1. NAME OF THE MEDICINAL PRODUCT

Gazyvaro 1 000 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 40 mL concentrate contains 1 000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

Obinutuzumab is a Type II humanised anti-CD20 monoclonal antibody of the IgG1 subclass derived by humanisation of the parental B-Ly1 mouse antibody and produced in the Chinese Hamster Ovary cell line by recombinant DNA technology.

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 (CLL)

Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1).

Follicular lymphoma (FL)

Gazyvaro in combination with chemotherapy followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced FL (see section 5.1)

Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Lupus nephritis (LN)

Gazyvaro in combination with mycophenolate mofetil (MMF) is indicated for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN).

4.2 Posology and method of administration

Gazyvaro should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available.

Posology

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 treatment such as urate oxidase (e.g. *rasburicase*), starting 12-24 hours prior to start of Gazyvaro 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 (IRRs)

Premedication to reduce the risk of IRRs is outlined in Table 1 (see also section 4.4). Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle and for patients with LN (see Table 1). Premedication for subsequent infusions and other premedication should be administered as described below.

Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration (see section 4.4).

Table 1 Premedication to be administered before Gazyvaro infusion to reduce the risk of IRRs (see section 4.4)

Indication/Day of treatment/ Cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1: Day 1 for CLL and FL	All patients	Intravenous corticosteroid[1,4] (mandatory for CLL, recommended for FL)	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
Cycle 1: Day 2 for CLL only	All patients	Intravenous corticosteroid[1] (mandatory)	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
All subsequent infusions for CLL and FL	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion

Indication/Day of treatment/ Cycle	Patients requiring premedication	Premedication	Administration
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/anti-pyretic[2] Anti-histaminic medicine[3]	
	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[1,4]	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2] Anti-histaminic medicine[3]	At least 30 minutes before Gazyvaro infusion
LN	All patients	Intravenous corticosteroid[5]	Completed between 30 and 60 minutes prior to Gazyvaro infusion *Starting from Dose 6, intravenous corticosteroid should only be administered to patients who have experienced an IRR in the prior infusion*
		Oral analgesic/anti-pyretic[6]	
		Anti-histaminic medicine[3]	

[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 IRR.
[2] e.g. 1 000 mg acetaminophen/paracetamol
[3] e.g. 50 mg diphenhydramine
[4] If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyvaro, the corticosteroid can be administered as an oral medicinal product if given at least 60 minutes prior to Gazyvaro, in which case additional IV corticosteroid as premedication is not required.
[5] 80 mg IV methylprednisolone
[6] 650-1 000 mg acetaminophen/paracetamol

<u>*Dose*</u>

Chronic lymphocytic leukaemia (CLL, in combination with chlorambucil[1])

For patients with CLL the recommended dose of Gazyvaro in combination with chlorambucil is shown in Table 2.

Cycle 1

The recommended dose of Gazyvaro in combination with chlorambucil is 1 000 mg administered over Day 1 and Day 2, (or Day 1 continued), and on Day 8 and Day 15 of the first 28 day treatment cycle.

Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), 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 second bag must be administered the following day.

Cycles 2 – 6

The recommended dose of Gazyvaro in combination with chlorambucil is 1 000 mg administered on Day 1 of each cycle.

Table 2 Dose of Gazyvaro to be administered during 6 treatment cycles each of 28 days duration for patients with CLL

Cycle	Day of treatment	Dose of Gazyvaro
Cycle 1	Day 1	100 mg
	Day 2 (or Day 1 continued)	900 mg
	Day 8	1 000 mg
	Day 15	1 000 mg
Cycles 2-6	Day 1	1 000 mg

[1]See section 5.1 for information on chlorambucil dose

Duration of treatment

Six treatment cycles, each of 28 day duration.

Delayed or missed doses

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

Follicular lymphoma

For patients with FL, the recommended dose of Gazyvaro in combination with chemotherapy is shown in Table 3.

Patients with previously untreated follicular lymphoma

Induction (in combination with chemotherapy[2])
Gazyvaro should be administered with chemotherapy as follows:

- Six 28-day cycles in combination with bendamustine[2] or,
- Six 21-day cycles in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), followed by 2 additional cycles of Gazyvaro alone or,
- Eight 21-day cycles in combination with cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone (CVP).

Maintenance
Patients who achieve a complete or partial response to induction treatment with Gazyvaro in combination with chemotherapy (CHOP or CVP or bendamustine) should continue to receive Gazyvaro 1 000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first).
Patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Induction (in combination with bendamustine[2])
Gazyvaro should be administered in six 28-day cycles in combination with bendamustine[2].

Maintenance
Patients who achieved a complete or partial response to induction treatment (i.e. the initial 6 treatment cycles) with Gazyvaro in combination with bendamustine or have stable disease should continue to receive Gazyvaro 1 000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first).

Table 3 Follicular lymphoma: Dose of Gazyvaro to be administered during induction treatment, followed by maintenance treatment

Cycle	Day of treatment	Dose of Gazyvaro
Cycle 1	Day 1	1 000 mg
	Day 8	1 000 mg
	Day 15	1 000 mg
Cycles 2–6 or 2–8	Day 1	1 000 mg
Maintenance	Every 2 months for 2 years or until disease progression (whichever occurs first)	1 000 mg

[2]See section 5.1 for information on bendamustine dose

Duration of treatment

Induction treatment of approximately six months (six treatment cycles of Gazyvaro, each of 28 day duration when combined with bendamustine, or eight treatment cycles of Gazyvaro, each of 21 day duration when combined with CHOP or CVP) followed by maintenance once every 2 months for 2 years or until disease progression (whichever occurs first).

Delayed or missed doses

If a planned dose of Gazyvaro 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 maintenance, maintain the original dosing schedule for subsequent doses.

Lupus nephritis

The recommended dosage of Gazyvaro is 1 000 mg administered intravenously (see Table 4).
Gazyvaro should be used in combination with mycophenolate mofetil.

Table 4 Dose of Gazyvaro for patients with Lupus Nephritis

Dose number	Timing of treatment	Dose
1	Initial infusion	1 000 mg
2	Week 2 *(two weeks after Dose 1)*	1 000 mg
3	Week 24	1 000 mg
4	Week 26 *(two weeks after Dose 3)*	1 000 mg
5* and thereafter	Every 6 months	1 000 mg

*Dose 5 should be administered six months after Dose 4

The patient's condition and response should be evaluated at Week 76 and beyond, and an appropriate risk-benefit analysis should be made for continuation of therapy.

Delayed or missed doses

If a planned dose of Gazyvaro is missed, it should be administered as soon as possible - do not wait until the next planned dose. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

Dose modifications during treatment (all indications)

No dose reductions of Gazyvaro are recommended.

For management of symptomatic adverse events (including IRRs), see paragraph below (Management of IRRs or section 4.4).

Special populations

Elderly

No dose adjustment is required in elderly patients (see section 5.2). The safety and efficacy of Gazyvaro in patients with LN above 65 years of age have not been established.

Renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min) (see section 5.2). The safety and efficacy of Gazyvaro have not been established in patients with severe renal impairment (CrCl < 30 mL/min) (see sections 4.8 and 5.2).

Hepatic impairment

The safety and efficacy of Gazyvaro in patients with impaired hepatic function have not been established. No specific dose recommendations can be made.

Paediatric population

The safety and efficacy of Gazyvaro in children and adolescents aged below 18 years have not been established. No data are available.

Method of administration

Gazyvaro is for intravenous use. It should be given as an intravenous infusion through a dedicated line after dilution (see section 6.6). Gazyvaro infusions should not be administered as an intravenous push or bolus.

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

Instructions on the rate of infusion are shown in Tables 5-8.

Chronic lymphocytic leukaemia (CLL)

Table 5 Chronic lymphocytic leukaemia: Standard infusion rate in the absence of IRRs/hypersensitivity and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
The infusion rate may be escalated provided that the patient can tolerate it. For management of IRRs that occur during the infusion, refer to Management of IRRs.</th></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1
(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)
(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 with administration at 25 mg/hr. The rate of infusion can be escalated in increments up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 8
(1 000 mg)</td><td rowspan="3">If no IRR occurred during the previous infusion, when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
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.</td></tr>
<tr><td>Day 15
(1 000 mg)</td></tr>
<tr><td>Cycles 2-6</td><td>Day 1
(1 000 mg)</td></tr>
</table>

Follicular lymphoma (FL)

Gazyvaro should be administered at the standard infusion rate in Cycle 1 (see Table 6). In patients who do not experience Grade ≥ 3 infusion related reactions (IRRs) during Cycle 1, Gazyvaro may be administered as a short (approximately 90 minutes) duration infusion (SDI) from Cycle 2 onwards (see Table 7).

Table 6 Follicular lymphoma: Standard infusion rate and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
The infusion rate may be escalated provided that the patient can tolerate it. For management of IRRs that occur during the infusion, refer to Management of IRRs.</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1
(1 000 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
(1 000 mg)</td><td rowspan="4">If no IRR or if an IRR Grade 1 occurred during the previous infusion when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

If the patient experienced an IRR 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.</td></tr>
<tr><td>Day 15
(1 000 mg)</td></tr>
<tr><td>Cycles 2–6 or 2–8</td><td>Day 1
(1 000 mg)</td></tr>
<tr><td>Maintenance</td><td>Every 2 months for 2 years or until disease progression (whichever occurs first)</td></tr>
</table>

Table 7 Follicular lymphoma: Short duration infusion (SDI) rate and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
For management of IRRs that occur during the infusion, refer to Management of IRRs.</th></tr>
<tr><td>Cycles 2–6 or 2–8</td><td>Day 1
(1 000 mg)</td><td rowspan="2">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, administer the next obinutuzumab infusion at the standard rate (see Table 6).</td></tr>
<tr><td>Maintenance</td><td>Every 2 months for 2 years or until disease progression (whichever occurs first)</td></tr>
</table>

Lupus nephritis

The initial Gazyvaro infusion should be administered at the standard infusion rate (see Table 8). Patients who do not experience Grade ≥ 3 infusion related reactions during the previous infusion may receive Gazyvaro as a short (approximately 90 minutes) duration infusion from Dose 2 onwards (see Table 9), with continued premedication.

