutropenia	221 (69)	131 (41)	257 (76)	155 (46)
Thrombocytopenia	127 (40)	26 (8)	160 (48)	44 (13)
Anaemia	118 (37)	31 (10)	130 (39)	35 (10)

Transient elevation in liver enzymes (AST, ALT, ALP) has been observed shortly after the first infusion of GAZYVA (see 8 ADVERSE REACTIONS).

Non-Hodgkin Lymphoma

Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

During the entire study GAO4753g period, which was treatment with GAZYVA plus bendamustine induction followed by GAZYVA monotherapy, the most frequently reported haematological laboratory abnormalities (any grade) were lymphopenia (99%), leukopenia (86%), low haemoglobin (83%), thrombocytopenia (77%) and neutropenia (75%). The most frequently reported haematological Grade 3-4 laboratory abnormalities were lymphopenia (93%), neutropenia (52%) and leukopenia (47%). The most frequently reported chemistry laboratory abnormalities (any grade) during the entire study were high creatinine (87%), BSA corrected creatinine clearance low (66%) and creatinine clearance low (58%). The most frequently reported chemistry Grade 3-4 laboratory abnormalities were uric acid high (15%), phosphorus low (7%) and creatinine clearance low (6%).

During the study GAO4753g GAZYVA monotherapy phase of treatment, the most frequently reported haematological laboratory abnormalities were lymphopenia (80%), leukopenia (63%), low haemoglobin (50%) and neutropenia (46%). The most frequently reported hematological Grade 3-4 laboratory abnormalities were lymphopenia (52%), neutropenia (27%) and leukopenia (20%). In the GAZYVA monotherapy phase of treatment, the most frequently reported chemistry laboratory abnormalities were hypercreatininemia (69%), decreased creatinine clearance (43%), hypophosphatemia (25%), AST (SGOT increased) (24%) and ALT (SGPT increased) (21%). The most frequently reported chemistry Grade 3-4 laboratory abnormalities were hypophosphatemia (5%) and hyponatremia (3%).

In the final analysis of study GAO4753g GAZYVA monotherapy phase of treatment, the most frequently reported haematological or chemistry laboratory abnormalities, in addition to those seen in the

primary analysis, were thrombocytopenia (37%) and high uric acid (3%).

Table 14 Post-Baseline Laboratory Abnormalities by NCI CTC AE Grade in ≥5% of iNHL Patients and ≥2 % Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm in Study GAO4753g [a, b]

Investigations	Bendamustine n = 198		GAZYVA + Bendamustine n = 194	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Chemistry				
Hypercreatininemia	183 (92)	4 (2)	169 (87)	8 (4)
Creatinine Clearance (decreased)	120 (61)	7 (4)	113 (58)	11 (6)
Hypophosphatemia	75 (38)	14 (7)	80 (41)	14 (7)
Hypocalcemia	51 (26)	3 (2)	73 (38)	3 (2)
ALT (SGPT increased)	62 (31)	7 (4)	68 (35)	2 (1)
Hematology				
Lymphopenia	196 (99)	169 (85)	192 (99)	181 (93)
Leukopenia	174 (88)	67 (34)	166 (86)	92 (47)
Neutropenia	153 (77)	84 (42)	145 (75)	100 (52)

[a] Two percent different in either the All Grades or Grade 3-4 Lab Abnormalities.
[b] Includes entire study duration (induction, monotherapy and follow-up)

In the final analysis of study GAO4753g, post-baseline laboratory abnormalities in ≥5% of iNHL patients (in all grades) and ≥2% greater (in all grades) in the GAZYVA plus bendamustine followed by GAZYVA monotherapy treated arm (n=204) as compared to the bendamustine arm (n=203) were phosphorus decreased (45%), hypocalcemia (42%), ALT increased (39%), activated partial thromboplastin time increased (30%), and hyperbilirubinemia (22%).

Previously Untreated Indolent Non-Hodgkin Lymphoma

In the induction phase of treatment with GAZYVA, the most frequently reported (incidence ≥ 1%) hematological laboratory abnormalities were lymphopenia (96%), leukopenia (88%), neutropenia (77%), anemia (72%), thrombocytopenia (65%), leukocytosis (2%), elevated international normalized ratio (1%), and elevated hemoglobin (1%). The most frequently reported hematological Grade 3 – 4 laboratory abnormalities during the induction period were lymphopenia (82%), neutropenia (50%), leukopenia (43%), thrombocytopenia (10%) and anemia (4%).

In the induction phase of treatment with GAZYVA, the most frequently reported (incidence ≥ 1%) chemistry laboratory abnormalities were elevated creatinine (78%), elevated lactate dehydrogenase (73%), decreased BSA-corrected creatinine clearance (51%), decreased creatinine clearance (46%), ALT/SGPT increased (40%), AST/SGOT increased (34%), hypoalbuminemia (31%), hypoproteinemia (29%), hyperuricemia (28%), hyperphosphatemia (26%), hypocalcemia (25%), hypophosphatemia (23%), hyponatremia (20%), hyperbilirubinemia (18%), hypokalemia (15%), hyperkalemia (14%), hypernatremia (8%), hypercalcemia (6%) and hyperproteinemia (3%). The most frequently reported chemistry Grade 3-4 laboratory abnormalities were hyperuricemia (28%), hypophosphatemia (3%), hyponatremia (2%), decreased creatinine clearance (2%), decreased BSA-corrected creatinine clearance (2%), hypokalemia (2%) and ALT/SGPT increased (1%).

In the monotherapy phase of treatment with GAZYVA, the most frequently reported (incidence ≥ 1%) hematological laboratory abnormalities were lymphopenia (80%), leukopenia (64%), neutropenia (47%) anemia (39%), and thrombocytopenia (30%). The most frequently reported hematological Grade 3–4 laboratory abnormalities during the monotherapy period were lymphopenia (38%), neutropenia (20%), leukopenia (12%) anemia (1%), and thrombocytopenia (1%).

In the monotherapy phase of treatment with GAZYVA, the most frequently reported (incidence ≥ 1%) chemistry laboratory abnormalities were elevated creatinine (82%), elevated lactate dehydrogenase (71%), hypophosphatemia (30%), ALT/SGPT increased (28%), hypocalcemia (16%), hyperkalemia (15%), hyponatremia (14%), hypoalbuminemia (14%), hyperbilirubinemia (13%), hypokalemia (12%), hypernatremia (12%), and hyperuricemia (3%). The most frequently reported chemistry Grade 3–4 laboratory abnormalities during the monotherapy period were hypophosphatemia (4%), hyperuricemia (3%), hyponatremia (2%), and decreased creatinine clearance (1%).

Table 15 Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with previously untreated iNHL and at Least 2% Greater in the GAZYVA plus Chemotherapy Followed by GAZYVA Monotherapy Treated Arm[a]

Laboratory Abnormalities	rituximab + chemotherapy followed by rituximab monotherapy n = 692		GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 698	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Chemistry				
Elevated creatinine	593 (86)	5 (<1)	616 (88)	6 (<1)
Elevated lactate dehydrogenase	554 (80)	3 (<1)	587 (84)	3 (<1)
ALT/SGPT increased	300 (43)	15 (2)	358 (51)	17 (2)
AST/SGOT increased	285 (41)	10 (1)	316 (45)	10 (1)
Hypophosphatemia	229 (33)	37 (5)	251 (36)	38 (5)
Hypoalbuminemia	190 (27)	7 (1)	249 (36)	10 (1)
Hypocalcemia	171 (25)	4 (<1)	221 (32)	5 (<1)
Hyperuricemia	163 (24)	163 (24)	208 (30)	208 (30)
Hyponatremia	140 (20)	21 (3)	187 (27)	29 (4)
Hyperkalemia	118 (17)	5 (<1)	161 (23)	8 (1)
Hypernatremia	89 (13)	0 (0)	111 (16)	2 (<1)
Haematology				
Lymphopenia	661 (96)	462 (67)	677 (97)	580 (83)
Leukopenia	611 (88)	265 (38)	639 (92)	332 (48)
Neutropenia	524 (76)	341 (49)	579 (83)	404 (58)
Thrombocytopenia	352 (51)	28 (4)	474 (68)	74 (11)

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

8.5 Post-Market Adverse Reactions

No additional adverse drug reactions have been identified in post-marketing experience for the approved indications.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug-drug interaction studies have been conducted with GAZYVA and a risk of interactions of GAZYVA with concomitantly used medications cannot be excluded.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

GAZYVA (obinutuzumab) is a recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of GAZYVA results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, and macrophages and monocytes as compared to non-glycoengineered antibodies.

In nonclinical studies, GAZYVA induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells. In addition, GAZYVA mediates low degree of complement dependent cytotoxicity (CDC). In animal models, GAZYVA mediates potent B cell depletion and antitumour efficacy. Compared to Type I CD20 antibodies, GAZYVA, a Type II antibody, is characterized by an enhanced direct cell death induction with a concomitant reduction in CDC. Compared to non-glycoengineered CD20 antibodies, GAZYVA is characterized by enhanced antibody dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP) as a consequence of the glycoengineering. This translates in superior B cell depletion and anti-tumour efficacy in animal models.

