NEW ZEALAND DATA SHEET – Gazyva (obinutuzumab)

1. PRODUCT NAME
Gazyva 1000mg in 40mL concentrate solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial 40mL concentrate contains 1000mg obinutuzumab, corresponding to a concentration before dilution of 25mg/mL

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.

Clear, colourless to slightly brownish liquid.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chronic Lymphocytic Leukaemia
Gazyva in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL).

Non-Hodgkin Lymphoma
Gazyva in combination with chemotherapy followed by Gazyva maintenance is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.

Gazyva in combination with bendamustine followed by Gazyva maintenance is indicated for the treatment of patients with indolent non-Hodgkin lymphoma (iNHL) who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

4.2 DOSE AND METHOD OF ADMINISTRATION
Dose
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

General
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 section 6.6).

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 a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to start of Gazyva infusion as per standard practice (see section 4.4). Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

Prophylaxis and Premedication for Infusion Related Reactions (IRR)

Premedication to reduce the risk of IRRs (see section 4.4) is outlined in Table 1. Corticosteroid premedication is recommended for iNHL 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 IRR, 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 section 4.4).

Table 1 Premedication to be administered before Gazyva infusion to reduce the risk of infusion-related reactions

Day of Treatment Cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1: **<u>CLL</u>** **Day 1*, Day 2** **<u>iNHL</u>** **Day 1**	All patients	Intravenous corticosteroid[1,2]	Completed at least 1 hour prior to Gazyva infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	
All subsequent infusions: CLL and iNHL	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	
	Patients with a Grade 3 IRR with the previous infusion OR patients with lymphocyte counts > 25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1,2]	Completed at least 1 hour prior to Gazyva infusion
		Oral analgesic/anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic drug[4]	

[*] If the 100 mg dose of Gazyva is administered without interruption or modification of the infusion rate the subsequent 900 mg dose may also be administered on the same day (see Table 2). In the event the 900 mg dose is given on the same day no additional premedication is required to commencement of the 900 mg dose.
[1] 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions
[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 60 minutes prior to Gazyva, in which case additional IV corticosteroid as premedication is not required.
[3] e.g. 1000 mg paracetamol
[4] e.g. 50 mg diphenhydramine

<u>Standard Dosage</u>

Chronic Lymphocytic Leukaemia (in combination with chlorambucil[*])
Cycle 1
The recommended dosage of Gazyva is 1000 mg administered over Day 1 and 2, and on Day 8 and Day 15 of the first 28 day treatment cycle as shown in Table 2.

For Cycle 1, Day 1, two infusion bags should be prepared; one for the first infusion of 100 mg and one for the second infusion of 900 mg. 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 (no dose delay necessary) 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).

Cycles 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

<table>
<tr><th colspan="2">Day of Treatment Cycle</th><th>Dose of Gazyva</th><th>Rate of infusion
For management of IRRs that occur during infusion, refer to Table 4</th></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1</td><td>100 mg</td><td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td></tr>
<tr><td>Day 2 or Day 1 (continued)</td><td>900 mg</td><td>If no IRR occurred during the previous infusion, administer at 50 mg/hr.
The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

If the patient experienced an IRR 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.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="3">If no IRR 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 infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 2 – 6</td><td>Day 1</td><td>1000 mg</td></tr>
</table>

* see section 5.1 for information on chlorambucil dose.

Delayed or missed doses (CLL)

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 thereafter.

Non-Hodgkin Lymphoma

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

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** 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.

Relapsed/refractory iNHL
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**.

Relapsed/refractory patients who achieve complete or partial response or have stable disease should continue to receive Gazyva 1000 mg alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

Table 3 Dose and infusion rate of Gazyva for patients with previously untreated FL or relapsed/refractory iNHL

<table>
<tr><th colspan="2">Day of Treatment Cycle</th><th>Dose of Gazyva</th><th>Rate of infusion
For management of IRRs that occur during infusion, refer to Table 4</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>1000 mg</td><td>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.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="4">If no IRR or Grade 1 IRR 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 a Grade 2 IRR 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.</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 2-6 or 2-8</td><td>Day 1</td><td>1000 mg</td></tr>
<tr><td>Maintenance</td><td>Every 2 months until progression or up to 2 years</td><td>1000 mg</td></tr>
</table>

** see section 5.1 for information on bendamustine dose.

Delayed or missed doses (previously untreated FL or relapsed/refractory iNHL)
If a planned dose of Gazyva is missed, it should be administered as soon as possible; do not omit 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 maintenance, maintain the original dosing schedule for subsequent doses.

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

For management of symptomatic adverse events (including IRRs), see Table 4 below and section 4.4.

Table 4 Infusion Rate Modification Guidelines for Infusion Related Reactions (see Section 4 4)

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). If 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 Tables 2 and 3). · 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 IRR, stop infusion and permanently discontinue therapy.
Grade 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion. If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 2 and 3). · 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.

Special Populations

Children
The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Elderly
No dose adjustment is required in elderly patients (see section 4.4).

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 < 30mL/min (see sections 4.4 and 5.2).

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

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 CONTRAINDICATIONS

Gazyva is contraindicated in patients with a known hypersensitivity to obinutuzumab or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded in the patient medical record.

Infusion Related Reactions (IRRs)
The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyva were infusion related reactions (IRRs) which occurred predominantly during infusion of the first 1000 mg.

In CLL patients who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medication in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) as described in section 4.2, decreased incidence of IRRs of all Grades was observed. The rates of Grade 3-4 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 should be followed (see section 4.2). The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during the second and subsequent administrations of Gazyva (see section 4.8).

In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumour burden and/or (high circulating lymphocyte count in CLL ($> 25 \times 10^9$/L)) may be at increased risk of severe IRR. See section 4.2 for information on prophylaxis and Table 4 for advice on how to manage IRRs based on Grade of reaction.

Patients should not receive further Gazyva infusions if they experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e. life-threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (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. 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.

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 section 4.3). Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys [C_{max} and $AUC_{0\text{-}168\ h}$ at steady state (Day 176) after weekly administration of 5, 25, and 50 mg/kg, were 377, 1,530, and 2,920 µg/mL and 39,800, 183,000, and 344,000 (µg•h)/mL, respectively]. Findings included acute anaphylactic or anaphylactoid reactions and 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 6/36 animals treated with Gazyva during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to Gazyva has been observed in humans.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) has been reported with Gazyva. Patients who are considered to be at risk of TLS [e.g. 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)] should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to the infusion of Gazyva as described in section 4.2. 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 should also be followed, according to standard practice. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Neutropenia
Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with Gazyva. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary, it should be administered in accordance with local guidelines, and administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate. Late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur.

Thrombocytopenia
Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with Gazyva. Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with Gazyva. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

Use of any concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Worsening of Pre-existing Cardiac Conditions
In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyva (see section 4.8). These events may occur as part of an IRR and can be fatal. Therefore 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.

Infections
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. Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Gazyva therapy. Fatal infections have been reported.