Table 8 Lupus nephritis: Standard infusion rate

Dose number	Timing of treatment	Rate of infusion
1	Initial infusion (1 000 mg)	Administer at a rate of 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. For management of IRRs that occur during infusion, refer to Management of IRRs.
2	Week 2 - *two weeks after Dose 1* (1 000 mg)	Administer at a rate of 100 mg/hr. The rate of infusion can be escalated at a rate of 100 mg/hr every 30 minutes to a maximum of 400 mg/hr.
3	Week 24 (1 000 mg)	
4	Week 26 - *two weeks after Dose 3* (1 000 mg)	
5* and thereafter	Every 6 months (1 000 mg)	

*Dose 5 should be administered six months after Dose 4

Table 9 Lupus nephritis: Short duration infusion (SDI) rate and recommendations in case an IRR occurred with previous infusion

Dose number	Rate of infusion
1	See Table 8
2 and thereafter	If no IRR of Grade ≥3 occurred during the previous infusion: 100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes. If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 or higher IRR occurred during the previous SDI, administer Gazyvaro at the standard infusion rate (see Table 8).

Management of IRRs

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below (see also section 4.4).

Chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL)

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. 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, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate

for the treatment dose (see Tables 5-7). For CLL patients receiving the Day 1 (Cycle 1) dose split over two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.
The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.

- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 5-7). For CLL patients receiving the Day 1 (Cycle 1) dose split over the two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

IRRs occurring during SDI:

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. 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 experiences a second Grade 3 IRR after resuming the infusion, the infusion must be stopped and therapy must be permanently discontinued. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion should be given at a rate not higher than the standard rate.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 6-7).

Lupus nephritis (LN)

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. 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, if the patient does not experience any further IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Table 8).
  The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced to half the rate that was used at the time of the reaction and symptoms treated. Infusion can be continued upon resolution of symptoms at the reduced rate for an additional 30 minutes. If the patient does not experience any further IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 8 and 9).

IRRs occurring during SDI:

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. 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 experiences a second Grade 3 IRR after resuming the infusion, the infusion must be stopped and therapy must be permanently discontinued. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion should be given at a rate not higher than the standard rate (See Table 8).

- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 8-9). If the patient experiences ongoing symptoms or a Grade 3 or higher IRR occurred during the previous 90-minute infusion, administer all subsequent Gazyvaro infusions at the standard infusion rate (see Table 8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Special warnings and precautions are presented separately for the Oncology (Chronic lymphocytic leukaemia and Follicular lymphoma), and for the Lupus nephritis indications.

Chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL)

Based on a subgroup analysis in previously untreated FL, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive (see section 5.1). A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro plus chemotherapy and the patient-specific situation.

Infusion related reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyvaro were IRRs, which occurred predominantly during infusion of the first 1 000 mg. IRRs may be related to cytokine release syndrome which has also been reported in Gazyvaro treated patients. In CLL patients who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) as described in section 4.2, a 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 1 000 mg was infused, with most patients having no IRRs during subsequent administrations of Gazyvaro (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 immunoglobulin E (IgE) mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumour burden and/or high circulating lymphocyte count in CLL [> 25 x 10^9/L] may be at increased risk of severe IRRs. Patients with renal impairment (CrCl < 50 mL/min) and patients with both Cumulative Illness Rating Scale (CIRS) > 6 and CrCl < 70 mL/min are more at risk of IRRs, including severe IRRs (see section 4.8). For management of IRRs see section 4.2 Posology and method of administration.

Patients must not receive further Gazyvaro 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 Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro 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 medicine.

Hypersensitivity reactions

Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to clinically distinguish from IRRs. Hypersensitivity symptoms can occur after previous exposure and very rarely with the first infusion. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated (see section 4.3).

Tumour lysis syndrome (TLS)

TLS has been reported with Gazyvaro. 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 oxidate (e.g. rasburicase) starting 12-24 hours prior to the infusion of Gazyvaro as per standard practice (see 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 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.

Neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with Gazyvaro. 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 the administration of granulocyte-colony stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate. Dose delays should be considered in case of severe or life-threatening neutropenia. It is strongly recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should also be considered (see section 4.2). 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. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia (see section 4.8).

Thrombocytopenia

Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with Gazyvaro. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of thrombocytopenia (see section 4.8). Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with Gazyvaro. 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 or 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.

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

DIC including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyvaro. The majority of cases involved non-overt DIC, with subclinical

(asymptomatic) changes in platelets and laboratory coagulation parameters occurring within 1-2 days after the first infusion with spontaneous resolution usually occurring within one to two weeks, not requiring drug discontinuation or specific intervention. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC were identified. Patients suspected to have non-overt DIC should be monitored closely with coagulation parameters including platelets and clinical observation for signs or symptoms of overt DIC. Gazyvaro should be discontinued at first onset of suspected overt DIC and appropriate treatment initiated.

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 Gazyvaro (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

Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro 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 Gazyvaro therapy. Fatal infections have been reported.

Patients (CLL) with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections (see section 4.8). In the follicular lymphoma studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in the maintenance phase. During the follow-up phase, Grade 3-5 infections are observed more in patients who received Gazyvaro 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 Gazyvaro (see section 4.8). HBV screening should be performed in all patients before initiation of treatment with Gazyvaro. At a minimum this should include hepatitis B surface antigen (HBsAg) status and hepatitis B core antibody (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 Gazyvaro. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Gazyvaro (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 nonspecific 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 (cerebrospinal fluid testing for John Cunningham viral DNA). Therapy with Gazyvaro 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 Gazyvaro 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 obinutuzumab 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 Gazyvaro during pregnancy, infants should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered. The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Lupus nephritis (LN)

Infections

Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro 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 Gazyvaro therapy. Fatal infections have been reported.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Gazyvaro. At 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 Gazyvaro. Patients with positive hepatitis B serology should be monitored and managed following local medical standards to prevent hepatitis reactivation.

Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with Gazyvaro. 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 the administration of granulocyte-colony stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate.

Infusion related reactions

In patients with LN, infusion related reactions (IRRs) occurred predominantly during infusion of the first 1 000 mg. IRRs were generally mild (Grade 1) to moderate (Grade 2) and could be managed by slowing or temporarily halting the infusion (see Management of IRRs). However, severe (Grade 3) and life-threatening (Grade 4) IRRs requiring symptomatic treatment were also reported. See section 4.2 for information on prophylaxis.

Patients must not receive further Gazyvaro 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 Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro 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 medicine.

Progressive multifocal leukoencephalopathy (PML)

PML has been reported in patients treated with Gazyvaro for CLL and/or FL (see section 4.8), and has not been reported in patients treated with Gazyvaro during the LN placebo-controlled studies. 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 nonspecific 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 (cerebrospinal fluid testing for John Cunningham viral DNA). Therapy with Gazyvaro 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 Gazyvaro 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 obinutuzumab 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 Gazyvaro during pregnancy, infants should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered. The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Elderly

The safety and efficacy of Gazyvaro in patients with LN above 65 years of age have not been established.

Renal impairment

The safety and efficacy of Gazyvaro have not been established in patients with severe renal impairment (CrCl < 30 mL/min).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed, although limited drug-drug interaction sub-studies have been undertaken for Gazyvaro with bendamustine, CHOP, fludarabine and cyclophosphamide (FC), and chlorambucil.

A risk for interactions with other concomitantly used medicinal products cannot be excluded.

Pharmacokinetic interactions

Obinutuzumab is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450), uridine diphosphate glucuronyltransferase (UGT) enzymes and transporters such as P-glycoprotein. Therefore, no pharmacokinetic interaction is expected with medicinal products known to be metabolised by these enzyme systems.

Co-administration with Gazyvaro had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP. In addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of Gazyvaro.

Pharmacodynamic interactions

Vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery because of the immunosuppressive effect of obinutuzumab (see section 4.4).

The combination of obinutuzumab with chlorambucil, bendamustine, CHOP or CVP may increase the risk of neutropenia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and for 18 months after treatment with Gazyvaro.

Pregnancy

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. Serum concentrations of obinutuzumab 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 obinutuzumab crosses the placenta (see section 5.3). There are no data from the use of obinutuzumab in pregnant women. Gazyvaro should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

In case of exposure during pregnancy, depletion of B-cells may be expected in infants due to the pharmacological properties of the product. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyvaro during pregnancy until the infant's B-cell levels are within normal ranges (see section 4.4).

Breast-feeding

Animal studies have shown secretion of obinutuzumab in breast milk (see section 5.3).

Since human immunoglobulin G (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 Gazyvaro therapy and for 18 months after the last dose of Gazyvaro.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Gazyvaro has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion of Gazyvaro, and patients experiencing infusion related symptoms should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Undesirable effects are presented separately for the Oncology (Chronic lymphocytic leukaemia and Follicular lymphoma), and for the Lupus nephritis indications.

Chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL)

Summary of the safety profile

The adverse drug reactions (ADRs) from clinical trials were identified during induction, maintenance and follow up for indolent Non-Hodgkin lymphoma (iNHL) including FL; treatment and follow up for CLL in the three pivotal clinical studies:

- BO21004/CLL11 (N=781): Patients with previously untreated CLL
- BO21223/GALLIUM (N=1390): Patients with previously untreated iNHL (86% of the patients had FL)
- GAO4753g/GADOLIN (N=409): Patients with iNHL (81% of the patients had FL) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

These trials investigated Gazyvaro in combination with chlorambucil for CLL and with bendamustine, CHOP or CVP followed by Gazyvaro maintenance therapy for iNHL. The studies BO21223/GALLIUM and GAO4753g/GADOLIN enrolled patients with iNHL including FL. Therefore, in order to provide the most comprehensive safety information, the analysis of ADRs presented in the following has been performed on the entire study population (i.e. iNHL).