10.2 Pharmacodynamics

In the pivotal clinical trial in patients with CLL BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with GAZYVA were B cell depleted (defined as CD19+ B-cell counts $<0.07 \times 10^9$/L) at the end of treatment period and remained depleted during the first 6 months of follow up. Recovery of B cells was observed within 12 to 18 months of follow up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease.

In study GAO4753g, of the 121 patients who had a B-cell result, 116 patients had B-cell depletion at the last obinutuzumab administration. Recovery cannot be assessed because of the low number of patients who had been followed for a sufficient length of time at the time of data cut-off. At 6-12 months after the last obinutuzumab administration, 26 patients had had a B cell assessment, and the B cells had recovered in 1 of the 26 patients. Results of B-cell assessment were available for the 11 patients with a follow-up of 12 months or longer and of those patients, the counts had recovered for 2 patients.

In the pivotal clinical study in patients with iNHL (GAO4753g/GADOLIN), 97% (171 out of 176) of evaluable patients treated with GAZYVA were B-cell depleted at the end of the treatment period, and 97% (61 out of 63) remained depleted for more than 6 months from the last dose. Recovery of B-cells was observed within 12-18 months of follow-up in 11% (5 out of 46) of evaluable patients.

10.3 Pharmacokinetics

In the phase II part of study BO20999, a cohort of patients with CLL received obinutuzumab as monotherapy (1000 mg Cycle 1 Days 1, 8 and 15, and Cycles 2-8 1000 mg).

Absorption

GAZYVA is administered intravenously. There have been no clinical studies performed with other routes of administration. In study BO20999 (Phase 2 CLL patients), after the Cycle 8 Day 1 infusion in CLL patients, the mean C_{max} value was 799 (+/- 307) µg/mL. In iNHL patients the estimated median C_{max} value was 539.3 µg/mL.

Distribution:

Following intravenous administration, the mean volume of distribution is 16.1 (+/- 31.4) L.

Metabolism:

The metabolism of GAZYVA has not been directly studied. Antibodies are mostly cleared by catabolism.

Elimination:

The mean clearance of GAZYVA on Cycle 8 in CLL patients is approximately 125 (+/- 81.5) mL/day with a mean elimination t½ of 23.9 (+/- 11.1) days.

Figure 1 **Study BO20999 Phase II Mean Obinutuzumab Serum Concentrations in CLL Patients Following Administration of 1000 mg Obinutuzumab during the Eight Cycles of Treatment Periods. Induction and Follow-up Periods**

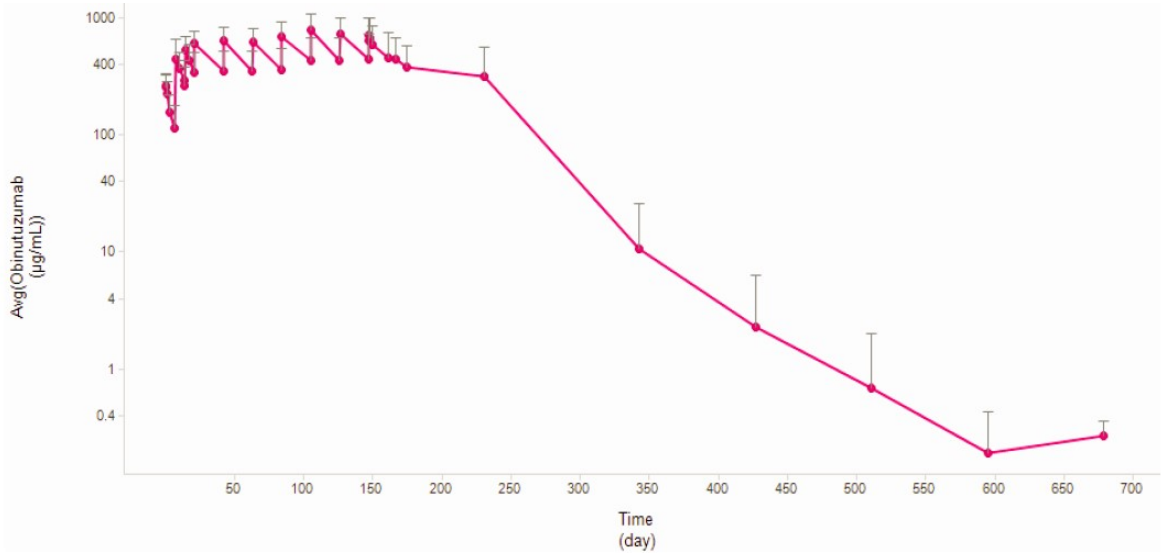


Table 16 **Study BO20999 Phase II: Obinutuzumab Serum PK Parameters for CLL Patients on Cycle 8 Following Administration of 1000 mg Obinutuzumab to CLL Patients (N=12)**

Descriptive Stats	Cmax (ug/ml)	AUC7d (day*ug/mL)	AUClast (day * ug/mL)	CLss (mL/day)	Vss (L)	t1/2 (days)
Mean	799	4350	42448	125	16.1	23.9
SD	307	2078	23877	81.5	31.4	11.1
GeoMean	741	3870	36000	105	7.20	21.0

% CV	38.4	47.8	56.2	65.1	194	46.2

Table 17 Study BO20999 Phase II: Trough Serum Concentrations (C_{trough} as ug/mL) of CLL Patients from Cycle 2 to Cycle 8 Following Administration of 1000 mg of Obinutuzumab

Descriptive Statistics	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
N	17	16	16	12	13	13	13
Mean	341	345	347	354	424	424	437
SD	167	176	163	194	242	238	291
GeoMean	305	292	286	276	314	330	306
% CV	48.8	50.8	47.1	54.7	57.2	56	66.7

CLL = chronic lymphocytic leukaemia; CV = coefficient of variance of the arithmetic mean; GeoMean = geometric mean; SD = standard deviation.

Table 18 Study BO21003 Phase I: Obinutuzumab Serum PK Parameters Following Administration of 200-2000 mg Obinutuzumab on Cycle 4 (Induction). Given as Monotherapy in Patients with CD20+ Malignant Disease

Dose (mg)	Descriptive Statistics	Cmax (µg/mL)	AUCLAST a (day *µg/mL)	AUC7d(day *µg/mL)	CLss (mL/day)	Vss (L)	t1/2 (day)	Ctrough µg/mL
200 N = 3	Mean	178	4688	875	360	14.8	61.1	109
	SD	87.0	4427	526	329	8.68	49.5	76.1
	GeoMean	161	2580	722	276	12.3	34.2	79
	% CV	48.9	94.4	60.1	91.4	58.6	81.0	69.8
400 N = 3	Mean	320	18172	2064	207	33.1	115	280
	SD	100	6218	693	59	34.4	134	115
	GeoMean	310	17500	1990	201	22.4	69.3	266
	% CV	31.3	34.2	33.6	28.5	104	117	41.1
800 N = 3	Mean	466	16886	2666	832	7.72	15.6	336
	SD	261	14796	1978	1080	4.24	17.8	282
	GeoMean	397	6310	1780	451	6.92	9.00	137
	% CV	56.0	87.6	74.2	129.8	55	114	83.9
1000 N = 6	Mean	620	22332	3654	813	26.8	102	477
	SD	324	19113	2293	1229	19.8	88.5	331
	GeoMean	510	8850	2510	398	19.8	55.8	121
	% CV	52.3	85.6	62.8	151	73.9	86.8	69.4
1200 N = 3	Mean	1106	28237	6564	196	17.1	57.6	640 b
	SD	368	14617	2221	58	18.5	55.2	NA
	GeoMean	1070	25700	6330	189	11.4	41.6	640 b
	% CV	33.3	51.8	33.8	30	108.2	95.8	NA
2000 N = 3	Mean	1422	32767	8947	243	11.8	38.8	1222
	SD	407	13906	2981	89.2	10.5	32.3	501
	GeoMean	1380	30700	8580	233	9.18	31.2	1150
	CV%						83.2	28.6

CV = coefficient of variance of the arithmetic mean; GeoMean = geometric mean; NA = Not Applicable; PT = patient SD = standard deviation.

In this dosing regimen AUCτ = AUC7d.

[a] Last time point of the AUC_{last} could vary from patient to patient depending on PK sample availability. For comparison across doses use AUCτ.

[b] C_{trough} value with N=1.

Noncompartmental analysis (NCA) was used to determine obinutuzumab PK parameters. The PK parameters C_{max}, AUC and C_{trough} appear to increase linearly with dose. During induction, an accumulation ratio approximating 3, based on AUCτ from Cycle 1 to Cycle 4, was observed for all dose-cohorts tested.

Special Populations and Conditions

- **Pediatrics:** No studies have been conducted to investigate the pharmacokinetics of GAZYVA in children.
- **Geriatrics:** No studies have been conducted to investigate the pharmacokinetics of GAZYVA in elderly patients.
- **Hepatic Insufficiency:** No formal pharmacokinetic study has been conducted nor was PK data collected in patients with hepatic impairment.
- **Renal Insufficiency:** No formal pharmacokinetic study has been conducted in patients with renal insufficiency.