In the iNHL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. During the follow-up phase, Grade 3-5 infections were observed more in patients who received Gazyva plus bendamustine in the induction phase.

Hepatitis B 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 including Gazyva (see section 4.8).

HBV screening should be performed in all patients before initiation of treatment with Gazyva. At a minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active Hepatitis B disease should not be treated with Gazyva. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed according to current clinical practice.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported in patients treated with Gazyva (see section 4.8). 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 depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (e.g. aphasia or visual-spatial disorientation) may occur. 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 and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

The safety of immunisation 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.

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. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants' B cell levels are within normal ranges (see section 4.6).

Use in 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 (see sections 4.2 and 5.2). No significant differences in efficacy were observed between patients with CrCl < 50mL/min and those with CrCl ≥ 50 mL/min. Patients with CrCl < 30 mL/min were excluded from the study (see section 5.1).

Non-Hodgkin Lymphoma

In the pivotal studies in iNHL, 6.9% of patients (14 of 204) in study GAO4753g and 5% of patients (35 of 698) in study BO21223 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 those associated with CrCl ≥ 50 mL/min (see sections 4.2 and 5.2). Patients with CrCl < 40 mL/min were excluded from the studies (see section 5.1).

Use in hepatic impairment

The safety and efficacy of Gazyva in patients with hepatic impairment have not been established.

Paediatric use

The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Use in the elderly

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 46% (156 out of 336) of patients treated with Gazyva plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than 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 section 5.1).

Non-Hodgkin Lymphoma
In the pivotal studies in iNHL, patients ≥ 65 years of age experienced more serious adverse events and adverse events leading to withdrawal or death than patients < 65 years of age. No clinically meaningful differences in efficacy were observed.

Effect on laboratory tests
See section 4.4.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies have been performed, although limited drug interaction sub-studies have been undertaken for Gazyva with bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), FC (fludarabine, cyclophosphamide) and chlorambucil. Co-administration with Gazyva had no effect on the pharmacokinetics of bendamustine, FC or the individual components of CHOP; in addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of Gazyva. A risk for interactions with concomitantly used medicinal products cannot be excluded.

4.6 FERTILITY, PREGNANCY AND LACTATION

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

Use in pregnancy – Category C
Gazyva should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Women of child-bearing potential should use effective contraception while receiving Gazyva and for 18 months following treatment with Gazyva (see section 5.2). Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants' B-cell levels are within normal ranges.

No studies in pregnant women have been performed. 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 immunologic function was restored within 6 months of birth. 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.

Pregnant animals received weekly intravenous Gazyva doses [Mean $AUC_{0\text{-}168\ h}$ at steady state (on Day 139 p.c.) was 125,000 and 250,000 (µg•h)/mL at 25 and 50 mg/kg, respectively. Mean C_{max} was 1,220 and 2,470 µg/mL at 25 and 50 mg/kg, respectively] 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 Gazyva 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.

Use in breast-feeding
As 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 breast-feeding during Gazyva therapy and for 18 months after the

last dose of Gazyva (see section 5.2). Animal studies have shown excretion of Gazyva in breast milk (see section 4.6).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 UNDESIRABLE EFFECTS

Clinical trials were conducted in patients with various haematologic malignancies (e.g. CLL and iNHL) who were treated with Gazyva, predominantly in combination with chemotherapy (CHOP, CVP, Chlorambucil or Bendamustine). The safety profile from the clinical trial population of approximately 4900 patients is presented in this section.

The most serious adverse drug reactions were:

- Infusion related reactions which is more common in CLL patients (see section 4.4)
- Tumour Lysis Syndrome, which is more common in patients with a high tumour burden and/or a high circulating lymphocyte count and/or renal impairment (see section 4.4)
- Thrombocytopenia, which can be fatal in Cycle 1 (see section 4.4)

The most frequently observed adverse drug reactions across clinical trials in patients receiving Gazyva were IRR, neutropenia, diarrhoea, constipation and cough.

Table 5 lists adverse drug reactions associated with the use of Gazyva in combination with different chemotherapy regimens in multiple indications. The adverse drug reactions listed in this table fall into the following categories: Very Common (≥10%); Common (≥ 1% - < 10%) and Uncommon (≥ 0.1% - < 1%). Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence (difference of ≥ 2% compared to the relevant comparator arm) seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order by system organ class.

Table 5: Adverse Reactions

ADR (MedDRA) System Organ Class	Grades 3-5 % [Reference]	All Grades % [Reference]	Frequency category (All Grades)
Injury, Poisoning and Procedural Complications			
Infusion Related Reactions‡	21.2	71.6	Very common
Blood and Lymphatic System Disorders			
Neutropenia	46.8	50.7	Very common
Thrombocytopenia	11.2	15.4	Very common
Anaemia	6.9	12.4	Very common
Leucopenia	8.7	12.5	Very Common
Febrile Neutropenia	6.6	7.0	Common
Infections and Infestations			
Upper Respiratory Tract Infection	2.0	22.1	Very common
Sinusitis	1.0	12.3	Very common
Herpes Zoster	1.6	11.0	Very common
Pneumonia	5.4	10.9	Very Common

ADR (MedDRA) System Organ Class	Grades 3-5 % [Reference]	All Grades % [Reference]	Frequency category (All Grades)
Urinary Tract Infection	2.9	11.8	Very common
Rhinitis	<1	8.3	Common
Nasopharyngitis	<1	10.8	Very Common
Pharyngitis	0	4.3	Common
Oral Herpes	<1	6.3	Common
Influenza	<1	5.2	Common
Lung Infection	2.5	4.4	Common
General Disorders and Administration Site Conditions			
Pyrexia	2.4	20.3	Very common
Asthenia	1.0	11.8	Very common
Chest Pain	<1	5.4	Common
Fatigue	2.5	34.0	Very Common
Respiratory, Thoracic and Mediastinal Disorders			
Cough	<1	30.8	Very common
Oropharyngeal pain	<1	9.6	Common
Nasal Congestion	0	7.4	Common
Rhinorrhoea	0	3.9	Common
Metabolism and Nutrition Disorders			
Hypokalaemia	1.0	7.4	Common
Tumour Lysis Syndrome	1.8	4.2	Common
Hyperuricaemia	<1	3.7	Common
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	<1	15.9	Very common
Back Pain	<1	13.5	Very Common
Pain In Extremity	1.0	10.3	Very Common
Bone Pain	<1	5.3	Common
Musculoskeletal Chest Pain	<1	2.5	Common
Psychiatric Disorders			
Insomnia	<1	14.3	Very common
Anxiety	<1	6.2	Common
Depression	<1	4.7	Common
Renal and Urinary Disorders			
Dysuria	<1	2.7	Common
Urinary Incontinence	<1	2.9	Common
Vascular Disorders			
Hypertension	1.7	6.2	Common
Investigations			
Neutrophil Count Decreased	2.1	2.1	Common
Weight Increased	0	2.1	Common