Table 10 summarises all ADRs including those of the pivotal studies (BO21004/CLL11, BO21223/GALLIUM GAO4753g/GADOLIN) that occurred at a higher incidence (difference of ≥ 2%) compared to the relevant comparator arm in at least one pivotal study in:

- Patients with CLL receiving Gazyvaro plus chlorambucil compared with chlorambucil alone or rituximab plus chlorambucil (study BO21004/CLL11)
- Patients with previously untreated iNHL receiving Gazyvaro plus chemotherapy (bendamustine, CHOP, CVP) followed by Gazyvaro maintenance in patients achieving a response, compared to rituximab plus chemotherapy followed by rituximab maintenance in patients achieving a response (study BO21223/GALLIUM)
- Patients with iNHL who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen receiving Gazyvaro plus bendamustine, followed by Gazyvaro maintenance in some patients, compared to bendamustine alone (study GAO4753g/GADOLIN)

The incidences presented in Table 10 (all grades and Grades 3-5) are the highest incidence of that ADR reported from any of the three studies.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 10 Summary of ADRs reported in patients[#] receiving Gazyvaro + chemotherapy*

System organ class **Frequency**	**All Grades** **Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)**	**Grades 3-5[†]** **Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)**
Infections and infestations		
Very common	Upper respiratory tract infection, sinusitis[§], urinary tract infection, pneumonia[§], herpes zoster[§], nasopharyngitis	
Common	Oral herpes, rhinitis, pharyngitis, lung infection, influenza	Urinary tract infection, pneumonia, lung infection, upper respiratory tract infection, sinusitis, herpes zoster
Uncommon	Hepatitis B reactivation	Nasopharyngitis, rhinitis, influenza, oral herpes
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Common	Squamous cell carcinoma of skin, Basal cell carcinoma	Squamous cell carcinoma of skin, Basal cell carcinoma
Blood and lymphatic system disorders		
Very common	Neutropenia[§], thrombocytopenia, anaemia, leukopenia	Neutropenia, thrombocytopenia
Common	Febrile neutropenia	Anaemia, leukopenia, febrile neutropenia
Uncommon	Disseminated intravascular coagulation[##]	
Metabolism and nutrition disorders		
Common	Tumour lysis syndrome, hyperuricaemia, hypokalaemia	Tumour lysis syndrome, hypokalaemia
Uncommon		Hyperuricaemia
Psychiatric disorders		
Very common	Insomnia	
Common	Depression, anxiety	
Uncommon		Insomnia, depression, anxiety
Nervous system disorders		
Very common	Headache	
Uncommon		Headache
Not known	Progressive multifocal leukoencephalopathy	
Cardiac disorders		
Common	Atrial fibrillation	Atrial fibrillation
Vascular disorders		
Common	Hypertension	Hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	Cough[§]	
Common	Nasal congestion, rhinorrhoea, oropharyngeal pain	
Uncommon		Cough, oropharyngeal pain
Gastrointestinal disorders		
Very common	Diarrhoea, constipation[§]	
Common	Dyspepsia, haemorrhoids gastrointestinal perforation	Diarrhoea
Uncommon		Constipation, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus	
Common	Eczema	

System organ class Frequency	All Grades Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)	Grades 3-5[†] Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)
Uncommon		Pruritus
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia[§], back pain, pain in extremity	
Common	Musculoskeletal chest pain, bone pain	Pain in extremity
Uncommon		Arthralgia, back pain, musculoskeletal chest pain, bone pain
Renal and Urinary Disorders		
Common	Dysuria, urinary incontinence	
Uncommon		Dysuria, urinary incontinence
General disorders and administration site conditions		
Very common	Pyrexia, Asthenia, fatigue	
Common	Chest pain	Pyrexia, asthenia, fatigue
Uncommon		Chest pain
Immune system disorders		
Rare	Cytokine release syndrome**	
Investigations		
Common	White blood cell count decreased, neutrophil count decreased, weight increased	White blood cell count decreased, neutrophil count decreased
Uncommon	Hypogammaglobulinemia	
Injury, poisoning and procedural complications		
Very common	IRRs	IRRs

[#] Only the highest frequency observed in the trials is reported (based on studies BO21004/previously untreated CLL, BO21223/previously untreated advanced iNHL and GAO4753g/rituximab refractory iNHL)
[##] Disseminated intravascular coagulation (DIC) including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyvaro (see section 4.4)
[†] No Grade 5 adverse reactions have been observed with a difference of ⩾ 2% between the treatment arms
* Chemotherapy: Chlorambucil in CLL; bendamustine, CHOP, CVP in iNHL including FL
[§] observed also during maintenance treatment with at least 2% higher incidence in Gazyvaro arm (BO21223)
**Based on clinical trial exposures in FL and CLL

The profile of adverse reactions in patients with FL was consistent with the overall iNHL population in both studies.

Description of selected adverse reactions

The incidences presented in the following sections if referring to iNHL are the highest incidence of that ADR reported from either pivotal study (BO21223/GALLIUM, GAO4753g/GADOLIN).

The study MO40597 was designed to characterize the safety profile of short duration infusions (approximately 90 minutes) from Cycle 2, in patients with previously untreated FL (see section 5.1 Pharmacodynamic properties).

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 higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm. The incidence of IRRs was 66% with the infusion of the first 1 000 mg of Gazyvaro (20% of patients experiencing a Grade 3-4 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs with subsequent infusions was 3% with the second 1 000 mg dose and 1% thereafter. No Grade 3-5 IRRs were reported beyond the first 1 000 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 IRRs of all Grades was observed. The rates of Grade 3-4 IRRs (which occurred in relatively few patients) were similar before and after mitigation measures were implemented.

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

Grade 3-4 IRRs occurred in 12% of patients. In Cycle 1, the overall incidence of IRRs was higher in patients receiving Gazyvaro plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyvaro 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 Gazyvaro alone. Beyond Cycle 1 the incidence of IRRs in subsequent infusions was comparable between the Gazyvaro and the relevant comparator arms. Overall, 4% of patients experienced an infusion related reaction leading to discontinuation of Gazyvaro.

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597 assessing the safety of SDI, a greater proportion of patients experienced any grade IRRs at Cycle 2 compared to the proportion who experienced IRRs after standard infusion at Cycle 2 in study BO21223 (10/99 [10.1%] vs. 23/529 [4.3%] respectively; IRRs attributed by the investigator to any component of study therapy). No patients experienced Grade ≥3 IRRs after SDI at Cycle 2 in MO40597; 3/529 (0.6%) experienced Grade ≥3 IRRs at Cycle 2 in study BO21223. IRR symptoms and signs were similar in both studies.
Infusion related reactions observed in Study MO40597/GAZELLE are summarized in Table 11.

Table 11 Study MO40597/GAZELLE Short-Duration Infusion: Infusion Related Reactions[a] by Cycle (Safety-Evaluable Population)

CTCAE Grade	C1 Overall (standard infusion)	C1[b] by day				C2[C]	C3	C4	C5	C6	C7	Over all induction cycles
		Day 1	Day 2[d]	Day 8	Day 15							
All Grade	65/113 (57.5%)	57/113 (50.4%)	4/51 (7.8%)	6/112 (5.4%)	5/111 (4.5%)	13/110 (11.8%)	9/108 (8.3%)	7/108 (6.5%)	6/107 (5.6%)	5/105 (4.8%)	2/55 (3.6%)	71/113 (62.8%)
Grade ≥3	6/113 (5.3%)	5/113 (4.4%)	1/51 (2.0%)	0	0	0	0	0	1/107 (0.9%)	0	0	7/113 (6.2%)

C=cycle; CTCAE = Common Terminology Criteria for Adverse Events; IRR=infusion related reaction

[a] Infusion related reaction defined as any event that occurred during or within 24 hours from the end of study treatment infusion that were judged by the investigator to be related to any components of therapy.

[b] C1 comprised three infusions at the standard infusion rate, administered at weekly intervals

[c] Patients received short-duration infusion from C2 onward. The denominator at C2 and subsequent cycles represents the number of patients who received SDI at that cycle.

[d] Patients treated with bendamustine on Cycle 1 Day 2.

Neutropenia and infections

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the Gazyvaro plus chlorambucil arm (41%) 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 Gazyvaro 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 Gazyvaro plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyvaro plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see section 4.4).

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

In the Gazyvaro plus chemotherapy arm, the incidence of Grade 1-4 neutropenia (50%) was higher relative to the comparator arm with an increased risk during the induction period. The incidence of prolonged neutropenia and late onset neutropenia was 3% and 8%, respectively. The incidence of infection was 81% in the Gazyvaro plus chemotherapy arm (with Grade 3-5 events reported in 22% of patients and fatal events reported in 3% of patients). Patients who received G-CSF prophylaxis had a lower rate of Grade 3-5 infections (see section 4.4).

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, neutropenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients receiving standard duration infusion 69/113 [61.1%] vs 247/595 [41.5%], respectively, throughout induction). The median and range of neutrophil count values were similar in both studies at each time point. Febrile neutropenia was reported in a similar proportion of patients in MO40597 and BO21223 (6/113 [5.3%] vs 31/595 [5.2%], respectively). Infection was reported less frequently in MO40597 than in BO21223 (45/113 [39.8%] vs 284/595 [47.7%], respectively).

Thrombocytopenia and haemorrhagic events

Chronic Lymphocytic Leukaemia

The incidence of thrombocytopenia was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm (16% vs. 7%) especially during the first cycle. Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyvaro infusion) (see section 4.4). The overall incidence of haemorrhagic events was similar in the Gazyvaro 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 Gazyvaro were reported in Cycle 1. No Grade 5 events of thrombocytopenia were reported. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

The incidence of thrombocytopenia was 15%. Thrombocytopenia occurred more frequently in Cycle 1 in the Gazyvaro plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of infusion (acute thrombocytopenia) was more frequently observed in patients in the Gazyvaro plus chemotherapy arm than in the comparator arm. The incidence of haemorrhagic events 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 the fatal adverse events occurred in Cycle 1.

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, thrombocytopenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients received standard duration infusion (21/113 [28.6%] vs 63/595 [10.6%], respectively, throughout induction). The median and range of platelet count values were similar in both studies at each time point. No thrombocytopenia events reported in MO40597 were associated with bleeding.

Lupus nephritis

Summary of the safety profile

In pooled data from placebo-controlled studies in 200 patients with lupus nephritis treated with Gazyvaro, the most frequently observed adverse drug reactions were upper respiratory tract infection (29%), COVID-19 (22.5%) and urinary tract infection (21%).