11 STORAGE, STABILITY AND DISPOSAL

Store vials in a refrigerator at 2 - 8°C.

GAZYVA (obinutuzumab) should not be used after the expiry date (EXP) shown on the vial and carton.

Keep vial in the outer carton in order to protect from light. **DO NOT FREEZE. DO NOT SHAKE.**

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 - 8°C followed by 24 hours at ambient temperature (≤ 30°C) followed by an infusion taking no longer than 24 hours.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

GAZYVA does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: GAZYVA

Chemical name: obinutuzumab

Molecular formula and molecular mass: 146,321 Daltons (peptide chains only, with heavy chain C-terminal lysine residue, with heavy chain N-terminal glutamines)

Structural formula: Two heavy chains (449 amino acid residues each) and two light chains (219 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG1 antibodies

Physicochemical properties: Concentrate for solution for infusion: clear, colourless to slightly brownish liquid

Pharmaceutical standard: Professed

Product Characteristics:

GAZYVA (obinutuzumab) is a recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Chronic Lymphocytic Leukaemia

Study BO21004/CLL11

GAZYVA was evaluated in a three arm, open-label, active control, randomized, multicentre trial (BO21004/CLL11) in patients with previously untreated CD20+ chronic lymphocytic leukaemia requiring treatment and had coexisting medical conditions and/or reduced renal function as measured by creatinine clearance (CrCl) <70 mL/min. Patients with CrCl <30 mL/min, active infections, positive hepatitis B (HBsAg or anti-HBc positive, patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, or immunization with live virus vaccine within 28 days prior to randomization were excluded from the trial. Patients were treated with chlorambucil control (Arm 1), GAZYVA in combination with chlorambucil (Arm 2) or rituximab in combination with chlorambucil (Arm 3). The safety of GAZYVA was evaluated in a Stage 1a comparison of Arm 1 vs. Arm 2 in 357 patients and a Stage 2 comparison of Arm 2 vs. Arm 3 in 657 patients. The efficacy of GAZYVA was evaluated in a Stage1a comparison of Arm 1 vs. Arm 2 in 356 patients and a Stage 2 comparison of Arm 2 vs. Arm 3 in 663 patients.

The majority of patients received 1000 mg of GAZYVA on days 1, 8, and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of GAZYVA was divided between day 1 (100 mg) and day 2 (900 mg) (see 4 DOSAGE AND ADMINISTRATION), 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).

The median age was 73 years, 61% were male, and 95% were Caucasian. At baseline, 22% of patients were Binet stage A, 42% were stage B, and 36% were stage C. For all patients enrolled in both treatment arms, the median comorbidity score was 8 and 76% of the patients enrolled had a comorbidity score above 6. The median estimated CrCl was 62 mL/min and 66% of all patients had a CrCl <70 mL/min. Forty-two percent of patients enrolled had both a CrCl <70 mL/min and a comorbidity score of >6. Thirty-four percent of patients were enrolled on comorbidity score alone, and 23% of patients were enrolled with only impaired renal function. The most frequently reported coexisting medical conditions (using a cut off of 30% or higher), in the MedDRA body systems are: Vascular disorders 73%, Cardiac disorders 46%, GI disorders 38%, Metabolism and Nutrition disorders 40%, Renal and Urinary disorders 38%, musculoskeletal and connective tissue disorders 33%. Eighty-one percent of patients treated with GAZYVA in combination with chlorambucil received all 6 cycles compared to 89% of patients in the rituximab treated arm and 67% of patients in the chlorambucil alone arm.

In the Stage 1a analysis, the median progression free survival (PFS) assessed by an independent review committee (IRC) was 27.2 in the GAZYVA plus chlorambucil arm vs. 11.2 months in the chlorambucil alone arm, which is consistent with the investigator's assessment (the primary endpoint of the study) with a median observation time of 22.8 months. Key secondary efficacy endpoints of the study include response rate, median duration of response and overall survival. The median overall survival 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 at the data cut-off (09 May 2013). The hazard ratio for OS was 0.41(95% CI: 0.23-0.74). Overall survival will continue to be followed.

In the Stage 2 analysis, the median PFS was 26.7 months in the GAZYVA plus chlorambucil arm and 14.9 months in the rituximab plus chlorambucil 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 cut-off 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). MRD was evaluated in bone marrow samples from 133 patients in the GAZYVA arm and 114 patients in the rituximab arm and in peripheral blood samples from 231 and 243 patients respectively. In the bone marrow analysis, 26 patients (20% of evaluable patients) had negative MRD in the GAZYVA arm compared to 3 patients (3% of evaluable patients) in the rituximab arm. In peripheral blood 87 patients (38% of evaluable patients) had negative MRD in the GAZYVA arm compared to 8 patients (3% of evaluable patients) in the rituximab arm.

Efficacy results are shown in Table 19 and the Kaplan-Meier curves for Stage 1a Overall Survival and Stage 2 IRC-assessed PFS is shown in Figure 2 and

Figure 3, respectively.

Table 19 Summary of Efficacy from Study BO21004 (CLL11) [4, 5]

	Stage 1a (data cut-off 09 May 2013)		Stage 2 (data cut-off 09 May 2013)	
	chlorambucil N=118	GAZYVA + chlorambucil N=238	rituximab + chlorambucil N = 330	GAZYVA + chlorambucil N = 333
	22.8 months median observation time		18.7 months median observation time	
IRC-assessed PFS (PFS-IRC)[1]				
Number (%) of patients with event	90 (76.3%)	89 (37.4%)	183 (55.5%)	103 (30.9%)
Median time to event (months)	11.2	27.2	14.9	26.7
HR (95% CI)	0.19 [0.14; 0.27]		0.42 [0.33; 0.54]	
p-value (Log-Rank test, stratified [2])	<0.0001		<0.0001	
End of Treatment Response Rate				
No. of patients included in the analysis	118	238	329	333
Responders (%)	37 (31.4%)	184 (77.3%)	214 (65.0%)	261 (78.4%)
Difference in response rate, (95% CI)	45.95 [35.6; 56.3]		13.33 [6.4; 20.3]	
p-value (Chi-squared Test)	<0.0001		0.0001	
No. of complete responders [3] (%)	0 (0.0%)	53 (22.3%)	23 (7.0%)	69 (20.7%)
Median Duration of Response				
No. of patients included in the analysis	41	189	220	269
Months	5.1	22.4	9.7	19.6
[95% CI]	[3.3; 6.7]	[17.1; -]	[8.9; 12.1]	[17.1; -]
Overall Survival				
No. of patients with event	24 (20.3%)	22 (9.2%)	Not Yet Mature	
HR (95% CI)	0.41 [0.23; 0.74]			
Molecular Remission at end of treatment (Blood)				
No. of patients included in the analysis	90	162	243	231
MRD negative [6] (%)	0 (0%)	67 (41%)	8 (3%)	87 (38%)
MRD positive [7] (%)	90 (100%)	95 (59%)	235 (97%)	144 (62%)
Difference in MRD rates, (95% CI)	41.36 [33.2; 49.5]		34.37 [27.5; 41.2]	
Molecular Remission at end of treatment (Bone marrow)				
No. of patients included in the analysis	31	100	114	133
MRD negative [6] (%)	0 (0%)	21 (21%)	3 (3%)	26 (20%)
MRD positive [7] (%)	31 (100%)	79 (79%)	111 (97%)	107 (80%)
Difference in MRD rates, (95% CI)	21.00 [11.4; 30.6]		16.92 [9.1; 24.7]	
Time to new anti-leukemic therapy				
No. (%) of patients with event	65 (55.1%)	51 (21.4%)	86 (26.1%)	55 (16.5%)
Median time to event (months)	14.8	-	30.8	-
HR (95% CI)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified [2])	<0.0001		0.0018	

	Stage 1a (data cut-off 09 May 2013)		Stage 2 (data cut-off 09 May 2013)	
	chlorambucil N=118	GAZYVA + chlorambucil N=238	rituximab + chlorambucil N = 330	GAZYVA + chlorambucil N = 333
	22.8 months median observation time		18.7 months median observation time	

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, MRD: Minimal Residual Disease

[1] Defined as the time from randomization to the first occurrence of progression, relapse or death from any cause as assessed by the investigator.

[2] stratified by Binet stage at baseline.

[3] Includes 11 patients in the GClb arm with a complete response with incomplete marrow recovery.

[4] Stage 1a: Investigator-assessed median PFS was 11.1 months in the Clb arm and 26.7 months in the GClb arm, the HR (95% CI) was 0.18 [0.13; 0.24] and p-value was <0.0001.