ADR (MedDRA) System Organ Class	Grades 3-5 % [Reference]	All Grades % [Reference]	Frequency category (All Grades)
White Blood Cell Count Decreased	2.1	2.1	Common
Cardiac Disorders			
Atrial Fibrillation	1.1	2.6	Common
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)			
Squamous Cell Carcinoma of Skin	1.2	2.1	Common
Basal Cell Carcinoma	1.0	2.9	Common
Gastrointestinal Disorders			
Constipation	<1	32.4	Very common
Diarrhoea	2.5	28.4	Very common
Dyspepsia	0	8.6	Common
Haemorrhoids	<1	2.5	Common
Skin and Subcutaneous Tissue Disorders			
Alopecia	0	12.6	Very common
Pruritus	<1	10.6	Very common
Eczema	0	2.9	Common
Nervous System Disorders			
Headache	<1	16.8	Very Common

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

Further information on selected adverse reactions

Infusion related reactions

Most frequently reported (≥ 5%) symptoms associated with an IRR were nausea, vomiting, diarrhoea, headache, dizziness, fatigue, chills, pyrexia, hypotension, flushing, hypertension, tachycardia, dyspnoea, and chest discomfort. Respiratory symptoms such as, bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and cardiac symptoms such as atrial fibrillation have also been reported (see section 4.4).

Chronic Lymphocytic Leukaemia

The incidence of IRRs was 65% with the infusion of the first 1000 mg of Gazyva (20% of patients experiencing a Grade 3-4 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyva. The incidence of IRR with subsequent infusions was 3% with the second 1000 mg dose and 1% thereafter. No Grade 3-5 IRR were reported beyond the first 1000 mg infusions of Cycle 1.

In patients who received the recommended measures for prevention of IRRs as described in section 4.2, 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

In Cycle 1, the overall incidence of IRRs was higher in patients receiving Gazyva plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyva plus chemotherapy, the incidence of IRRs was highest on Day 1 and gradually decreased with subsequent infusions. This decreasing trend continued during maintenance therapy with Gazyva.

Overall, 4% of patients experienced an IRR leading to discontinuation of Gazyva.

Neutropenia and infections

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. The incidence of infection was 38% in the Gazyva plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms)]. 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 section 4.4).

Non-Hodgkin Lymphoma
In the Gazyva plus chemotherapy arm, the incidence of neutropenia was higher relative to the comparator arm with an increased risk during the induction period. The incidence of prolonged neutropenia and late onset neutropenia in the Gazyva plus chemotherapy arm were 3% and 7%, respectively. The incidence of infection was 81% in the Gazyva plus chemotherapy arm (with Grade 3-5 events reported in 22% of patients and fatal events reported in 2% of patients). Patients who received G-CSF prophylaxis had a lower rate of Grade 3-5 infections (see section 4.4).

Thrombocytopenia and haemorrhagic events
Chronic Lymphocytic Leukaemia
The incidence of thrombocytopenia was higher in the Gazyva plus chlorambucil arm compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyva plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyva infusion) (see section 4.4). The overall incidence of haemorrhagic events was similar in the Gazyva treated arm and in the rituximab treated arm. The number of fatal haemorrhagic events was balanced between the treatment arms; however all of the events in patients treated with Gazyva were reported in Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Non-Hodgkin Lymphoma
Thrombocytopenia occurred more frequently during Cycle 1 in the Gazyva plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of infusion (acute thrombocytopenia) was more frequently observed in patients treated with Gazyva plus chemotherapy than in the relevant comparator arm. The incidence of haemorrhagic AEs was similar across all treatment arms. Haemorrhagic events and Grade 3-5 haemorrhagic events occurred in 12% and 4% of patients, respectively. While fatal haemorrhagic events occurred in less than 1% of patients, none of these fatal AEs occurred in Cycle 1.

Progressive multifocal leukoencephalopathy (PML)
PML has been reported in patients treated with Gazyva (see section 4.4).

Hepatitis B Reactivation
Cases of hepatitis B reactivation have been reported in patients treated with Gazyva (see section 4.4).

Worsening of Pre-existing Cardiac Conditions
Cases of fatal cardiac events have been reported in patients treated with Gazyva (see section 4.4).

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

Maintenance treatment in iNHL patients
In GAO4753g, patients in the B arm received 6 months of induction treatment only, whereas after the induction period, patients in the G+B arm continued on with Gazyva maintenance treatment. During the maintenance period with Gazyva, the most common adverse reactions were cough (20.3%), neutropenia (12.7%), upper respiratory tract infections (12.0%), diarrhoea (10.1%), bronchitis (9.5%), sinusitis (9.5%), nausea (8.9%), fatigue (8.9%), infusion related reactions (8.2%), urinary tract infections (7.0%), nasopharyngitis (7.0%), pyrexia (7.0%), arthralgia (6.3%), vomiting (5.7%), rash (5.7%), pneumonia (5.1%), dyspnoea (5.1%) and pain in extremity (5.1%). The most common grade 3-5 adverse reactions were

neutropenia (10.8%), febrile neutropenia (1.9%) and anaemia, thrombocytopenia, pneumonia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1.3%).

Laboratory Abnormalities
Transient elevation in liver enzymes (AST, ALT, ALP) has been observed shortly after the first infusion of Gazyva.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE
No experience with overdosage is available from human clinical trials. In clinical trials with Gazyva, 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.

Treatment of overdose should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC15

Mechanism of Action
Obinutuzumab 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 haemopoietic stem cells, pro B cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of *obinutuzumab* results in higher affinity for FcϒRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages and monocytes as compared to non-glycoengineered antibodies.

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

In the pivotal clinical trial BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with Gazyva were B cell depleted (defined as CD19+ B-cell counts < 0.07×10^9/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.

Clinical trials
Chronic Lymphocytic Leukaemia (CLL)

A phase III, international, multicentre, open-label, randomised, two-stage, three arm study (BO21004/CLL11) investigating the safety and efficacy profile of Gazyva plus chlorambucil compared to rituximab plus chlorambucil or chlorambucil alone was conducted in patients with previously untreated CLL with comorbidities.

Prior to enrolment, patients had to have documented CD20+ CLL, and one or both of the following measures of coexisting medical conditions; comorbidity score [total Cumulative Illness Rating Scale (CIRS)] of greater than 6 or reduced renal function as measured by CrCl < 70 mL/min. Patients with inadequate liver function (NCICTC Grade 3 liver function tests (AST, ALT > 5 x ULN for > 2 weeks; Bilirubin > 3 x ULN) and renal function (CrCl < 30 mL/min) were excluded).

A total of 781 patients were randomised 2:2:1 to receive Gazyva plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1 compared Gazyva plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyva plus chlorambucil to rituximab plus chlorambucil in 663 patients. Efficacy results are summarised in Table 6 and in Figures 1-3.