Tabulated list of adverse reactions

The ADRs listed in Table 12 are based on pooled safety data from two clinical studies in patients with ISN/RPS 2003 Class III or IV with or without concomitant Class V lupus nephritis, up to week 76:

- REGENCY (CA41705): a Phase III study which included 136 patients treated with Gazyvaro plus standard therapy consisting of mycophenolate mofetil (MMF) and corticosteroids.
- NOBILITY (WA29748): a Phase II study which included 64 patients treated with Gazyvaro plus standard therapy with MMF/mycophenolic acid and corticosteroids.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 12 ADRs reported in patients receiving Gazyvaro + standard therapy* in LN

System Organ Class Frequency	All Grades	Grades 3-5
Infections and infestations		
Very common	Upper respiratory tract infection, COVID-19, urinary tract infection, bronchitis,	
Common	Pneumonia, herpes simplex	COVID-19, urinary tract infection, pneumonia
Injury, Poisoning and Procedural Complications		
Very common	IRR	
Common		IRR
Blood and Lymphatic System Disorders		
Very common	Neutropenia	
Common		Neutropenia
Investigations		
Very common	Blood immunoglobulin M decreased**	

*mycophenolate mofetil (MMF) and corticosteroids
**Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials.

Description of selected adverse reactions

Infections

Infections were reported in 72.0% of patients in the Gazyvaro arm vs. 61.7% of patients in the placebo arm. The most frequently reported infections were upper and lower respiratory tract infections.

Grade 3-5 infections events were reported in 11.5% of patients in the Gazyvaro arm vs 9.8% of patients in the placebo arm. Fatal infection events were reported in 1% of patients in the Gazyvaro arm vs 0.5% of patients in the placebo arm (see section 4.4).

Neutropenia

Neutropenia and related events were reported in 14.0% of patients in the Gazyvaro arm vs 6.2% of patients in the placebo arm. Grade 3-4 neutropenia was reported in 7% of patients treated with Gazyvaro vs 0.5% of patients in the placebo arm. The majority of neutropenia and related events resolved/improved spontaneously or with use of granulocyte colony-stimulating factors (see section 4.4).

Infusion-related reactions

IRRs were reported in 13.5% of patients in the Gazyvaro arm vs 10.4% of patients in the placebo arm. IRRs in both arms were predominantly Grade 1-2 and occurred during/after the first infusion. Grade 3-4 IRRs were reported in 1.5% of patients in the Gazyvaro arm vs 0.5% of patients in the placebo arm. All Grade 3-4 events occurred during/after either the first or second infusion. The incidence and severity of IRRs decreased with subsequent infusions (see section 4.4).
In the REGENCY study, most common IRR signs/symptoms included headache, nausea and vomiting. In the NOBILITY study, the most common IRR symptoms were pyrexia and tachycardia.

Special populations

Elderly

Chronic Lymphocytic Leukaemia

In the pivotal BO21004/CLL11 study, 46% (156 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil were 75 years or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than those patients < 75 years of age.

Indolent Non Hodgkin Lymphoma including Follicular Lymphoma

In the pivotal studies (BO21223/GALLIUM, GAO4753g/GADOLIN) in iNHL, patients 65 years or older experienced more serious adverse events and adverse events leading to withdrawal or death than patients < 65 years of age.

Renal impairment

Chronic Lymphocytic Leukaemia

In the pivotal BO21004/CLL11 study, 27% (90 out of 336) of patients treated with Gazyvaro plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than patients with a CrCl ≥ 50 mL/min (see section 4.2, 4.4 and 5.2). Patients with a CrCl < 30 mL/min were excluded from the study (see section 5.1).

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

In the pivotal studies (BO21223/GALLIUM, GAO4753g/GADOLIN) in iNHL, 5% (35 out of 698) and 7% (14 out of 204) of patients treated with Gazyvaro, respectively, 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 BO21223 only) than patients with a CrCl ≥ 50 mL/min (see section 4.2 and 5.2). Patients with a CrCl < 40 mL/min were excluded from the studies (see section 5.1).

Lupus Nephritis

The population pharmacokinetic analysis (n = 196) of Gazyvaro showed that creatinine clearance does not affect the pharmacokinetics of obinutuzumab in patients with LN. The pharmacokinetics of obinutuzumab in patients with mild (CrCl 60 - <90 mL/min, n=45) or moderate (CrCl 30 - <60 mL/min, n=17) renal impairment were similar to those in patients with normal kidney function. The safety and efficacy of Gazyvaro in patients with severe renal impairment has not been formally studied.

Additional safety information from clinical studies experience

Worsening of pre-existing cardiac conditions

Cases of arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro in CLL and NHL (see section 4.4). These events may occur as part of an IRR and can be fatal.

Laboratory abnormalities

Transient elevation in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) has been observed in CLL shortly after the first infusion of Gazyvaro.

Obinutuzumab treatment resulted in a decrease in total immunoglobulins in pooled LN data from placebo-controlled studies, mainly driven by reduction in IgM.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: https://medicinesauthority.gov.mt/adrportal

4.9 Overdose

No experience with overdose is available from human clinical studies. In clinical studies with Gazyvaro, doses ranging from 50 mg up to and including 2,000 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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies,
ATC code: L01FA03

Mechanism of action

Obinutuzumab is a recombinant monoclonal humanised 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 obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, 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 FcγRIII positive immune effector cells. In addition, in vivo, obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC). Compared to Type I antibodies, obinutuzumab, a Type II antibody, is characterised by an enhanced direct cell death induction with a concomitant reduction in CDC at an equivalent dose. Obinutuzumab, as a glycoengineered antibody, is characterised by enhanced ADCC and ADCP compared to non-glycoengineered antibodies at an equivalent dose. In animal models obinutuzumab mediates potent B-cell depletion and antitumour efficacy.

In the pivotal clinical study in patients with CLL (BO21004/CLL11), 91% (40 out of 44) of evaluable patients treated with Gazyvaro were B-cell depleted (defined as CD19+ B-cell counts < 0.07 x 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 12-18 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 the pivotal clinical study in patients with iNHL (GAO4753/GADOLIN), 97% (171 out of 176) of evaluable patients treated with Gazyvaro 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.

In the pivotal clinical study in patients with LN (CA41705/REGENCY), 99.2% (127 out of 128) of evaluable patients treated with Gazyvaro were B-cell depleted (defined as CD19+ B-cell counts < 10 cells/µl) at Week 4 and 95% (117 out of 123) were B cell depleted at Week 76. Reductions in circulating naïve B, memory B, and plasmablasts/plasma cells were observed by Week 4 and remained low through Week 76 after treatment initiation.

Clinical efficacy and safety

Chronic Lymphocytic Leukaemia

A Phase III international, multicentre, open label, randomised, two-stage, three-arm clinical study (BO21004/CLL11) investigating the efficacy and safety of Gazyvaro plus chlorambucil (GClb) compared to rituximab plus chlorambucil (RClb) or chlorambucil (Clb) 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 (CIRS) of greater than 6 or reduced renal function as measured by CrCl < 70 mL/min. Patients with inadequate liver function (National Cancer Institute – Common Terminology Criteria for Adverse Events 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. Patients with one or more individual organ/system impairment score of 4 as assessed by the CIRS definition, excluding eyes, ears, nose, throat and larynx organ system, were excluded.

A total of 781 patients were randomised 2:2:1 to receive Gazyvaro plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1a compared Gazyvaro plus chlorambucil to chlorambucil

alone in 356 patients and Stage 2 compared Gazyvaro plus chlorambucil to rituximab plus chlorambucil in 663 patients.

In the majority of patients, Gazyvaro was given intravenously as a 1 000 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 Gazyvaro dose administered over 2 days (Day 1 [100 mg] and Day 2 [900 mg]) (see section 4.2 and 4.4). For each subsequent treatment cycle (Cycles 2 to 6), patients received Gazyvaro 1 000 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 arms. The majority of patients were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% of 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%).

Efficacy results for patients with previously untreated CLL are summarised in Table 13. Kaplan-Meier curves for progression-free survival (PFS) and Overall Survival (OS) are shown in Figures 1-4.

Table 13 Summary of efficacy from BO21004/CLL11 study

	Stage 1a		**Stage 2**	
	Chlorambucil N=118	**Gazyvaro + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyvaro + chlorambucil N= 333**
	22.8 months median observation time[g]		**18.7 months median observation time[g]**	
Primary endpoint				
Investigator-assessed PFS (PFS-INV)[a]				
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
Hazard ratio (95% CI)	0.18 [0.13; 0.24]		0.39 [0.31; 0.49]	
p-value (Log-Rank test, stratified[b])	< 0.0001		< 0.0001	
Key secondary endpoints				
IRC-assessed PFS (PFS-IRC)[a]				
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
Hazard ratio (95% CI)	0.19 [0.14; 0.27]		0.42 [0.33; 0.54]	
p-value (Log-Rank test, stratified[b])	< 0.0001		< 0.0001	
End of treatment response rate				

	Stage 1a		Stage 2	
	Chlorambucil N=118	**Gazyvaro + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyvaro + chlorambucil N= 333**
	22.8 months median observation time[g]		**18.7 months median observation time[g]**	
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% 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[c] (%)	0 (0.0%)	53 (22.3%)	23 (7.0%)	69 (20.7%)
Molecular remission at end of treatment[d]				
No. of patients included in the analysis	90	168	244	239
MRD negative[e] (%)	0 (0%)	45 (26.8%)	6 (2.5%)	61 (25.5%)
MRD positive[f] (%)	90 (100%)	123 (73.2%)	238 (97.5%)	178 (74.5%)
Difference in MRD rates, (95% CI)	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
Hazard ratio (95% CI)	0.19 [0.14; 0.25]		0.43 [0.34; 0.54]	
p-value (Log-Rank test, stratified[b])	< 0.0001		< 0.0001	
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	NR	30.8	NR
Hazard ratio (95% CI)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified[b])	< 0.0001		< 0.0018	
Overall survival				
No. (%) of patients with event	57 (48.3%)	93 (39.1%)	147 (44.5%)	121 (36.3%)
Median time to event (months)	66.7	NR	73.1	NR
Hazard ratio (95% CI)	0.68 [0.49; 0.94]		0.76 [0.60; 0.97]	
p-value (Log-Rank test, stratified[b])	0.0196		0.0245	