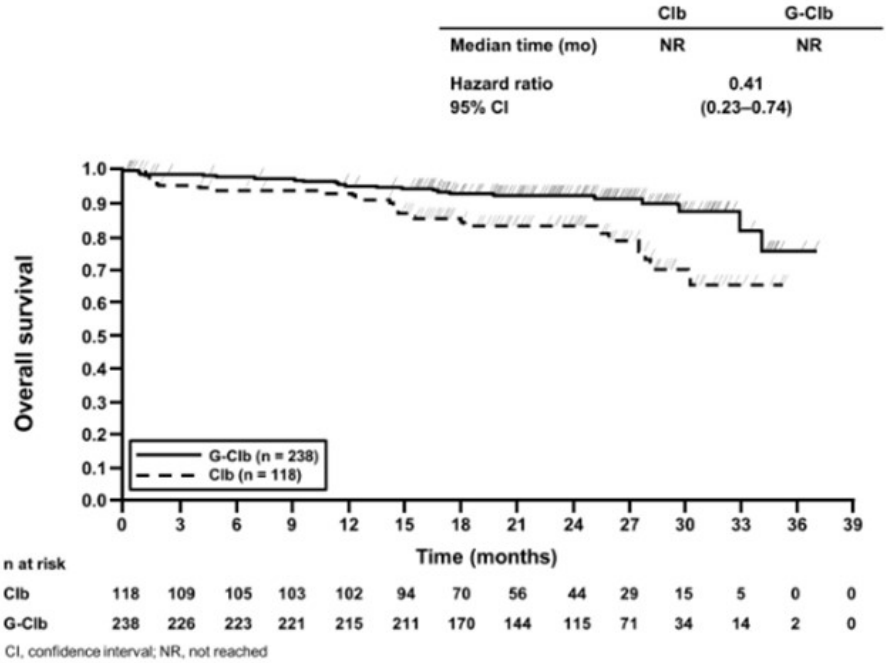
[5] Stage 2: Investigator-assessed median PFS was 15.2 months in the RClb arm and 26.7 months in the GClb arm, the HR (95% CI) was 0.39 [0.31; 0.49] and p-value was <0.0001. The concordance between IRC- assessed PFS and investigator-assessed PFS were 92% in the RClb arm and 92% in the GClb arm.

[6] MRD negativity is defined as a result below 0.0001.

[7] Includes MRD positive patients and patients who progressed or died before end of treatment.

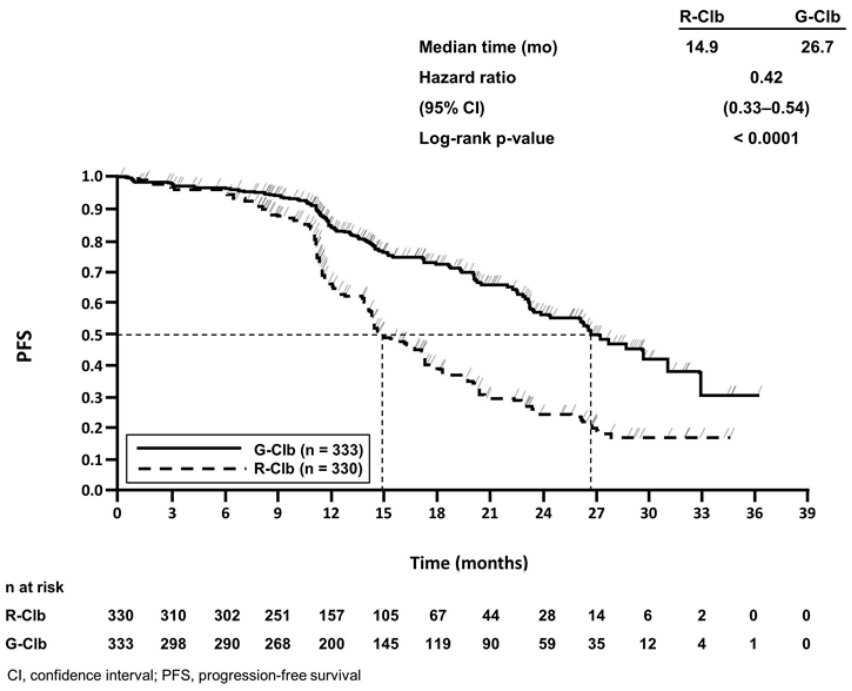
The results of other secondary endpoints assessed, including molecular remissions at end of treatment in blood and bone marrow, event free survival and time to new anti-leukaemic therapy, are in favour of GAZYVA in combination with chlorambucil over chlorambucil alone (Stage 1a) as well as GAZYVA in combination with chlorambucil over rituximab in combination with chlorambucil (Stage 2).

Figure 2 Kaplan-Meier Curve of Overall Survival (Stage 1a)



CI, confidence interval; NR, not reached

Figure 3 Kaplan-Meier curve of IRC-assessed progression-free survival (Stage 2)



CI, confidence interval; PFS, progression-free survival

Non-Hodgkin Lymphoma (Follicular Lymphoma)

Relapsed/Refractory Follicular Lymphoma: Study GAO4753g/GADOLIN

GAZYVA was evaluated in a phase III, open-label, multicenter, randomized and controlled trial (GAO4753g/GADOLIN) in 396 patients with indolent Non-Hodgkin lymphoma (iNHL) (81% with follicular lymphoma) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. Patients were randomized 1:1 to receive either bendamustine alone (n = 202) or GAZYVA in combination with bendamustine (n = 194) for 6 cycles, each of 28 days duration. Patients in the GAZYVA plus bendamustine arm who did not have disease progression [i.e. patients with a complete response (CR), partial response (PR) or stable disease (SD)] at the end of the sixth cycle continued receiving GAZYVA monotherapy until disease progression or for up to two years, whichever occurred first. Patients were stratified according to iNHL subtype (follicular vs. non follicular), rituximab-refractory type (refractory to prior rituximab monotherapy versus rituximab in combination with chemotherapy) and the number of prior therapies (≤2 versus >2).

GAZYVA was given intravenously as a 1000 mg dose on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2-6, and in patients who did not have disease progression, every 2 months for up to 2 years or until disease progression. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with GAZYVA or 120 mg/m^2/day when given alone.

The demographic data and baseline characteristics were in general balanced between the two treatment groups [median age was 63 years (age range was 21 to 87 years in the bendamustine arm

and 34 to 87 years in the GAZYVA plus bendamustine arm); the majority of patients were Caucasian (88%) and male (58%)]. The median time from initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10); 44% of patients had received 1 prior therapy and 34% of patients had received 2 prior therapies. Demographic characteristics in the follicular lymphoma patients were consistent with the iNHL population of the trial.

The primary analysis was progression-free survival (PFS) in the iNHL population assessed by an independent review committee (IRC). Median observation time was 21.1 months. The median PFS was 14.9 months in the bendamustine arm and had not been reached in the GAZYVA plus bendamustine arm (stratified HR 0.55 [0.40, 0.74], stratified log-rank test p value = 0.0001). The secondary endpoints included PFS as assessed by investigator, best overall response rate (BOR), duration of the response and overall survival. The median PFS as assessed by investigator was 14.0 months in the bendamustine arm and 29.2 months in the GAZYVA plus bendamustine arm (HR 0.52 [0.39, 0.70]). BOR was 76.6% in the bendamustine arm and 78.6% in the GAZYVA plus bendamustine arm. The median duration of response was 13.2 months in the bendamustine arm and had not been reached in the GAZYVA plus bendamustine arm (stratified HR 0.42 [0.29, 0.61]). The median overall survival was not reached in both arms.

The efficacy results in the FL population were consistent with the efficacy results in the iNHL population. The median PFS as assessed by IRC was 13.8 months in the bendamustine arm and had not been reached in the GAZYVA plus bendamustine arm (HR 0.48 [95% CI: 0.34, 0.68], stratified log-rank test p value <0.0001). The median PFS as assessed by investigator was 13.7 months in the bendamustine arm and 29.2 in the GAZYVA plus bendamustine arm (HR 0.48 [0.35, 0.67]). The BOR was 77.0% in the bendamustine arm and 79.7% in the GAZYVA plus bendamustine arm. The median duration of response was 11.9 months in the bendamustine arm and had not been reached in the GAZYVA plus bendamustine arm (stratified HR 0.36 [0.24, 0.54]). Median overall survival was not reached in both arms.

Table 20 summarizes the efficacy results in iNHL and FL patients. Kaplan-Meier curves for PFS are shown in Figure 4 and Figure 5. Kaplan-Meier curves for OS are shown in Figure 6 and Figure 7.