In the majority of patients, Gazyva was given intravenously as a 1000 mg initial dose administered on Day 1, Day 8 and Day 15 of the first treatment cycle. In order to reduce the rate of infusion related reactions in patients, an amendment was implemented and 140 patients received the first Gazyva dose administered over 2 days [Day 1 (100mg) and Day 2 (900mg)] (see section 4.2). For each subsequent treatment cycle (Cycles 2 to 6), patients received Gazyva 1000 mg on Day 1 only. Chlorambucil was given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients enrolled were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% patients had Binet Stage A, 42% had Binet Stage B and 36% had Binet Stage C. 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%, Gastrointestinal disorders 38%, Metabolism and Nutrition disorders 40%, Renal and Urinary disorders 38%, musculoskeletal and connective tissue disorders 33%.

The primary endpoint of the study was investigator assessed progression-free survival (PFS-INV). In addition, an independent review committee (IRC) assessed all patients for progression and IRC assessed PFS (PFS-IRC) was evaluated.

Key secondary efficacy endpoints were end of treatment response rate, molecular remission at end of treatment (minimal residual disease status) and time to event endpoints (event-free survival, new anti-leukemic therapy). Overall survival for Stage 1 is presented in Figure 2. Overall survival for Stage 2 will continue to be followed and is not yet mature.

Table 6 Summary of efficacy from BO21004 (CLL11) study

	Stage 1		**Stage 2**	
	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**	
Investigator-assessed PFS (PFS-INV)* Number (%) of patients with event	96 (81.4%)	93 (39.1%)	199 (60.3%)	104 (31.2%)
Median time to event (months)	11.1	26.7	15.2	26.7
HR (95% Cl)	0.18 [0.13; 0.24]		0.39 [0.31; 0.49]	
p-value (Log-Rank test, stratified[†])	< 0.0001		< 0.0001	
IRC-assessed PFS (PFS-IRC)* 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% Cl)	0.19 [0.14; 0.27]		0.42 [0.33; 0.54]	
p-value (Log-Rank test, stratified[†])	< 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%)
Non-responders (%)	81 (68.6%)	54 (22.7%)	115 (35.0%)	72 (21.6%)
Difference in response rate (95% Cl)	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[‡] (%)	0 (0.0%)	53 (22.3%)	23 (7.0%)	69 (20.7%)
Molecular Remission at end of treatment[§] No. of patients included in the analysis	90	168	244	239
MRD negative[¶] (%)	0 (0%)	45 (26.8%)	6 (2.5%)	61 (25.5%)
MRD positive[\\] (%)	90 (100%)	123 (73.2%)	238 (97.5%)	178 (74.5%)
Difference in MRD rates (95% Cl)	26.79 [19.5; 34.1]		23.06 [17.0; 29.1]	
Event Free Survival No. (%) of patients with event	103 (87.3%)	104 (43.7%)	208 (63.0%)	118 (35.4%)
Median time to event (months)	10.8	26.1	14.3	26.1
HR (95% Cl)	0.19 [0.14; 0.25]		0.43 [0.34; 0.54]	
p-value (Log-Rank test, stratified[†])	<0.0001		<0.0001	

	Stage 1		Stage 2	
	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**	
Time to new anti-leukaemic 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% Cl)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified†)	<0.0001		0.0018	
Overall Survival				
No.(%) of patients with event	24 (20.3%)	22 (9.2%)	41 (12.4%)	28 (8.4%)
Median time to event (months)	NR	NR	NR**	NR**
HR (95% CI)	0.41 [0.23; 0.74]		0.66 [0.41; 1.06]**	
p-value (Log-Rank test, stratified†)	0.0022		0.0849**	

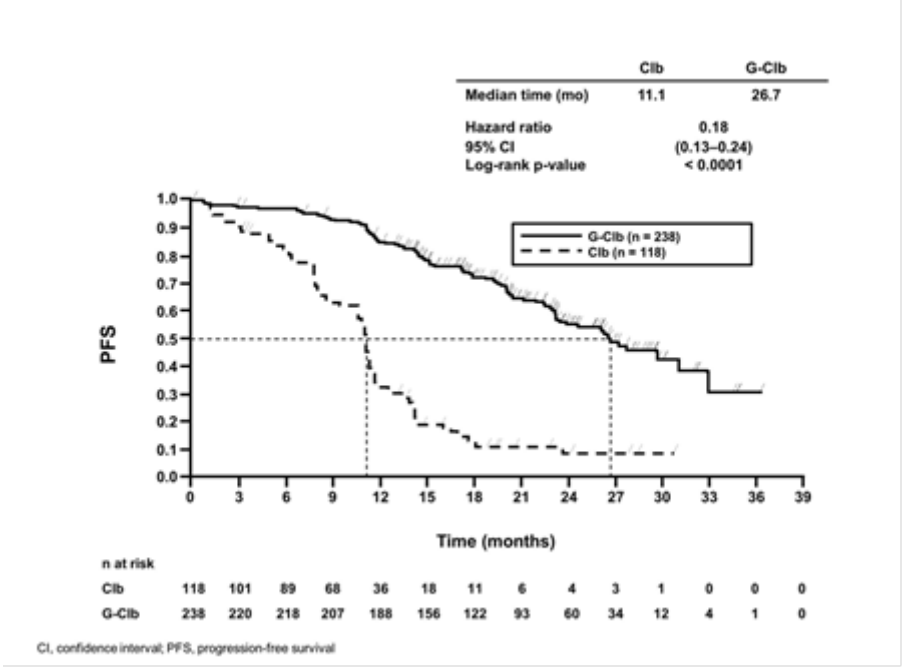
IRC: Independent Review Committee; PFS: progression-free survival; HR: hazard ratio; CI: confidence intervals; MRD: minimal residual disease
* Defined as the time from randomisation to the first occurrence of progression, relapse or death from any cause as assessed by the investigator
† stratified by Binet stage at baseline
‡ includes 11 patients in the GClb arm with a complete response with incomplete marrow recovery
§ blood and bone marrow combined
¶ MRD negativity is defined as a result below 0.0001
\\ includes MRD positive patients and patients who progressed or died before the end of treatment
NR = not reached
** Data not yet mature

Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the Gazyva plus chlorambucil arm (GClb) compared to the rituximab plus chlorambucil arm (RClb) and chlorambucil alone arm (Clb) in all subgroups. The hazard ratios ranged from 0.08 to 0.42 for GClb vs Clb and 0.28 to 0.71 for GClb vs RClb.

Patient Reported Outcomes
In the QLQC30 and QLQ-CLL-16 questionnaires conducted during the treatment period, no substantial difference in any of the subscales was observed. Data during follow up, especially for the chlorambucil alone arm, is limited. However, no notable differences in quality of life during follow up have been identified to date.