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, MRD: Minimal Residual Disease, NR = Not reached

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

[b] stratified by Binet stage at baseline

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

[d] Blood and bone marrow combined

[e] MRD negativity is defined as a result below 0.0001

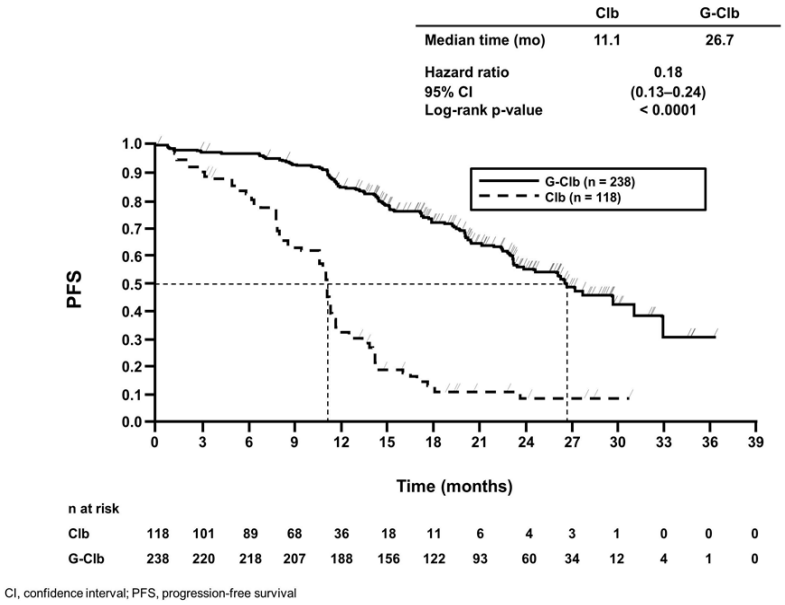
[f] Includes MRD positive patients and patients who progressed or died before the end of treatment

[g] Median observation time for overall survival (OS) data corresponds to 62.5 months median observation time in Stage 1a and to 59.4 months median observation time in Stage 2.

Results of subgroup analyses

Results of the progression free survival (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 Intent-to-Treat population. The risk of disease progression or death was reduced in the GClb arm compared to the RClb arm and Clb arm in all subgroups except in the subgroup of patients with deletion 17p. In the small subgroup of patients with deletion 17p, only a positive trend was observed compared to Clb (HR=0.42, p=0.0892); no benefit was observed compared to RClb. For subgroups, reduction of the risk of disease progression or death ranged from 92% to 58% for GClb versus Clb and 72% to 29% for GClb versus RClb.

Figure 1 Kaplan-Meier curve of Investigator assessed PFS from Stage 1a in patients with CLL (Study BO21004/CLL11)



CI, confidence interval; PFS, progression-free survival

Figure 2 Kaplan-Meier curve of OS from Stage 1a in patients with CLL (Study BO21004/CLL11)

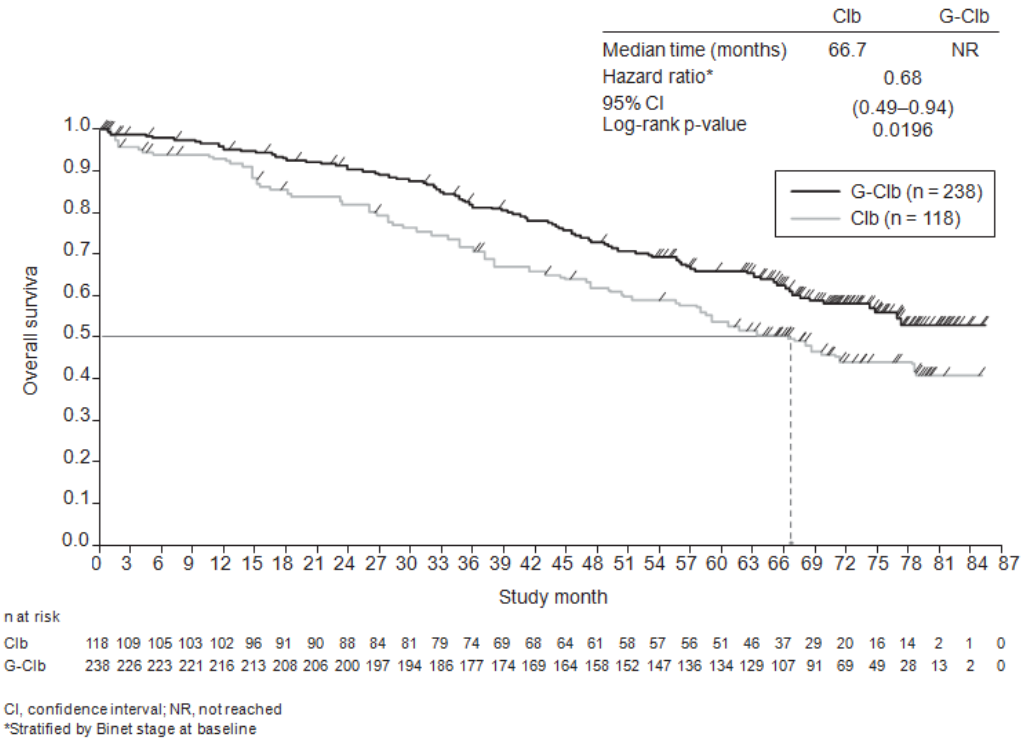


Figure 3 Kaplan-Meier curve of investigator assessed PFS from Stage 2 in patients with CLL (Study BO21004/CLL11)

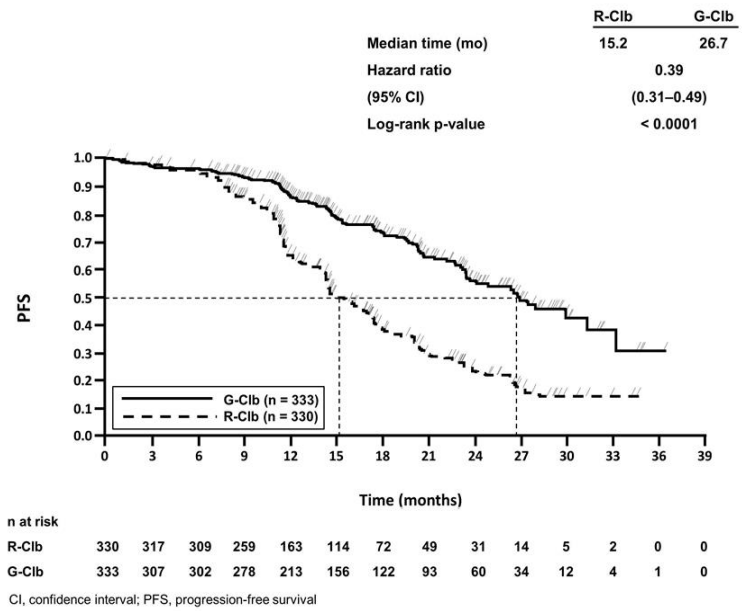
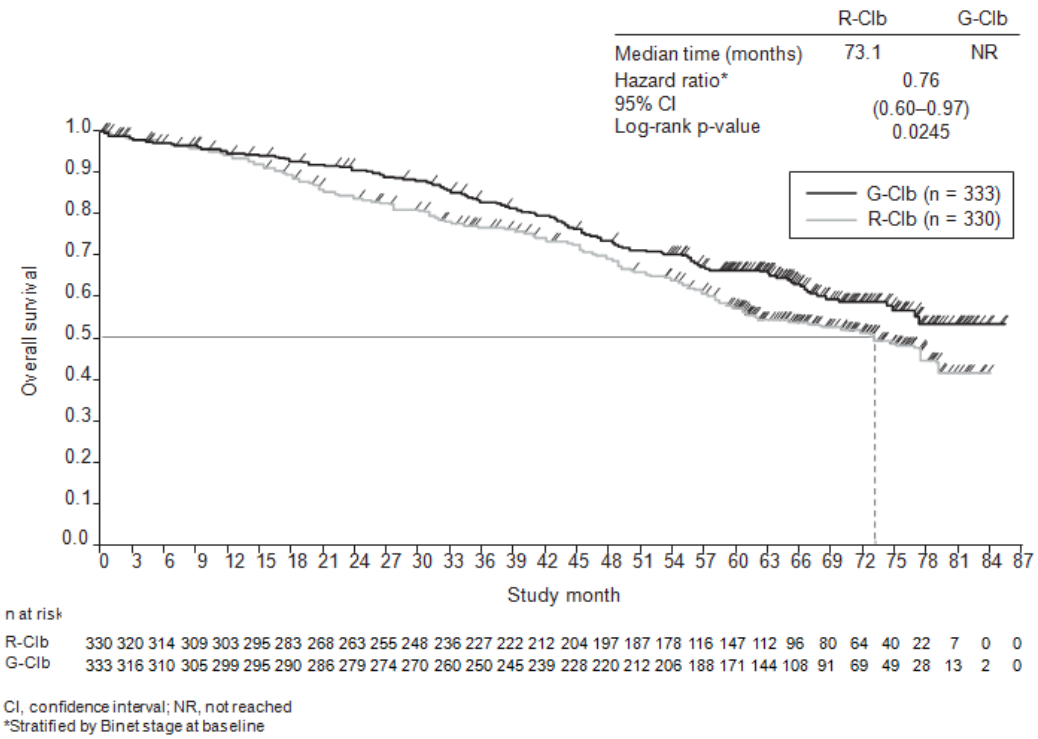


Figure 4 Kaplan-Meier curve of OS from Stage 2 in patients with CLL (Study BO21004/CLL11)



Quality of life

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 Gazyvaro to a chlorambucil regimen does not increase the experience of fatigue for patients.