Table 20 Summary of Efficacy in iNHL and FL Patients from the GAO4753g (GADOLIN) Study

	iNHL		**FL**	
	Bendamustine N=202	**GAZYVA plus bendamustine followed by GAZYVA monotherapy N=194**	**Bendamustine N=166**	**GAZYVA plus bendamustine followed by GAZYVA monotherapy N=155**
	Median observation time 20 months	**Median observation time 22 months**	**Median observation time 20 months**	**Median observation time 22 months**
Median PFS-assessed by IRC (months) HR [95% CI] p-value (Log-Rank test, stratified*)	14.9 0.55 [0.40, 0.74] 0.0001	NR	13.8 0.48 [0.34, 0.68] < 0.0001	NR
Median PFS-assessed by investigator (months)	14.0	29.2	13.7	29.2

	iNHL		FL	
	Bendamustine N=202	GAZYVA plus bendamustine followed by GAZYVA monotherapy N=194	Bendamustine N=166	GAZYVA plus bendamustine followed by GAZYVA monotherapy N=155
HR [95% CI]	0.52 [0.39, 0.70]		0.48 [0.35, 0.67]	
Best Overall Response (BOR) (IRC-assessed)§ (%) (CR, PR)	151 (76.6%)	151 (78.6%)	124 (77.0%)	122 (79.7%)
Difference in response rate (%) [95% CI]	2.00 [-6.56, 10.55]		2.72 [-6.74, 12.18]	
Complete response (CR)	34 (17.3%)	32 (16.7%)	31 (19.3%)	24 (15.7%)
Partial response (PR)	117 (59.4%)	119 (62.0%)	93 (57.8%)	98 (64.1%)
Median duration of response (IRC-assessed) (months)	13.2	NR	11.9	NR
HR [95% CI]	0.42 [0.29, 0.61]		0.36 [0.24, 0.54]	
Median Overall Survival (months)	NR ¶	NR ¶	NR ¶	NR ¶
HR [95% CI]	0.82 [0.52, 1.30] ¶		0.71 [0.43, 1.19] ¶	

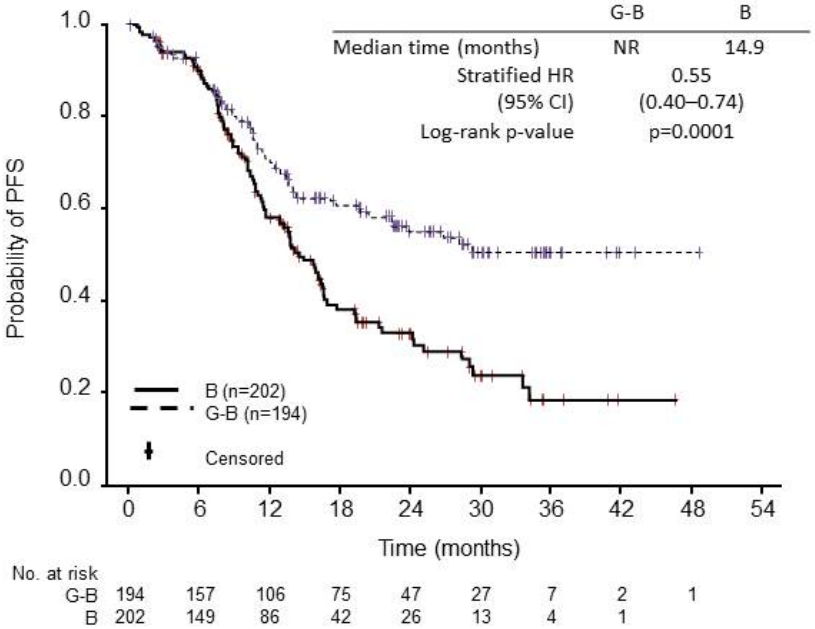
IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, NR: Not Reached

* Stratification factors were iNHL subtype (follicular vs. non-follicular: not used in analysis of patients with FL), refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2)

§ Best response within 12 months of start of treatment

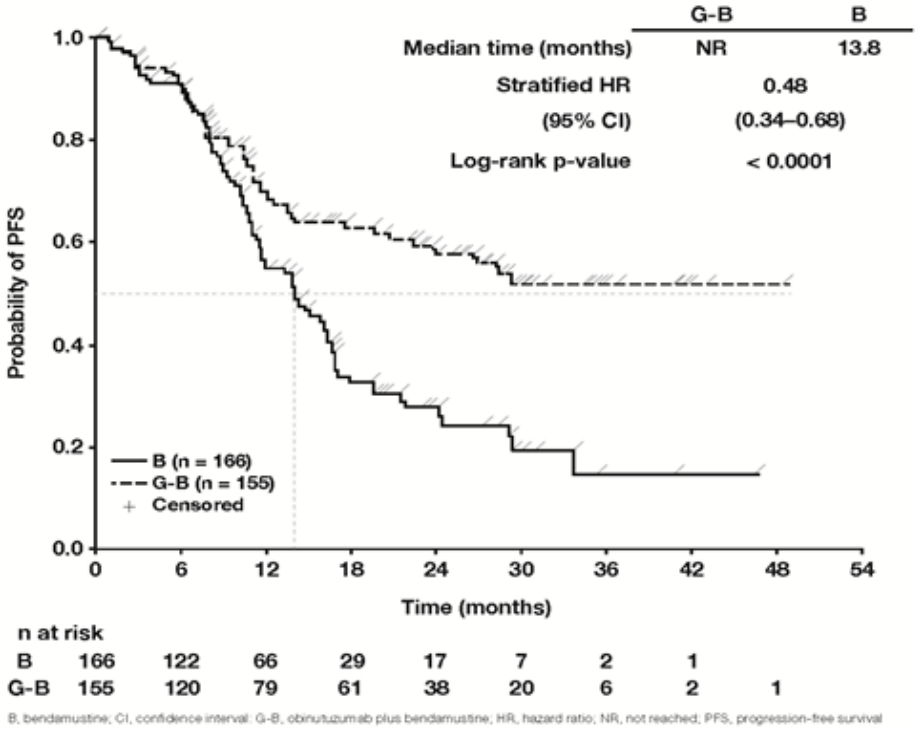
¶ Data Not Yet Mature

Figure 4 **Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival in iNHL Patients (Cut-off date: 01 September 2014)**



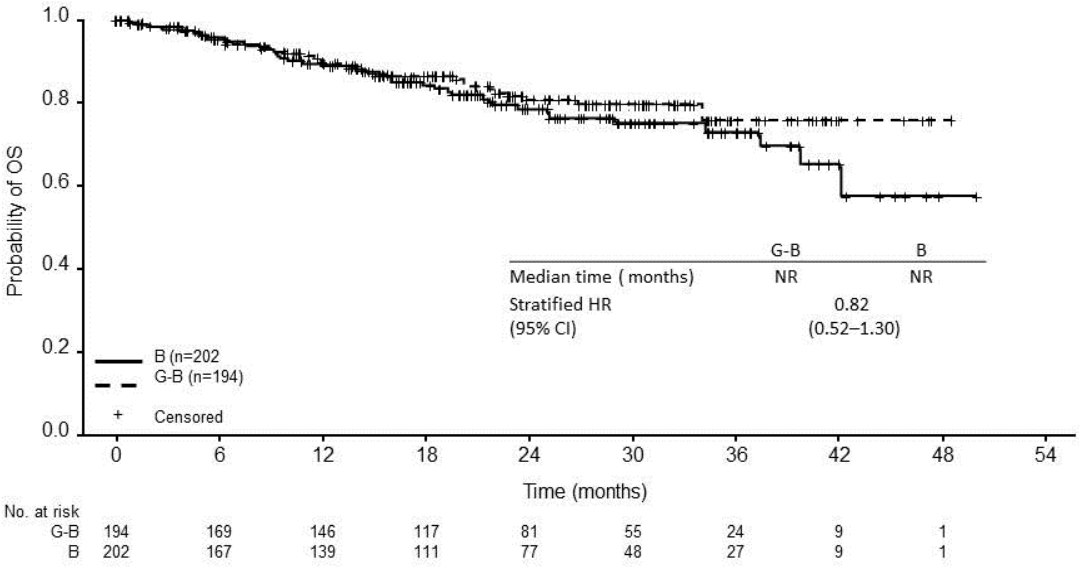
B, bendamustine; CI, confidence interval; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Figure 5 **Kaplan-Meier Curve of IRC-assessed Progression-Free Survival in FL Patients (Cut-off date: 01 September 2014)**



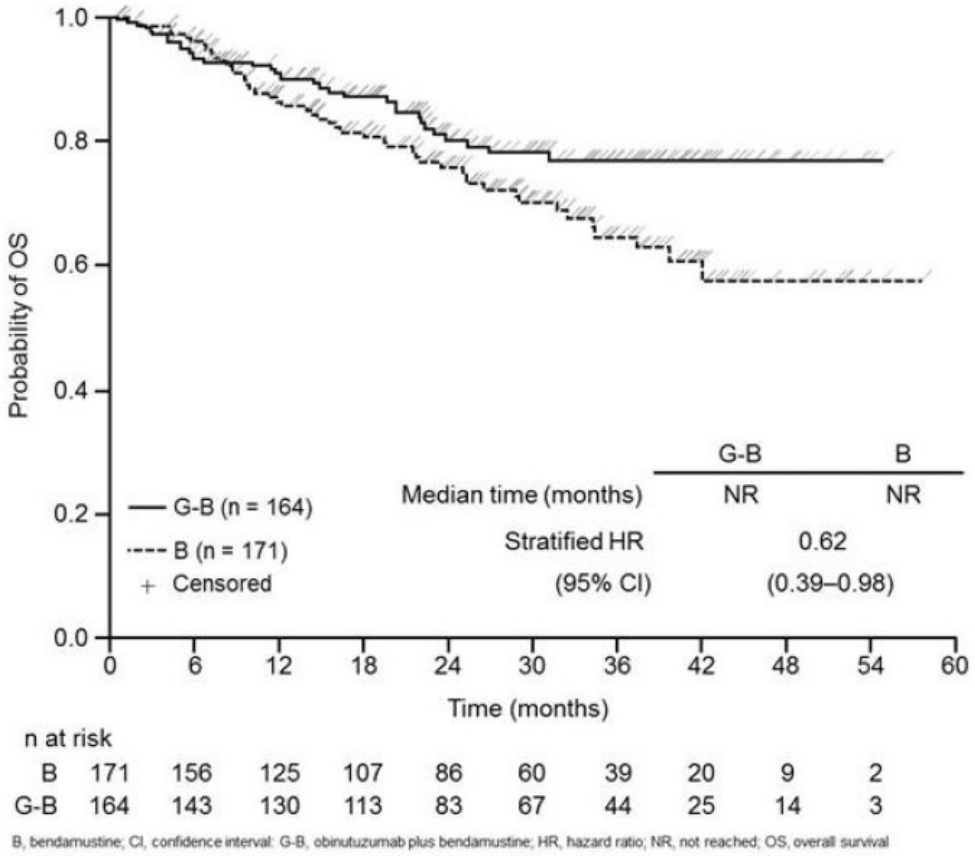
B, bendamustine; CI, confidence interval; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NR, not reached; PFS, progression-free survival