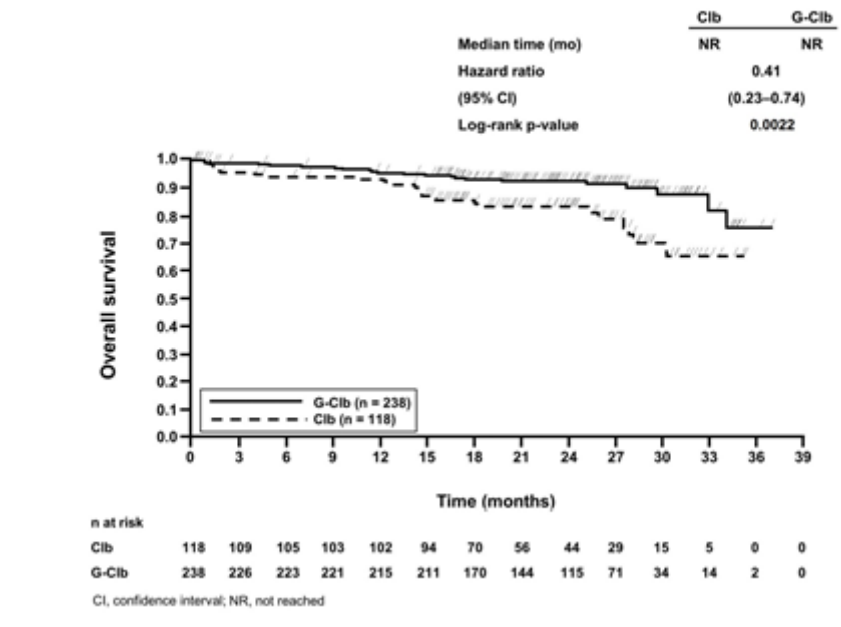
Health-related quality of life assessments, specific to fatigue through treatment period, show no statistically significant difference suggesting that the addition of Gazyva to chlorambucil regimen does not increase the experience of fatigue for patients.

Figure 1 Kaplan-Meier curve of Investigator-assessed PFS from Stage 1



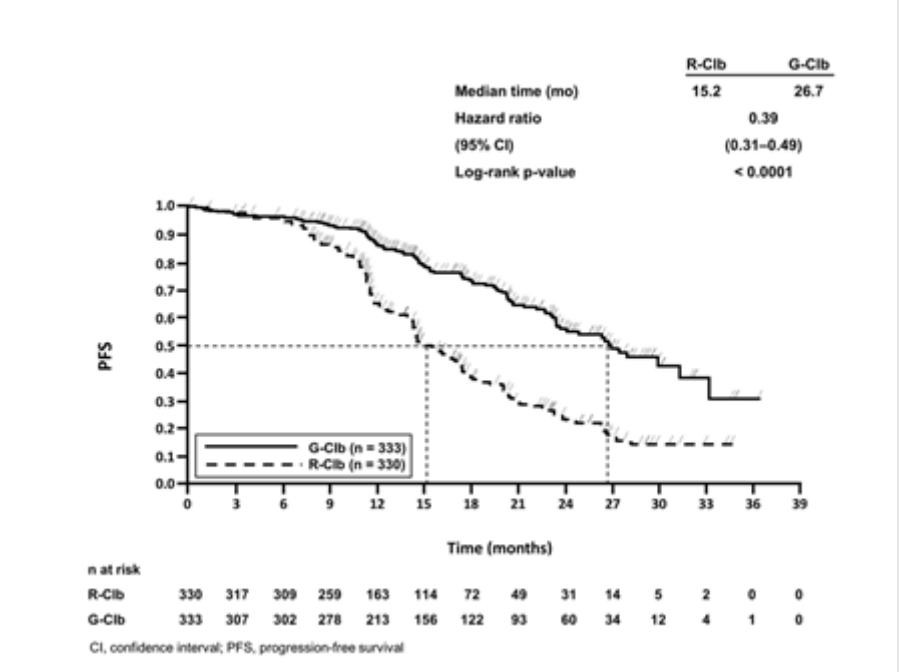
CI, confidence interval; PFS, progression-free survival

Figure 2 Kaplan-Meier curve of overall survival from Stage 1



CI, confidence interval; NR, not reached

Figure 3 Kaplan-Meier curve of Investigator-assessed PFS from Stage 2



Non-Hodgkin Lymphoma (NHL)

Previously Untreated Follicular Lymphoma
In a multicentre phase III, open-label, randomised study (BO21223/GALLIUM), 1202 previously untreated patients with stage II (bulky)/III/IV follicular lymphoma (FL) were evaluated. Patients were randomised 1:1 to receive either Gazyva or rituximab in combination with chemotherapy (CHOP, CVP, or bendamustine) followed by Gazyva or rituximab maintenance in patients who achieved a complete or partial response.

The demographic data and baseline characteristics of the FL population were well balanced. The median age was 59 years, the majority of patients were Caucasian (81%), and female (53%). Seventy-nine percent of patients had a FLIPI score of ≥ 2. Seven percent had Stage II (bulky) disease, 35% had Stage III disease 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 prior to chemotherapy as described under section 4.2. 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 Cycles 6-8, when Gazyva was given in combination with chemotherapy, Gazyva maintenance therapy was given every 2 months for 2 years for responding patients or until disease progression.

Efficacy results are summarised in Table 7. Kaplan-Meier curves for PFS are shown in Figure 4.

Table 7 Summary of efficacy in FL patients from BO21223 (GALLIUM) study

	Rituximab + chemotherapy followed by rituximab maintenance n=601	**Gazyva + chemotherapy followed by Gazyva maintenance n=601**
	Median observation time 34 months	**Median observation time 35 months**
Primary Endpoint		
Investigator-assessed PFS[§] (PFS-INV)		
Number (%) of patients with event	144 (24.0%)	101 (16.8%)
HR [95% CI]	0.66 [0.51, 0.85]	
p-value (Log-Rank test, stratified*)	0.0012	
2 year PFS estimate	80.9	87.7
[95% CI]	[77.4, 84.0]	[84.6, 90.1]
3 year PFS estimate	73.3	80.0
[95% CI]	[68.8, 77.2]	[75.9, 83.6]
Key Endpoints		
IRC-assessed PFS[§] (PFS-IRC)		
Number (%) of patients with event	125 (20.8%)	93 (15.5%)
HR [95% CI]	0.71 [0.54, 0.93]	
p-value (Log-Rank test, stratified*)	0.0138	
2 year PFS estimate	82.0	87.2
[95% CI]	[78.5, 85.0]	[84.1, 89.7]
3 year PFS estimate	77.9	81.9
[95% CI]	[73.8, 81.4]	[77.9, 85.2]
Time to next anti-lymphoma therapy		
Number (%) of patients with event	111 (18.5%)	80 (13.3%)
HR [95% CI]	0.68 [0.51, 0.91]	
p-value (Log-Rank test, stratified*)	0.0094	
Overall Survival		
Number (%) of patients with event	46 (7.7%)	35 (5.8%)
HR [95% CI]	0.75 [0.49, 1.17][¶]	
p-value (Log-Rank test, stratified*)	0.21[¶]	
Overall Response Rate at End of Induction[‡] (INV-assessed, CT)**		
Responders (%) (CR, PR)	522 (86.9%)	532 (88.5%)
Difference in response rate (%) [95% CI]	1.7% [-2.1%, 5.5%]	
p-value (Cochran-Mantel-Haenszel test)	0.33	
Complete Response (CR)	143 (23.8%)	117 (19.5%)
95% CI Clopper-Pearson	[20.4%, 27.4%]	[16.4%, 22.9%]
Partial Response (PR)	379 (63.1%)	415 (69.1%)
95% CI Clopper-Pearson	[59.1%, 66.9%]	[65.2%, 72.7%]
Conversion Rate from End Of Induction		
Patients in PR at end of induction	222	271
Conversion from PR to CR	97 (43.7%)	134 (49.4%)
Difference in rate (%) [95% CI]	5.7% [-3.1, 14.6%]	
Overall Response Rate at End of Maintenance		