Follicular lymphoma

Previously untreated follicular lymphoma (study BO21223/GALLIUM)

In a phase III, open label, multicentre, randomised clinical study (BO21223/GALLIUM), 1202 patients with previously untreated Grade 1-3a advanced (stage II bulky disease, stage III/IV) FL were evaluated. Patients with FL Grade 3b were excluded from the study. Patients were randomised to 1:1 to receive either Gazyvaro (n=601 patients) or rituximab (n=601 patients) in combination with chemotherapy (bendamustine, CHOP or CVP), followed by Gazyvaro or rituximab maintenance in patients achieving a complete or partial response.

Gazyvaro was given by intravenous infusion as a dose of 1 000 mg on Days 1, 8 and 15 of Cycle 1, on Day 1 of subsequent cycles. In total, six cycles of Gazyvaro (every 28 days) were given in combination with six cycles of bendamustine, and a total of eight cycles of Gazyvaro (every 21 days) were given in combination with six cycles of CHOP or eight cycles of CVP. Gazyvaro was administered 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 Gazyvaro. Standard dosing of CHOP and CVP was given. Following Cycles 6-8, in combination with chemotherapy, responding patients received Gazyvaro maintenance therapy every 2 months until disease progression or for up to 2 years.

The demographic data and baseline characteristics of the patient population were well balanced between the treatment arms; median age was 59 years, 81% were Caucasian, 53% were female, 79% had a FLIPI score of ≥ 2 and 7% had Stage II (bulky), 35% had Stage III and 57% had Stage IV disease, 44% 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. Fifty-seven percent received bendamustine, 33% received CHOP, and 10% received CVP chemotherapy.

Efficacy results for patients with previously untreated FL are summarised in Table 14. Kaplan-Meier curves for progression-free survival (PFS) are shown in Figure 5.

Table 14 Summary of efficacy in patients with previously untreated FL from BO21223/ GALLIUM study

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	**Gazyvaro +Chemotherapy followed by Gazyvaro maintenance N=601**
Primary Endpoint		
Investigator-assessed PFS[§] (PFS-INV) primary analysis		
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	
3 year PFS estimate [%] [95% CI]	73.3 [68.8, 77.2]	80.0 [75.9, 83.6]
PFS-INV final analysis[§§]		
Number (%) of patients with event	244 (40.6%)	206 (34.3%)
HR [95% CI]	0.77 [0.64, 0.93]	
p-value (Log-Rank test, stratified*)	0.0055	
3 year PFS estimate [%] [95% CI]	75.5 [71.8, 78.9]	82.4 [79.0, 85.3]
7 year PFS estimate [%] [95% CI]	55.7 [51.3, 59.9]	63.4 [59.0, 67.4]
Key Endpoints		
IRC-assessed PFS (PFS-IRC) primary analysis		
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	
Time to next anti-lymphoma therapy[#] primary analysis		
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	

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	Gazyvaro +Chemotherapy followed by Gazyvaro maintenance N=601
Overall Survival[#] primary analysis		
No. (%) 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 Survival final analysis[§§]		
No. (%) of patients with event	86 (14.3%)	76 (12.6%)
HR [95% CI]	0.86 [0.63, 1.18]	
p-value (Log-Rank test, stratified*)	0.36	
Overall Response Rate at End of Induction[‡] (INV-assessed, CT) [#] primary analysis**		
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%)
Partial Response (PR)	379 (63.1%)	415 (69.1%)

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Interval

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

[§] Significance level at this efficacy interim analysis/primary analysis: 0.012, data cut-off 31 January 2016, median observation time 34/35 months

[§§] Final analysis, data cut-off 30 July 2021, median observation time 94 months

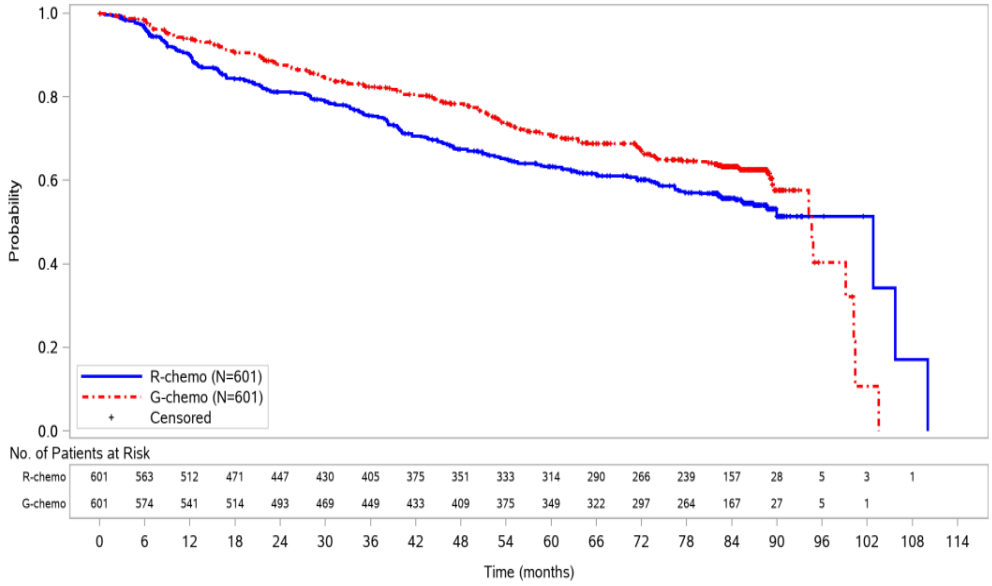
[¶] Data Not Yet Mature. Median was not reached at time of analysis

not adjusted for multiplicity

**Assessed as per modified Cheson 2007 criteria

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

Figure 5 Kaplan-Meier curve of INV-assessed progression-free survival in patients with previously untreated FL (Study BO21223/GALLIUM), final analysis*



R-Chemo: Rituximab plus chemotherapy, G-Chemo: Gazyvaro plus chemotherapy, HR: hazard ratio, CI: confidence interval *Final analysis, data cut-off 30 July 2021, median observation time 94 months

Results of subgroup analyses
Results of subgroup analyses (not adjusted for multiplicity) were, in general, consistent with the results seen in the FL population, supporting the robustness of the overall result (primary analysis, data cut-off 31 January 2016). The subgroups evaluated included IPI, FLIPI, Bulky Disease, B Symptoms at baseline, Ann Arbor Stage and ECOG at baseline. In patients with FLIPI score 0-1 (low risk), no difference between Gazyvaro plus chemotherapy and rituximab plus chemotherapy was observed (INV-assessed PFS HR 1.17 (95%CI 0.63;2.19, 40 PFS events). This subgroup comprised 21% (253/1202) of the FL ITT population and experienced 16.3% (40/245) of the PFS events. In addition, exploratory subgroup analyses of PFS across chemotherapy regimens (bendamustine, CHOP and CVP) were consistent with the results seen in the Gazyvaro plus chemotherapy population. The observed HRs by chemotherapy subgroup were as follows; CHOP (n=398): HR 0.77 (95% CI: 0.50, 1.20), CVP (n=118): HR 0.63 (95% CI: 0.32, 1.21), and bendamustine (n=686): HR 0.61 (95% CI: 0.43, 0.86).

Patient Reported Outcomes
Based on the FACT-Lym questionnaire collected during treatment and follow-up phases, patients in both treatment 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 HRQOL or health status measures.

Due to the open label design the patient reported outcomes should be interpreted with caution.

Patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen (study GAO4753g/GADOLIN).

In a phase III, open label, multicentre, randomised clinical study (GAO4753g/GADOLIN), 396 patients with iNHL who had no response during treatment or who progressed within 6 months following the last dose of rituximab or a rituximab-containing regimen (including rituximab monotherapy as part of induction or maintenance treatment) were evaluated. Patients were randomised 1:1 to receive either bendamustine (B) alone (n = 202) or Gazyvaro 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 Gazyvaro maintenance once every two months for two years or until disease progression (whichever occurred first). Patients were stratified according to region, iNHL subtype (follicular versus non-follicular), rituximab-refractory type (whether refractory to prior rituximab monotherapy or rituximab in combination with chemotherapy) and the number of prior therapies (≤ 2 versus > 2).

The demographic data and baseline characteristics were well balanced between the treatment arms (median age 63 years, the majority were Caucasian [88%] and male [58%]). The majority of patients had follicular lymphoma (81%). 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.

Gazyvaro was given by intravenous infusion as a dose of 1 000 mg 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, once every two months for two years or until disease progression (whichever occurs first). 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 Gazyvaro or 120 mg/m^2/day when given alone. In patients treated with G+ B, 79.4% received all six treatment cycles compared to 66.7% of patients in the B arm.

The primary analysis, based on independent Review Committee (IRC) assessment demonstrated a statistically significant - 45% reduction in the risk of disease progression or death, in patients with iNHL receiving G+B followed by Gazyvaro maintenance, compared with patients receiving bendamustine alone. The reduction in the risk of disease progression or death seen in the iNHL population is driven by the subset of patients with FL.

The majority of the patients in study GAO4753g had FL (81.1%). Efficacy results from the primary analysis in the FL population are shown in Table 15 and Figures 6 and 8. 11.6% of the patients had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL). In the non-FL population the HR for IRC-assessed PFS was 0.94 [95% CI: 0.49, 1.90]. No definitive conclusions could be drawn on efficacy in the MZL and SLL sub-populations.

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 investigator assessed 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 7); the HR for risk of death was 0.71 (95%CI: 0.51, 0.98).