Figure 6 **Kaplan-Meier Curve of Overall Survival in iNHL Patients (Cut-off date: 01 September 2014)**



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

Figure 7 Kaplan-Meier Curve of Overall Survival in FL Patients (Cut-off date: 01 May 2015)*



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

*An analysis conducted with 24.1 months of median observation time revealed that the median overall survival was not yet reached in either arm.

At the final exploratory analysis, the median observation time was 45.9 months (range: 0-100.9 months) for FL patients in the B arm and 57.3 months (range: 0.4-97.6 months) for patients in the G+B arm, representing an additional 25.6 months and 35.2 months of median follow-up in B and G+B arms, respectively, since the primary analysis. Only Investigator (INV) assessed endpoints were reported at the final analysis since IRC assessments did not continue. Based on the final exploratory analysis, the overall survival (OS) HR for risk of death in patients with FL was 0.71 (95%CI: 0.51, 0.98).

Previously Untreated Follicular Lymphoma

Study BO21223/GALLIUM

In a multicentre phase III, open-label, randomized study (BO21223/GALLIUM), 1202 previously untreated patients with stage II (bulky)/III/IV follicular lymphoma (FL) were evaluated. Patients were randomized 1:1 to receive either GAZYVA or rituximab in combination with chemotherapy (CHOP, CVP, or bendamustine) followed by GAZYVA or rituximab monotherapy in patients who achieved a complete or partial response. Randomization was stratified by chemotherapy (selected by each investigational site; all patients at that site received the chosen chemotherapy regimen for the duration of the study), FLIPI risk group and geographic region. The study excluded patients with follicular lymphoma grade 3b or transformed disease.

The demographic data and baseline characteristics of the FL population were well balanced [median age was 59 years, the majority of patients were Caucasian (81%), and female (53%)]. Seventy-nine percent had a FLIPI score of ≥2 and 7% had Stage II (bulky), 35% had Stage III and 57% had Stage IV disease. Fifty-seven percent received bendamustine, 33% received CHOP, and 10% received CVP chemotherapy. Forty-four percent had bulky disease (>7 cm), 34% had at least one B-symptom at baseline and 97% had an ECOG performance status of 0-1 at baseline.

GAZYVA (1000 mg) was administered intravenously (see 4 DOSAGE AND ADMINISTRATION) prior to chemotherapy. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with GAZYVA. Standard dosing of CHOP and CVP was given. Following 6-8 cycles of treatment with GAZYVA in combination with chemotherapy, patients who responded to induction therapy were given GAZYVA monotherapy every 2 months for 2 years or until disease progression.

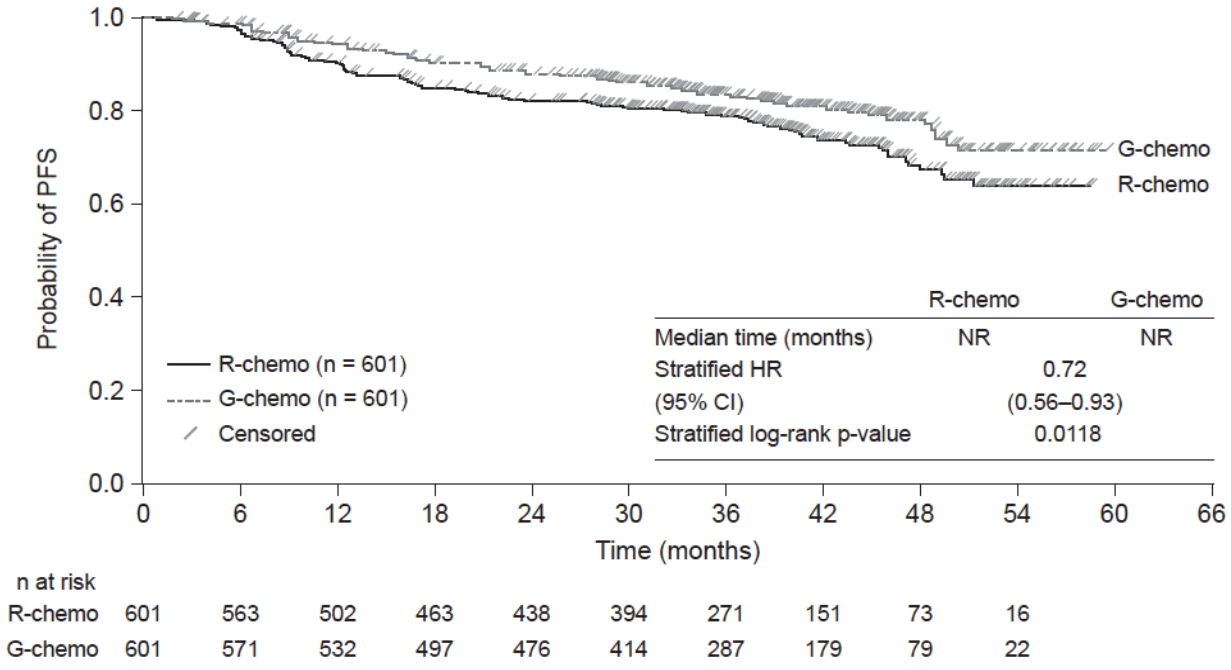
Primary efficacy evaluation was based on progression free survival (PFS) defined as the time from randomization to the first occurrence of progression or relapse as assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) or death from any cause. PFS based on Independent Review Committee (IRC) was analyzed to support the primary analysis, and was consistent.

Table 21 Summary of Efficacy in FL Patients from Study BO21223 (GALLIUM)*

	rituximab + chemotherapy followed by rituximab monotherapy n = 601	**GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 601**
PFS (IRC-assessed)		
Number of events (%)	141 (23.5%)	108 (18%)
Hazard Ratio	0.72 [95% CI: 0.56, 0.93]	
p-value	0.0118	
3 year PFS estimate [95% CI]	78.9 % [75.2, 82.1]	83.4% [79.9, 86.3]
Complete response rates at end of induction as assessed by CT (IRC-assessed)	161 (27%)	171 (28%)
Overall response rates as assessed by CT (IRC-assessed)	529 (88%)	549 (91%)

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Interval
Note: p-values and hazard ratios were calculated using the stratified log-rank test and stratified Cox regression for time-to-event endpoints, respectively. Stratification factors were chemotherapy and FLIPI.
*Following a pre-specified interim analysis, the Independent Data Monitoring Committee (IDMC) recommended the study to be unblinded and fully analyzed because the pre-specified boundary for the primary endpoint of Investigator-assessed PFS had been met. These findings are based on an updated efficacy analysis of IRC-assessed PFS, with a median observation time of 41.1 months.

Figure 8 **Kaplan-Meier Curve of IRC-assessed Progression-Free Survival in Patients with Previously Untreated FL (Cut-off date: 10 September 2016)**

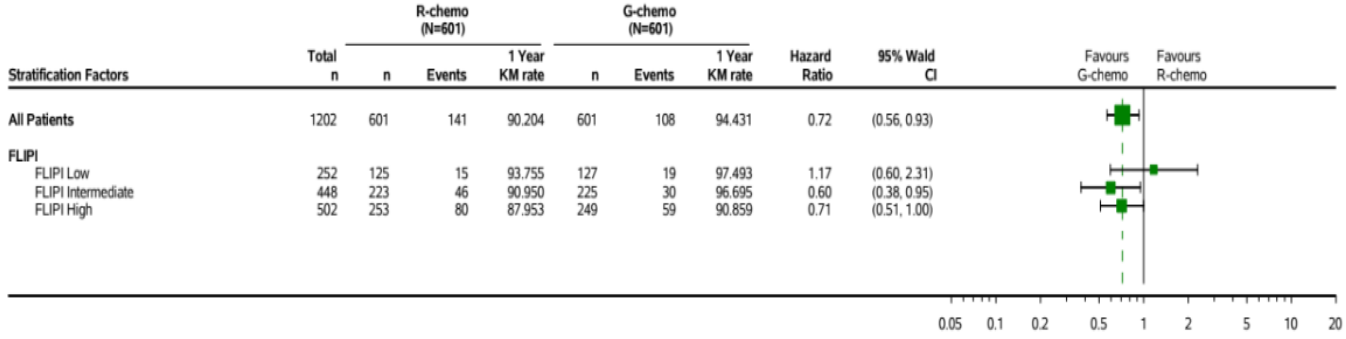


CI, confidence interval; G-chemo, obinutuzumab plus chemotherapy; HR, hazard ratio; NR, not reached; PFS, progression-free survival; R-chemo, rituximab plus chemotherapy

At a median observation time of 41.1 months, the estimate of the hazard ratio based on Independent Review Committee (IRC) assessed PFS events was 0.72 with a 95% CI of 0.56-0.93 and the stratified log-rank test p-value was 0.0118. Please see Table 21 and Figure 8 for more details. On the basis of Kaplan-Meier estimates, 78.9% (95% CI: 75.2, 82.1) of patients in the rituximab containing arm and 83.4% (95% CI: 79.9, 86.3) of patients in the GAZYVA containing arm were progression-free at 3 years. The median PFS was not reached in either arm.