	Rituximab + chemotherapy followed by rituximab maintenance n=601	Gazyva + chemotherapy followed by Gazyva maintenance n=601
Patients assessed at end of maintenance	533	525
Responders (%) (CR, PR)	341 (64.0%)	371 (70.7%)
Difference in response rate (%) [95% CI]	6.7% [1.0%, 12.4%]	
p-value (Cochran-Mantel-Haenszel test)	0.0197	
Complete response (CR)	195 (36.6%)	205 (39.0%)
95% CI Clopper-Pearson	[32.5%, 40.8%]	[34.9%, 43.4%]
Partial response (PR)	146 (27.4%)	166 (31.6%)
95% CI Clopper-Pearson	[23.7%, 31.4%]	[27.7%, 35.8%]

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

* Stratification factors were chemotherapy regimen, FLIPI risk group for follicular lymphoma, geographic region

¶ Data Not Yet Mature. Median was not reached at time of analysis

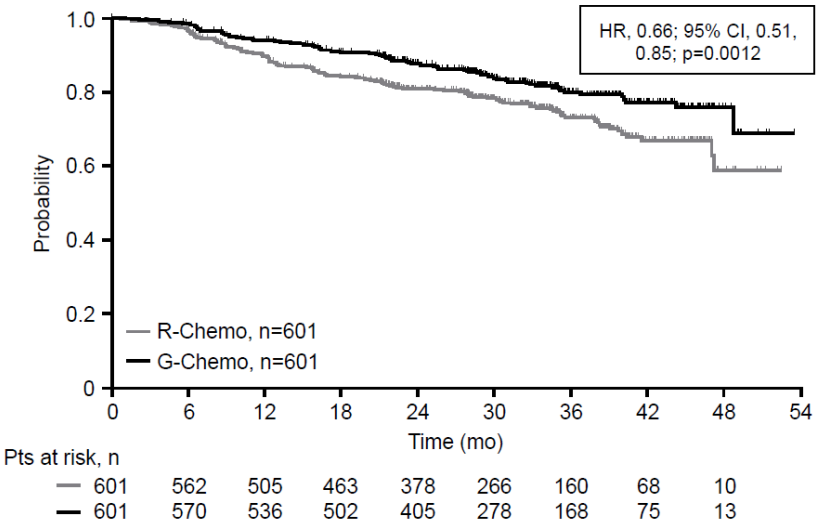
‡ End of Induction = end of Induction phase, does not include monotherapy maintenance

**Assessed as per modified Cheson 2007 criteria

§ Significance level at this efficacy interim analysis: 0.012

Response rates at the end of induction assessed by positron emission tomography (PET) were available for 297 of 601 patients in the Gazyva plus chemotherapy arm and 298 of 601 patients in the rituximab plus chemotherapy arm of the study. Complete response rates at end of induction as assessed by PET were 62.3% in the Gazyva plus chemotherapy arm and 56.7% in the rituximab plus chemotherapy arm. Overall response rates were similar in the two arms, with a difference of 4.3% in favour of the Gazyva plus chemotherapy arm (85.9% for G-chemo vs 81.5% for R-chemo).

Figure 4 Kaplan-Meier estimates of INV-assessed progression-free survival in FL patients



R-Chemo: rituximab plus chemotherapy; G-Chemo: Gazyva plus chemotherapy; HR: hazard ratio; CI: confidence interval

Results of subgroup analyses

Results of subgroup analyses were, in general, consistent with the results seen in the FL population, supporting the robustness of the overall result. The subgroups evaluated included IPI, FLIPI, Chemo Regimen, Bulky Disease, B Symptoms at Baseline, Ann Arbor Stage and ECOG at Baseline.

Relapsed/Refractory indolent NHL

In a phase III, open-label, multicenter, randomised study (GAO4753g/GADOLIN), 396 patients with indolent NHL (iNHL) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen were evaluated. Patients were randomised 1:1 to receive either bendamustine (B) alone (n=202) or Gazyva in combination with bendamustine (G+B) (n=194) for 6 cycles, each of 28 days duration. Patients in the G+B 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 induction continued receiving Gazyva maintenance until disease progression or for up to two years (whichever occurred first).

The demographic data and baseline characteristics were well balanced [median age was 63 years; 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. The majority of the patients had follicular lymphoma (FL) (81.1%). Of the non-follicular patients, 11.6% had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL).

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 primary analysis demonstrated a statistically significant and clinically meaningful 45% reduction in the risk of disease progression (PD) or death, based on IRC assessment, in patients with iNHL receiving G+B followed by G maintenance vs B alone (stratified log-rank test p value=0.0001). IRC-assessed response rates at the end of induction treatment and IRC-assessed best overall response within 12 months of start of treatment were similar in the two treatment arms.

At final 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 final analysis since IRC assessments did not continue. Overall, the efficacy results were consistent with what was observed in the primary analysis. The overall survival (OS) in patients with FL was stable with longer follow-up (see Figure 6); the HR for risk of death was 0.71 (95% CI: 0.51, 0.98).

Table 8 Summary of efficacy in iNHL patients from GAO4753g (GADOLIN) study (primary analysis results)

	Bendamustine n = 202	**G+B followed by Gazyva maintenance n = 194**
	Median observation time 20 months	**Median observation time 22 months**
Primary Endpoint		
IRC-assessed PFS (PFS-IRC)		
Number (%) of patients with event	104 (51.5%)	71 (36.6%)
Median duration of PFS (months)	14.9	NR
HR [95% CI]	0.55 [0.40, 0.74]	
p-value (Log-Rank test, stratified*)	0.0001	
Secondary Endpoints		
Investigator-assessed PFS (PFS-INV)		
Number (%) of patients with event	115 (56.9%)	77 (39.7%)
Median duration of PFS (months)	14.0	29.2
HR [95% CI]	0.52 [0.39, 0.70]	
p-value (Log-Rank test, stratified*)	<0.0001	