Table 15 Summary of primary efficacy analysis in patients with FL[#] from GAO4753g/GADOLIN study

	Bendamustine N=166	Gazyvaro + Bendamustine followed by Gazyvaro maintenance N=155
	Median observation time: 20 months	**Median observation time: 22 months**
Primary Endpoint in FL population		
IRC-assessed PFS (PFS-IRC)		
Number (%) of patients with event	90 (54.2%)	54 (34.8%)
Median time to event (months, 95% CI)	13.8 (11.4, 16.2)	NR (22.5,-)
HR (95% CI)	0.48 (0.34, 0.68)	
p-value (Log-Rank test, stratified*)	< 0.0001	
Secondary Endpoints		
Investigator-assessed PFS (PFS-INV)		
Number (%) of patients with event	102 (61.4%)	62 (40.0%)
Median time to event (months, 95% CI)	13.7 (11.0, 15.5)	29.2 (17.5,-)
HR (95% CI)	0.48 (0.35, 0.67)	
p-value (Log-Rank test, stratified*)	< 0.0001	
Best Overall Response (BOR) (IRC-assessed)[§]		
No. of patients included in the analysis	161	153
Responders (%) (CR/PR)	124 (77.0%)	122 (79.7%)
Difference in response rate (95% CI)	2.72 (-6.74, 12.18)	
p-value (Cochran-Mantel-Haenszel test)	0.6142	
Complete Responders (%)	31 (19.3%)	24 (15.7%)
Partial Responders (%)	93 (57.8%)	98 (64.1%)
Stable Disease (%)	18 (11.2%)	13 (8.5%)
Duration of response (DOR) (IRC-assessed)		
No of patients included in the analysis	127	122
No. (%) of patients with event	74 (58.3%)	36 (29.5%)
Median duration (months) of DOR (95% CI)	11.9 (8.8, 13.6)	NR (25.4,-)
HR (95% CI)	0.36 (0.24, 0.54)	

	Bendamustine N=166	Gazyvaro + Bendamustine followed by Gazyvaro maintenance N=155
	Median observation time: 20 months	**Median observation time: 22 months**
Overall Survival		
No. (%) of patients with event	36 (21.7%)	25 (16.1%)
Median time to event (months)	NR	NR
HR (95% CI)	0.71 (0.43, 1.19)	
p-value (Log-Rank test, stratified*)	0.1976	

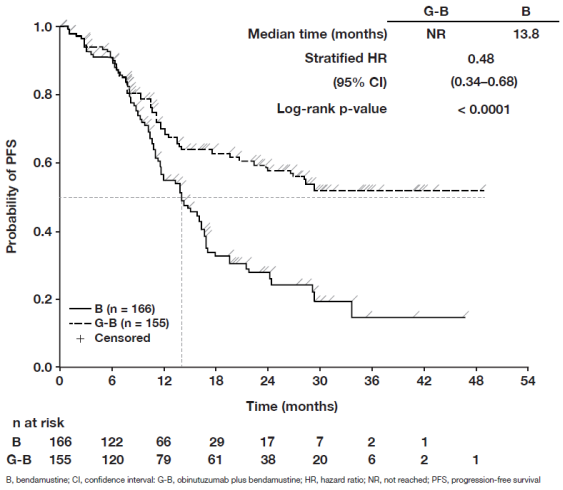
IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, NR = Not Reached

[#] Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

*Stratification factors for analysis were refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs > 2). Follicular versus non-follicular was also a stratification factor for the study but is not applicable in the subgroup analysis of patients with FL.

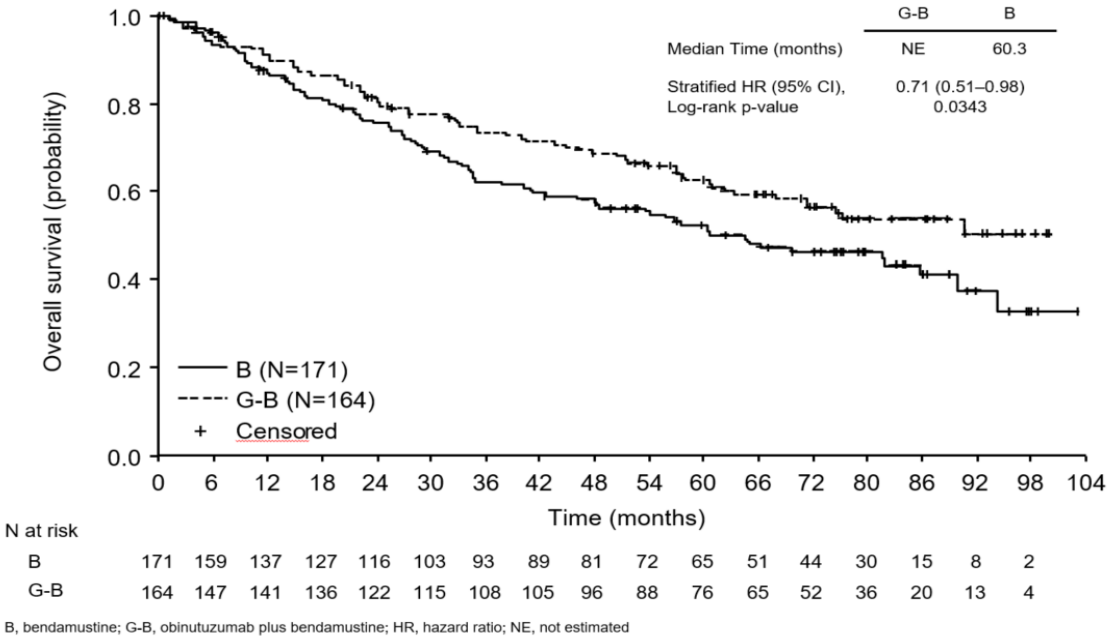
§ Best response within 12 months of start of treatment

Figure 6 Kaplan-Meier curve of IRC-assessed PFS in patients with FL [#] (Study GAO4753g/GADOLIN)



[#] Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Figure 7 Kaplan-Meier curve of Overall Survival in FL patients at Final Analysis (Study GAO4753g/GADOLIN)



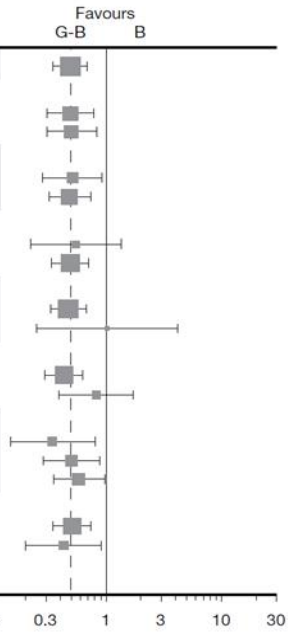
B, bendamustine; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NE, not estimated

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.

Figure 8 IRC-assessed PFS by patient subgroup in FL *# (Study GAO4753g/GADOLIN)

Baseline factors	Total n	B (n = 166) n	B Events	B 1-year KM rate	G-B (n = 155) n	G-B Events	G-B 1-year KM rate	HR	95% Wald CI
All patients	321	166	90	54.888	155	54	69.219	0.49	(0.35, 0.68)
Sex									
Male	180	95	47	55.028	85	28	72.507	0.49	(0.30, 0.78)
Female	141	71	43	54.593	70	26	65.083	0.50	(0.31, 0.82)
Bulky disease at BL (6 cm threshold)									
Yes	107	58	33	53.774	49	17	69.568	0.51	(0.28, 0.91)
No	212	106	57	55.515	106	37	69.113	0.48	(0.32, 0.74)
B symptoms (≥1) at BL									
Yes	47	27	16	54.444	20	7	68.177	0.55	(0.22, 1.34)
No	271	137	73	55.366	134	47	69.376	0.49	(0.34, 0.70)
ECOG at BL									
0–1	304	157	85	55.820	147	50	70.512	0.47	(0.33, 0.67)
2	15	7	4	41.667	8	4	50.000	1.02	(0.25, 4.17)
No. of prior therapies									
≤2	255	130	74	55.100	125	41	69.826	0.43	(0.29, 0.63)
>2	66	36	16	54.092	30	13	65.660	0.82	(0.39, 1.72)
Refractory to									
R-mono	64	39	20	63.982	25	8	82.143	0.34	(0.15, 0.80)
R-chemo induction	120	64	34	48.448	56	20	72.098	0.50	(0.28, 0.87)
R-maintenance after chemo induction	133	62	35	56.561	71	26	60.648	0.58	(0.35, 0.97)
Double refractory status									
Yes	252	133	73	51.224	119	42	67.441	0.51	(0.34, 0.74)
No	69	33	17	69.156	36	12	74.829	0.43	(0.20, 0.91)



Unstratified HR is displayed. X-axis with logarithmic scale.
B, bendamustine; BL, baseline; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; KM, Kaplan-Meier; R-chemo, rituximab plus chemotherapy; R-maintenance, rituximab maintenance; R-mono, rituximab monotherapy

*pre-specified analyses performed on the intent to treat (ITT) population were repeated on the FL population; analysis of double refractory (i.e. unresponsive to or disease progression during or within 6 months of the last dose of an alkylating agent-based regimen) status was exploratory.
Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

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). See section 4.8 Undesirable Effects.

Patient-reported Outcomes

Due to the open label design the patient reported outcomes should be interpreted with caution. Based on the FACT-Lym questionnaire and EQ-5D index scale collected during the treatment and during follow-up periods, health-related quality of life was generally maintained in the pivotal study with no meaningful difference between the arms. However, in patients with FL the addition of Gazyvaro to bendamustine delayed the time to worsening of health-related quality of life as measured by the FACT-Lym TOI score by 2.2 months (median 5.6 versus 7.8 months for B and G+B respectively HR = 0.83; 95% CI: 0.60, 1.13).

Lupus nephritis

A Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study (CA41705/REGENCY) was conducted in patients with ISN/RPS 2003 Class III or IV, with or without concomitant Class V, lupus nephritis, treated with standard therapy consisting of mycophenolate mofetil (MMF) and corticosteroids.

Patients had active or active/chronic ISN/RPS 2003 Class III or IV, with or without concomitant Class V proliferative LN determined by kidney biopsy, current or past positive antinuclear antibody (ANA), urine protein-to-creatinine ratio (UPCR) ≥ 1 g/g, and had received at least one dose of pulse methylprednisolone IV (≥ 250 mg) or equivalent treatment for LN during the 6 months prior to screening or during screening.

Patients with eGFR <30 ml/min/1.73 m^2 or in need of dialysis or transplantation, with sclerosis in > 50% of glomeruli on kidney biopsy, presence of rapidly progressive glomerulonephritis, evidence of active infection, receipt of anti-CD20 therapy < 9 months before or during screening, or receipt of cyclophosphamide, tacrolimus, ciclosporin, or voclosporin within 2 months of or during screening were excluded.