Prospectively planned exploratory subgroup analyses of IRC-assessed PFS were conducted for the stratification factors for the updated analysis. The results across all subgroups, with the exception of one, were in the same direction (point estimates of HR<1) as for the FL ITT population. In the analyses of PFS stratified by FLIPI risk category (low, intermediate, high), the proportion of patients in the FLIPI-low group with disease progression or death was 14.9% (19/127) in the GAZYVA arm and 12% (15/125) in the rituximab arm (see Figure 9).

Figure 9 **IRC-assessed Progression-Free Survival based on FLIPI risk category (Cut-off date: 10 September 2016)**



Unstratified hazard ratio is displayed.
CI = confidence interval

These results should be interpreted with caution given the inherent limitations associated with sub-group analysis.

Short Duration Infusion Study (MO40597/GAZELLE)
The safety of short (approximately 90 minutes) duration infusion (SDI) of obinutuzumab administered in combination with CHOP, CVP or bendamustine chemotherapy was evaluated in a multicenter, open-label, single arm study in 113 patients with previously untreated advanced follicular lymphoma (Study MO40597/GAZELLE).

Patients received the first cycle of obinutuzumab at the standard infusion rate on Day 1, 8, and 15 of cycle 1. Patients who did not experience any Grade ≥3 IRRs during the first cycle received SDI from Cycle 2 onwards.

The primary endpoint of the study was the proportion of patients who experienced a Grade ≥3 IRR associated with SDI during Cycle 2, among those who had previously received 3 administrations of obinutuzumab at the standard infusion rate during Cycle 1 without experiencing a Grade ≥3 IRR.

No Grade ≥3 IRRs were observed among patients receiving SDI at Cycle 2. After Cycle 2 only one patient experienced a Grade 3 IRR (hypertension at Cycle 5).

No life-threatening, fatal, or serious IRRs were observed following 90-minute infusions.

14.2 Comparative Bioavailability Studies

Not applicable.

14.3 Immunogenicity

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, assay robustness to quantities of GAZYVA/antibody in circulation, sample handling, timing of sample collection, concomitant medications and underlying disease. For

these reasons, comparison of incidence of antibodies to GAZYVA with the incidence of antibodies to other products may be misleading.

Of the GAZYVA-treated previously untreated CLL patients in the pivotal clinical trial, BO21004/CLL11, 7% (18 / 271) tested positive for anti-GAZYVA antibodies at one or more time points during the treatment period of GAZYVA and/or 12 month follow-up period. Neutralization activity of anti-GAZYVA antibodies has not been assessed.

In iNHL patients, no patients developed anti-GAZYVA antibodies during or following GAZYVA treatment in study GAO4753g, while 0.2% (1 / 565) had a detectable positive result of anti-GAZYVA antibodies post-baseline in study BO21223. While the clinical significance of anti-GAZYVA antibodies is not known, a potential correlation between anti-GAZYVA antibodies and clinical course cannot be ruled out.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-dose toxicity studies using the IV route of administration consisted of a 2-week, 13-week, and a 26-week study conducted in cynomolgus monkeys. Doses administered were 1 and 10 mg/kg/wk in the 2-week study, 10, 30, and 100 mg/kg/wk in the 13-week study, and 5, 25, and 50 mg/kg/wk in the 26-week study. The 13-week and 26-week studies were each followed by a 37-week recovery period. Results from these studies showed decreases in circulating B cells and corresponding B-cell depletion in lymphoid tissues at doses of $\geq$ 1 mg/kg/wk (IV); by the end of a 37-week recovery period, circulating B-cell recovery was variable (individual peak values ranged from 7% to 152% of baseline values), while lymphoid tissue B cells fully reversed compared with controls. B-cell depletion is consistent with the desired pharmacology of obinutuzumab. In addition, transient decreases in NK cells were observed at doses of $\geq$ 5 mg/kg (IV); this finding is also consistent with the pharmacologic effect of FcγRIIIa binding and ADCC. Hypersensitivity reactions were noted at all doses ($\geq$ 5 mg/kg, IV) in the 26-week study, and were attributed to the foreign recognition of the drug construct in cynomolgus monkeys. Findings included acute anaphylactic or anaphylactoid reactions, an increased prevalence of systemic inflammation, and infiltrates consistent with immune complex–mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation. These reactions led to unscheduled termination of up to 6 animals during the dosing and recovery phases of the 26-week study. Due to species differences in protein structure and the perceived antigenicity of the drug construct in monkeys, immunogenicity in monkeys is not considered predictive of potential immunogenicity in humans. However immune-complex–mediated hypersensitivity reactions cannot be fully excluded in case of ADA formation in humans. Suspected opportunistic infections in an additional three unscheduled deaths from shorter-term repeat-dose studies were considered a possible secondary result of B-cell depletion.

No effects on the cardiovascular (electrocardiogram, blood pressure, and heart rate), respiratory (respiration rate) and neurological systems were seen after the first dose or following chronic

exposure.

Carcinogenicity:
No carcinogenicity studies have been performed to establish the carcinogenic potential of obinutuzumab.

Genotoxicity:
No studies have been performed to establish the mutagenic potential of obinutuzumab.

Reproductive and Developmental Toxicology:
An enhanced pre- and postnatal development (ePPND) toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received weekly intravenous obinutuzumab doses during gestation (organogenesis period; post-coitum days 20 through delivery). Exposed offspring did not exhibit any teratogenic effects but B-cells were completely depleted on day 28 postpartum. Offspring exposures on day 28 postpartum suggest that obinutuzumab can cross the blood-placenta-barrier. Concentrations in infant serum on day 28 postpartum, were in the range of concentrations in maternal serum, whereas concentrations in milk on the same day were very low (less than 0.5% of the corresponding maternal serum levels) suggesting that exposure of infants must have occurred in utero. B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]GAZYVA®
Obinutuzumab for injection

Read this carefully before you start taking **GAZYVA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **GAZYVA**.

Serious Warnings and Precautions

In patients treated with GAZYVA, the following serious side effects have occurred and were fatal in some cases:

- Severe and life-threatening infusion related reactions.
- Recurrence of hepatitis B virus infection can occur with GAZYVA treatment.
- Serious and life threatening brain condition called progressive multifocal leukoencephalophathy (PML).
- Tumour Lysis Syndrome (TLS) that is caused by breakdown of tumour cells and may lead to kidney damage.
- Serious, including fatal, cardiovascular events could occur in patients with GAZYVA treatment.
- Serious and life-threatening infections, some of which resulted in death.
- Serious and life-threatening thrombocytopenia (low level of cells that help to stop bleeding). This may result in bleeding or promote bleeding caused by other factors.
- See below for signs and symptoms of these serious side effects. Immediately report to your doctor if you notice any of the described symptoms.

What is GAZYVA used for?
GAZYVA contains obinutuzumab, which belongs to a group of medicines called monoclonal antibodies and is used to treat two different types of cancer.

- Chronic Lymphocytic Leukaemia (CLL)
  - GAZYVA is used in adults who have not had any treatment before. It is used together with another medicine for cancer called chlorambucil.
- Follicular Lymphoma (FL) - a type of Non-Hodgkin Lymphoma. GAZYVA is used:
  - in combination with other cancer medications to treat patients with stage II bulky, III or IV follicular lymphoma (FL) who have not been treated for FL before.
  - with another medicine for cancer, called bendamustine, in patients who have had at least one treatment with a medicine called rituximab before and whose FL has come back or got worse after this treatment.
  - Patients who respond to treatment with GAZYVA in combination with other cancer medications can continue to be treated with GAZYVA on its own (monotherapy) for up to 2 years.

CLL and FL are types of cancers of the blood which affect a type of white blood cell called "B lymphocytes". The affected B lymphocytes multiply too quickly and live too long. This means that there are too many of them circulating in your blood. CLL can also make your lymph nodes get larger; they are part of a network of vessels running round your body that is filled with clear watery fluid called "lymph".

How does GAZYVA work?
GAZYVA binds to the surface of the "B lymphocyte" cells and causes them to die.

What are the ingredients in GAZYVA?
Medicinal ingredients: obinutuzumab
Non-medicinal ingredients: L-histidine, L-histidine hydrochloride, poloxamer 188, trehalose, water for injection.