	Bendamustine n = 202	G+B followed by Gazyva maintenance n = 194
Best Overall Response (BOR) (IRC-assessed)[§]		
No. of patients included in the analysis	197	192
Responders (%) (CR, PR)	151 (76.6%)	151 (78.6%)
Difference in response rate (%) [95% CI]	-0.59 [-8.33, 7.15]	
p-value (Cochran-Mantel-Haenszel test)	0.9878[¶]	
Duration of response (IRC-assessed)		
No. of patients included in the analysis	154	154
No. (%) of patients with event	85 (55.2%)	48 (31.2%)
Median duration of response (months)	13.2	NR
HR [95% CI]	0.42 [0.29, 0.61]	
Overall Survival		
No. (%) of patients with event	41 (20.3%)	34 (17.5%)
Median time to event (months)	NR[¶]	NR[¶]
HR [95% CI]	0.82 [0.52, 1.30] [¶]	
p-value (Log-Rank test, stratified*)	0.4017[¶]	
Overall Response Rate at End of Induction[‡] **(IRC-assessed)**		
Patients assessed at end of treatment	189	188
Responders (%) (CR, PR)	119 (63.0%)	130 (69.1%)
Difference in response rate (%) [95% CI]	6.19 [-3.64, 16.02]	
p-value (Cochran-Mantel-Haenszel test)	0.3062	
Complete response (CR)	23 (12.2%)	21 (11.2%)
Partial response (PR)	96 (50.8%)	109 (58.0%)
Stable disease (SD)	18 (9.5%)	19 (10.1%)
Progressive disease (PD)	17 (9.0%)	17 (9.0%)
Unable to evaluate (UE)	5 (2.6%)	4 (2.1%)
Missing (NA)	30 (15.9%)	18 (9.6%)

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), 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

[‡] End of Induction=end of Induction phase, does not include monotherapy maintenance

Figure 5 Kaplan-Meier curve of IRC-assessed PFS in iNHL patients from GAO4753g (GADOLIN) study

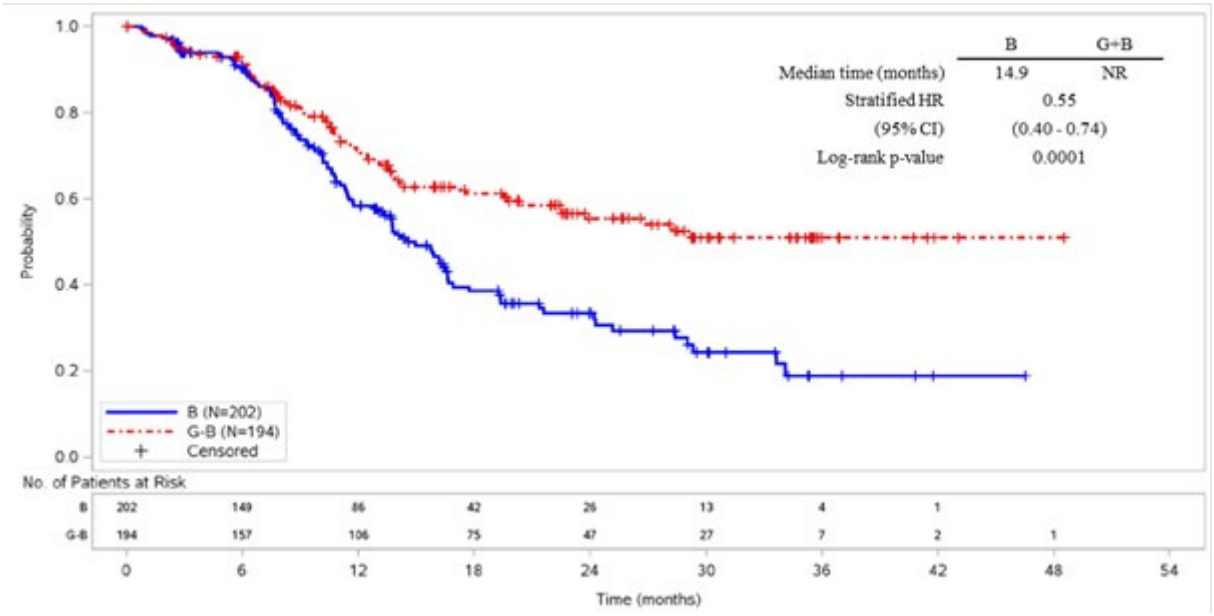
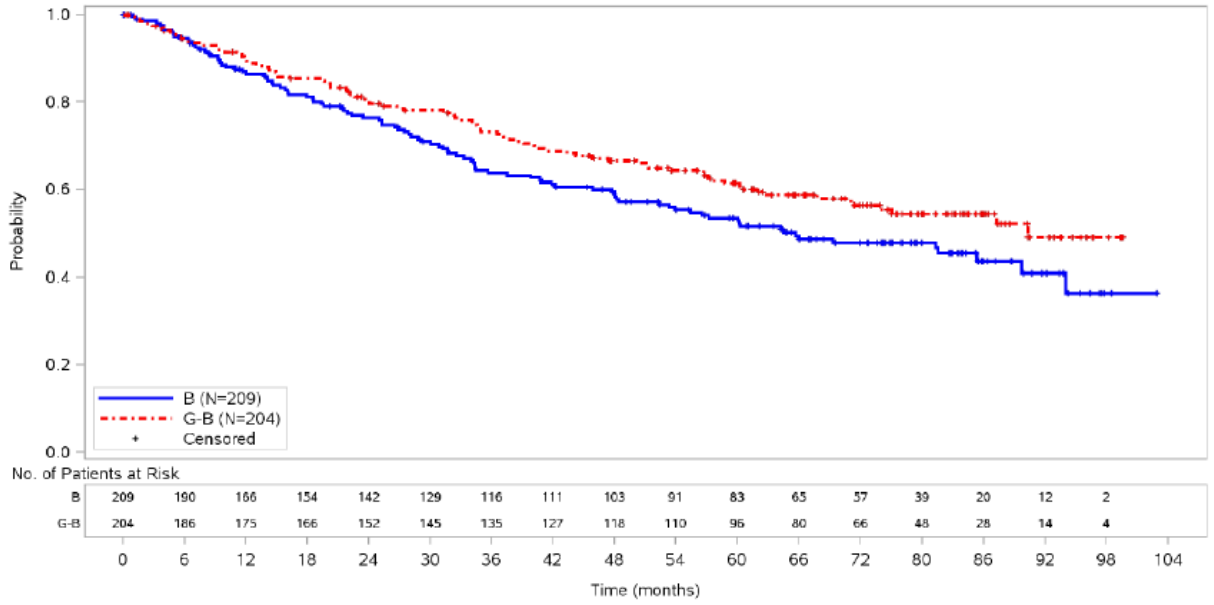


Figure 6 Kaplan-Meier curve of Overall Survival in iNHL patients from GAO4753g (GADOLIN) study (final analysis)



Results of subgroup analyses

Results of subgroup analyses were in general consistent with the results seen in the ITT population, supporting the robustness of the overall result.

Patient Reported Outcomes

Previously Untreated Follicular Lymphoma

Based on the FACT-Lym questionnaire collected during treatment and follow-up periods, both arms experienced clinically meaningful improvements in lymphoma-related symptoms as defined by a ≥ 3 point increase from baseline in the Lymphoma subscale, a ≥ 6 point increase from baseline in the FACT Lym TOI and a ≥ 7 point increase from baseline in the FACT Lym Total score. EQ-5D utility scores were similar at baseline, during treatment and follow-up. No meaningful differences were seen between the arms in health-related quality of life (HRQoL) or health status measures.