GAZYVA comes in the following dosage forms:
Each 50 mL single-use glass vial contains a single 1000 mg dose of obinutuzumab in 40 mL of liquid concentrate (25 mg/mL), to be diluted in 0.9% aqueous sodium chloride solution, for intravenous administration. GAZYVA is available in a pack containing 1 vial.

Do not use GAZYVA if:

- If you are allergic to obinutuzumab, any of the other ingredients of this medicine, or the container it is in.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GAZYVA and talk about any health conditions or problems you may have, including:

- Infusion related reactions: GAZYVA is an infusion ("drip") which is given intravenously (into your veins). Very commonly patients being given GAZYVA have some side effects while the infusion is being given. Most patients are also given medication such as acetaminophen, antihistamines, and steroids (such as prednisone) for allergic reactions before the infusion to prevent these reactions. If you notice any trouble breathing, feel hot or shivery, have hives or an itchy rash, tell the person giving you the infusion immediately; these side effects are more common with the first infusions of GAZYVA, and decreased with subsequent infusions of GAZYVA. Let your doctor know if you have ever had breathing problems or lung problems. If you develop any of these symptoms, the infusion will be slowed down or stopped for a while. Once these symptoms go away, or improve, the infusion can be continued.

- Heart Disease: If you have ever had heart disease, or are taking medicines for high blood pressure, your doctor will take special care of you during therapy with GAZYVA.

- Hepatitis B infection: Tell the doctor if you had or think you had hepatitis; you will be carefully checked for signs of active hepatitis B virus.

- Infection: 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 or if you have ever taken medicines which affect your immune system (such as chemotherapy or immunosuppressants). The symptoms of infection can include one or more of the following: fever of 38ºC or greater, chills, cough, sore throat, or pain on urination. 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.

- Progressive multifocal leukoencephalopathy (PML): Cases of PML have been observed in patients treated with GAZYVA. PML is a condition that causes nerve damage within the brain. Tell your doctor immediately if you have memory loss, trouble thinking, and difficulty with walking, clumsiness, falls or weakness on one side of the body, changes in mood or loss of vision. Your doctor will check if you need to see a neurologist.

- Tumour Lysis Syndrome (TLS): Cases of TLS have been reported during the use of GAZYVA. TLS is a condition that causes sudden kidney failure and abnormal heart rhythms due to changes in blood chemistry, which may be fatal. Tell your doctor immediately if you have palpitations/irregular heartbeats; vomiting; fatigue/weakness; difficulty concentrating/trouble thinking; swelling, numbness or tingling in hands, face or feet; back pain; muscle cramps; fainting or trouble breathing. Some patients with TLS in its early stages have no symptoms, and your doctor will be performing blood tests for this and other side effects.

- 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, 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. Let your doctor know if you are taking medicines which may increase bleeding risk (platelet inhibitors, anticoagulants). 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.

- Gastrointestinal perforation (a hole in the stomach or intestines): Gastrointestinal perforation has been reported in patients treated with GAZYVA. Most cases occurred in patients with Non-Hodgkin Lymphoma. One patient died of gastrointestinal perforation. Some patients experienced serious events.

- Allergic reactions: Immediate (e.g. anaphylaxis) and delayed (e.g. serum sickness) allergic reactions have been reported in patients treated with GAZYVA. If an allergic reaction is suspected during or after an infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), your doctor will permanently take you off treatment.

- Vaccination: Certain vaccine may not be recommended during treatment with GAZYVA and the safety of certain vaccines following treatment with GAZYVA has not been studied. Talk to your doctor if you are due to have a vaccine or may need one in the near future.

Other warnings you should know about:

GAZYVA has not been studied in pregnant or breastfeeding women. If you are pregnant, could become pregnant or are breastfeeding, be sure to discuss with your doctor whether GAZYVA is right for you. Women should avoid pregnancy and use effective birth control methods during treatment with GAZYVA and for 18 months after the last dose GAZYVA. Women should avoid breastfeeding during treatment and for 18 months after the last dose of GAZYVA. If you have given birth while on GAZYVA treatment, your newborn will be monitored for reduced immunity. Postponing your child's vaccinations, that use live virus vaccines, may be considered until your child's immunity levels are acceptable.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take GAZYVA:

- A health professional in a healthcare facility will give you GAZYVA as prescribed by your doctor. It is given into a vein (intravenously) as a drip (infusion) over several hours.

Usual dose:

Chronic Lymphocytic Leukaemia
You will be given 6 treatment cycles of GAZYVA. Each cycle lasts 28 days. A typical schedule is shown below.

Your first cycle:
- Day 1 – 100 mg
- Day 1 (continued) or Day 2 – 900 mg
- Day 8 – 1000 mg
- Day 15 – 1000 mg

If you are able to tolerate the first 100 mg of the infusion on Day 1 without any changes to the infusion rate or interruptions to the infusion, the second 900 mg infusion may be given on Day 1 as well.

Your next cycles 2, 3, 4, 5, and 6:
- Day 1 – 1000 mg.

Follicular Lymphoma (that has returned)
You will be given 6 treatment cycles of GAZYVA with bendamustine (each cycle lasts 28 days) followed by GAZYVA only treatment (infusion every 2 months) for up to 2 years. A typical schedule is shown below.

Your first cycle:
- Day 1 – 1000 mg
- Day 8 – 1000 mg
- Day 15 – 1000 mg

Your next cycles 2, 3, 4, 5, and 6, as well as monotherapy:
- Day 1 – 1000 mg.

Follicular Lymphoma (previously untreated)

You will be given 6 treatment cycles of GAZYVA with bendamustine (each cycle lasts 28 days) or 6 treatment cycles of GAZYVA with CHOP (each cycle lasts 21 days) followed by 2 additional cycles of GAZYVA alone, or 8 treatment cycles of GAZYVA with CVP (each cycle lasts 21 days). If your lymphoma responds to the treatment, you will be given GAZYVA-only treatment (infusion every 2 months) for up to 2 years or until your cancer returns. A typical schedule is shown below.

Your first cycle:
- Day 1 – 1000 mg
- Day 8 – 1000 mg
- Day 15 – 1000 mg

Your next cycles 2-6 or 2-8, as well as monotherapy:
- Day 1 – 1000 mg.

Before each infusion of GAZYVA, you will be given medicines which help to reduce possible infusion related reactions or tumour lysis syndrome. These may include
- Fluids
- Medicines to reduce an allergic reaction (anti-histamines)
- Medicines to reduce inflammation (corticosteroids)
- Painkillers (analgesics)
- Medicines to reduce a fever
- Medicines to prevent "tumour lysis syndrome"

Overdose:
It is unlikely that you will receive too much GAZYVA as you will be closely monitored by health professionals during your infusion. However, if you suspect you received too much GAZYVA, contact your doctor and poison control centre immediately.

If you think you, or a person you are caring for, have taken too much GAZYVA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of GAZYVA, contact your doctor immediately. Your doctor will decide when you should receive your next dose.

What are possible side effects from using GAZYVA?

These are not all the possible side effects you may feel when taking GAZYVA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects with using GAZYVA

Very common: may affect 1 in 10 or more people

- Nausea
- Decreased number of red blood cells in the blood that carry oxygen (symptoms include feeling of weakness or fatigue in general or during exercise, poor concentration)
- Diarrhoea
- Constipation
- Hair loss
- Headache
- Vomiting

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
VERY COMMON Infusion related reaction: • trouble breathing, feel hot or shivery, have hives or an itchy rash		✓	
COMMON Neutropenia (decreased number of white blood cells): • fever, sore throat, infection		✓	
Tumour lysis syndrome (TLS): • producing less urine than normal and muscle spasms – these are symptoms of kidney problems		✓	
Gastrointestinal perforation (a hole in the stomach or intestines): • abdominal pain, constipation, vomiting		✓	
UNCOMMON Infection: • fever (temperature at 38ºC or higher), sore throat, cough, any redness or swelling, pain when you pass your urine		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
Thrombocytopenia (decreased number of platelets in the blood: • fatigue, weakness		✓	
Heart disease: • chest pain, fast heart rate or an irregular or uneven heart rate		✓	
Progressive multifocal leukoencephalopathy (PML): • memory loss, trouble thinking, difficulty with walking or loss of vision		✓	
Disseminated Intravascular Coagulation (DIC): bleeding from many places in the body, blood clots, bruising, drop in blood pressure, shortness of breath, confusion, memory loss or change of behavior, fever		✓	
RARE Hepatitis B virus infection: • mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain, yellowing of whites of the eyes, skin and tongue		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
GAZYVA will be stored by the health professionals at the hospital or clinic. The storage details are as follows:

- Store in a refrigerator (2 - 8 °C)
- Do not use this medicine after the expiry date shown on the vial and carton
- Keep vial in outer carton to protect from light.
- Do not freeze or shake.

Do not throw away any medicines via wastewater or household waste. Your health professional will properly discard any medicines that are no longer being used.

Keep out of reach and sight of children.

If you want more information about GAZYVA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.rochecanada.com, or by calling 1-888-762-4388.

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