Relapsed/refractory iNHL
Based on the FACT-Lym questionnaire and EQ-5D index scale collected during the treatment and follow-up periods, HRQoL was generally maintained in the pivotal study with no meaningful difference between the arms. However, the addition of Gazyva to bendamustine delayed the time to worsening of quality of life as measured by the FACT-Lym TOI score (HR=0.83; 95% CI: 0.60, 1.13).

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.

Patients in the pivotal CLL trial, BO21004/CLL11, were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Gazyva. In Gazyva treated patients, 8 out of 140 in the randomised phase and 2 out of 6 in the run-in phase tested positive for ATA at 12 months of follow-up. Of these patients, none experienced either anaphylactic or hypersensitivity reactions that were considered related to ATA, nor was clinical response affected.

No post-baseline HAHA (Human Anti-Human Antibody) were observed in patients with iNHL treated in study GAO4753g/GADOLIN. In study BO21223/GALLIUM, 1/565 patient (0.2% of patients with a post-baseline assessment) developed HAHA at induction completion. While the clinical significance of HAHA is not known, a potential correlation between HAHA and clinical course cannot be ruled out.

5.2 PHARMACOKINETIC PROPERTIES
A population pharmacokinetic (PK) model was developed to analyse the PK data in 469 patients with indolent non-Hodgkin lymphoma (iNHL), 342 patients with chronic lymphocytic leukaemia (CLL), and 130 patients with diffuse large B-cell lymphoma who received Gazyva in phase I, phase II and phase III studies. From the population PK model, after the Cycle 6 Day 1 infusion in CLL patients, the estimated median C_{max} value was 465.7 µg/mL and AUC(T) value was 8,961 µg*d/mL. In iNHL patients the estimated median C_{max} value was 539.3 µg/mL and AUC(T) value was 10,956 µg*d/mL.

Absorption
Obinutuzumab is administered intravenously. There have been no clinical studies performed with other routes of administration.

Distribution
Following intravenous administration, the volume of distribution of the central compartment (2.72 L), approximates serum volume, which indicates distribution is largely restricted to plasma and interstitial fluid.

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

Elimination
The clearance of *obinutuzumab* was approximately 0.11 L/day in CLL patients and 0.08 L/day in iNHL patients with a median elimination t½ of 26.4 days in CLL patients and 36.8 days in iNHL patients.

Obinutuzumab elimination comprises two parallel pathways which describe clearance, a linear clearance pathway and a non-linear clearance pathway which changes as a function of time. During initial treatment, the non-linear time-varying clearance pathway is dominant and is consequently the major clearance pathway. As treatment continues, the impact of this pathway diminishes and the linear clearance pathway predominates. This is indicative of target mediated drug disposition (TMDD), where the initial abundance of CD20 cells causes rapid removal of *obinutuzumab* from the circulation. However, once the majority of CD20 cells are bound to *obinutuzumab*, the impact of TMDD on PK is minimised.

Pharmacokinetic/Pharmacodynamic relationship
In the population pharmacokinetic analysis, gender was found to be a covariate which explains some of the inter-patient variability, with a 22% greater steady state clearance (CLss) and a 19% greater volume of distribution (V) in males. However, results from the population analysis have shown that the differences in exposure are not significant (with an estimated median AUC and C_{max} in CLL patients of 11282 µg•d/mL and 578.9 µg/mL in females and 8451 µg•d/mL and 432.5 µg/mL in males, respectively at Cycle 6 and AUC and C_{max} in iNHL of 13172 µg•d/mL and 635.7 µg/mL in females and 9769 µg•d/mL and 481.3 µg/mL in males, respectively), indicating that there is no need to dose adjust based on gender.

Pharmacokinetics in special populations
Elderly Patients
The population pharmacokinetic analysis of *obinutuzumab* showed that age did not affect the pharmacokinetics of *obinutuzumab*. No significant difference was observed in the pharmacokinetics of *obinutuzumab* among patients <65 years (n=454), patients between 65-75 years (n=317) and patients >75 years (n=190).

Paediatric Patients
No studies have been conducted to investigate the pharmacokinetics of *obinutuzumab* in children.

Renal impairment
The population pharmacokinetic analysis of *obinutuzumab* showed that creatinine clearance does not affect the pharmacokinetics of *obinutuzumab*. Pharmacokinetics of *obinutuzumab* in patients with mild creatinine clearance (CrCl 50 to 89 mL/min, n=464) or moderate (CrCl 30 to 49 mL/min, n=106) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=383). PK data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=8), therefore no dosage recommendations can be made.

Hepatic impairment
No formal PK study has been conducted and no population PK data was collected in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Histidine
Histidine hydrochloride monohydrate
Trehalose dehydrate
Poloxamer 188

6.2 INCOMPATIBILITIES
No incompatibilities between Gazyva and polyvinyl chloride, polyethylene, polypropylene or polyolefine bags, polyvinyl chloride, polyurethane, or polyethylene infusion sets, as well as optional inline filters with product contact surfaces of polyethersulfon, a 3-way stopcock infusion aid made from polycarbonate, and catheters made from polyetherurethane 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.

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.

6.3 SHELF LIFE
36 months

Shelf-life of reconstituted solution
Gazyva does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

Physical and chemical stability of the prepared infusion solution of Gazyva has been demonstrated for 24 hours at 2°C - 8°C followed by 24 hours at ambient temperature (≤ 30°C) followed by an infusion taking no longer than 24 hours. To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, hold at 2°C - 8°C for not more than 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store vial in a refrigerator at 2°C - 8°C. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
Gazyva 40 mL concentrate solution for infusion (25mg/mL) in a sterile, preservative free, non-pyrogenic 50 mL vial (clear Type I glass).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Gazyva should be prepared by a healthcare professional using aseptic technique.

For all iNHL cycles and CLL cycles 2-6
Withdraw the required amount of Gazyva liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see section 6.2).

For CLL cycle 1, Day 1 only: Preparation of infusion bags for dose administered over 2 days
The table below provides guidance on the volume of Gazyva liquid concentrate to be diluted and the volume of sterile 0.9% sodium chloride solution it is to be diluted in. Withdraw the required amount of Gazyva liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see section 6.2).

To ensure differentiation of the two infusion bags for the initial 1000 mg dose, the recommendation is to utilise 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 the vial and dilute 4 mL into a 100 mL infusion bag and the remaining 36 mL into a 250 mL PVC or non-PVC polyolefin infusion bag containing sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Clearly label each infusion bag.

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

Dose of Gazyva to be administered	**Required amount of Gazyva liquid concentrate**	**Volume 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

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

Gazyva is for single use in one patient only. Once the infusion is prepared it should be administered immediately (see sections 6.4 and 6.5).

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

13 November 2014

10. DATE OF REVISION OF THE TEXT

04 November 2019

Summary of Changes Table

Section Changed	Summary of new information
4.4, 4.8, 5.1	Updated to reflect the final analysis of the GADOLIN study
4.8	Table 5 updated as a result of the final analysis of the GADOLIN study (3 ADRs were added and ADRs which no longer met the 2% difference threshold were removed).