A total of 271 patients were randomised 1:1 to receive Gazyvaro 1 000 mg or placebo intravenously, in combination with MMF 2-2.5 g/day and a tapering course of corticosteroids, and were evaluated over 76 weeks. Patients randomised to receive Gazyvaro were further randomised in a 1:1 ratio to receive either Gazyvaro 1 000 mg IV on Day 1, Weeks 2, 24, 26, 50, and 52 (Arm 1) or Gazyvaro 1 000 mg IV on Day 1, Weeks 2, 24, 26, and 52 (Arm 2). The totality of the Gazyvaro efficacy data combining both treatment arms is shown on Table 16.

All patients received oral prednisone 0.5 mg/kg/day (maximum 60 mg/day) and remained at this dose until Week 2. Beginning on Day 15, prednisone was tapered to achieve a target dose of 5 mg/day by Week 24. Prednisone was maintained at a low dose (5 mg/day) from Week 24 until Week 80.

The median age of patients was 31 years; 84.5% were female, 57.6% were Hispanic or Latino, 47.6% were White, 14.8% were Black or African American. The distribution by kidney biopsy class was 39.5% Class III, 60.5% Class IV and 31.4% had concomitant Class V. Mean (SD) eGFR at baseline 102.3 (±30.8) mL/min/1.73 m^2. Mean (SD) UPCR at baseline was 3.34 (±2.87) mg/mg with 42.2% of patients exhibiting UPCR ≥ 3 mg/mg at baseline. At baseline, 17% of patients had mild (eGFR 60 - <90 mL/min/1.73m^2) and 11.4% had moderate (eGFR 30 - <60 mL/min/1.73m^2) renal impairment.

The primary outcome measure was proportion of patients who achieved complete renal response (CRR) at Week 76, defined as meeting all of the following criteria: UPCR < 0.5 g/g; estimated glomerular filtration rate (eGFR) ≥ 85% of baseline, as calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; with no occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.

Key secondary outcome measures included: proportion of patients who achieved CRR with successful prednisone taper at Week 76, proportion of patients who achieved a proteinuric response at Week 76 and proportion of patients who experience death or kidney-related events through Week 76.

Results

The proportion of patients with lupus nephritis achieving CRR at Week 76 was significantly greater (46.4%) in patients treated with Gazyvaro in combination with standard therapy compared to patients who received placebo plus standard therapy (33.1%). Efficacy results are summarised in Table 16.

Table 16 Efficacy results in adults with lupus nephritis (REGENCY/CA41705)

	Placebo + standard therapy^ (N=136)	**Gazyvaro + standard therapy^ (N=135)**
Primary endpoint		
CRR at Week 76 (%)	33.1	46.4
Treatment difference (95% CI)	13.40 (1.95, 24.84)	
p-value	0.0232	
Components of CRR:		
UPCR < 0.5	49 (36.0%)	64 (47.4%)
eGFR ≥ 85% of baseline	103 (75.7%)	113 (83.7%)
No occurrence of intercurrent events	102 (75.0%)	120 (88.9%)
Key secondary endpoints		
CRR with successful prednisone taper at Week 76 (%)*	30.9	42.7
Treatment difference (95% CI)	11.88 (0.57, 23.18)	
p-value	0.0421	
Proteinuric response at Week 76 (%)#	41.9	55.5
Treatment difference (95% CI)	13.68 (2.01, 25.36)	
p-value	0.0227	

CRR: complete renal response; CI: Confidence Interval; UPCR: urine protein-to-creatinine ratio; eGFR: estimated glomerular filtration rate

^mycophenolate mofetil (MMF) and corticosteroids

*CRR at Week 76 without receiving prednisone taper > 7.5 mg/day or equivalent from Week 64 through Week 76

#UPCR < 0.8 g/g at Week 76 and no occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal

Immunogenicity

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, assay robustness to quantities of Gazyvaro/antibody in the circulation, sample handling, timing of sample collection, concomitant medicines and underlying disease. For these reasons, comparison of incidence of antibodies to Gazyvaro with the incidence of antibodies to other products may be misleading.

Patients in the CLL pivotal study BO21004/CLL11 were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Gazyvaro. In patients treated with Gazyvaro 8 out of 140 patients 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 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.

In Gazyvaro-treated patients in the LN studies, a total of 12 out of 200 (6%) had at least one ADA-positive sample recorded at any time during the studies. Six (3%) subjects had ADA-positive samples recorded at baseline. Two of the 6 patients who were ADA-positive at baseline remained ADA-positive throughout the studies, 1 had a single post-baseline sample that was ADA-positive and in the remaining 3 patients all post-baseline samples were ADA-negative. Six (3%) patients for whom the baseline sample was ADA-negative had a positive ADA titre post-baseline (treatment-induced ADA).
None of the 12 patients with positive ADA titres at any time during the treatment period experienced an IRR or anaphylactic or hypersensitivity reaction during the study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Gazyvaro in all subsets of the paediatric population in CLL and FL (see section 4.2 for information on paediatric use).
The European Medicines Agency has deferred the obligation to submit the results of studies with Gazyvaro in one or more subsets of the paediatric population, in systemic lupus erythematosus including LN (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

A population pharmacokinetic (PK) model was developed to analyse the PK data in 469 iNHL, 342 CLL and 130 diffuse large B-cell lymphoma (DLBCL) patients from Phase I, Phase II and Phase III studies who received obinutuzumab alone or in combination with chemotherapy.

A population PK model was developed to analyse the PK data in 196 LN patients from Phase II and Phase III studies who received obinutuzumab.

Absorption

Obinutuzumab is administered intravenously, therefore absorption is not applicable. There have been no studies performed with other routes of administration. 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(τ) value was 8961 µg•d/mL and in iNHL patients the estimated median C_{max} value was 539.3 µg/mL and AUC(τ) value was 10956 µg•day/mL. Based on the population PK model in LN patients, the estimated median C_{max} at steady state was 468 µg/mL and AUC at steady state was 8740 µg•d/mL.

Distribution

Following intravenous administration, the volume of distribution of the central compartment (2.98 L in patients with CLL, 2.97 L in patients with iNHL, and 2.22 L in patients with LN) 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 the 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 a rapid removal of obinutuzumab from the circulation. However, once the majority of CD20 cells are bound with obinutuzumab, the impact of TMDD on PK is minimised.

In LN patients the steady state clearance of obinutuzumab was approximately 0.13 L/day with a median elimination $t_{1/2}$ of 22.4 days. 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. The time-varying clearance decreases with time with an exponential decay coefficient, likely related to CD20 target reduction and proteinuria improvement over time and a time-independent one related to the endogenous catabolic processes of IgG.

Pharmacokinetic/pharmacodynamic relationship(s)

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.

Elderly

Chronic lymphocytic leukaemia and follicular lymphoma
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=375), patients between 65-75 years (n=265) and patients > 75 years (n=171).

Lupus nephritis
No studies have been conducted to investigate the pharmacokinetics of obinutuzumab in patients ≥ 65 years of age.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of obinutuzumab in paediatric patients.

Renal impairment
Chronic lymphocytic leukaemia and follicular lymphoma
The population pharmacokinetic analysis of obinutuzumab showed that creatinine clearance does not affect pharmacokinetics of obinutuzumab. Pharmacokinetics of obinutuzumab in patients with mild creatinine clearance (CrCl 50-89 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). Pharmacokinetic data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=8), therefore no dose recommendations can be made.

Lupus nephritis
The population pharmacokinetic analysis (n = 196) of obinutuzumab showed that creatinine clearance does not affect the pharmacokinetics in patients with LN. The pharmacokinetics of obinutuzumab in patients with mild (CrCl 60 - <90 mL/min, n=45) or moderate (CrCl 30 - <60 mL/min, n=17) renal impairment were similar to those in patients with normal kidney function.

Hepatic impairment

No formal pharmacokinetic study has been conducted in patients with hepatic impairment.

5.3 Preclinical safety data

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

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

An enhanced pre and postnatal development (ePPND) toxicity study in pregnant cynomolgus monkeys showed no evidence of teratogenic effects. However, weekly obinutuzumab dosing from post-coitum day 20 to delivery resulted in complete depletion of B-cells in infant monkeys at weekly intravenous obinutuzumab doses of 25 and 50 mg/kg (2-5 times the clinical exposure based on C_{max} and AUC). Offspring exposure on day 28 post-partum suggests that obinutuzumab can cross the blood-placenta barrier. Concentrations in infant serum on day 28 post-partum 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. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months post-partum.

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys (0.7-6 times the clinical exposure based on C_{max} and AUC at steady state after weekly administration of 5, 25, and 50 mg/kg). 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 obinutuzumab during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to obinutuzumab has been observed in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Poloxamer 188
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After dilution

After dilution, chemical and physical stability have been demonstrated in sodium chloride 9 mg/mL (0.9%) solution for injection at concentrations of 0.4 mg/mL to 20 mg/mL for 72 hours at 2°C to 8°C followed by 48 hours (including infusion time) at ≤ 30°C.

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°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

40 mL concentrate in a 50 mL vial (clear Type I glass) with stopper (butyl rubber). Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for dilution

Gazyvaro should be prepared by a healthcare professional using aseptic technique. Do not shake the vial. Use a sterile needle and syringe to prepare Gazyvaro.

For CLL cycles 2 – 6, all FL cycles, and throughout LN treatment

Withdraw 40 mL of concentrate from the vial and dilute in polyvinyl chloride (PVC) or non-PVC polyolefin infusion bags containing sodium chloride 9 mg/mL (0.9%) solution for injection.

CLL only – Cycle 1

To ensure differentiation of the two infusion bags for the initial 1 000 mg dose, it is recommended 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 concentrate from the vial and dilute 4 mL into a 100 mL PVC or non-PVC polyolefin infusion bag and the remaining 36 mL in a 250 mL PVC or non-PVC polyolefin infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection. Clearly label each infusion bag. For storage conditions of the infusion bags see section 6.3.

Table 17 Dilution of Gazyvaro (CLL only)

Day of treatment	Dose of Gazyvaro to be administered	Required amount of Gazyvaro concentrate	Size of PVC or non-PVC polyolefin infusion bag
Cycle 1 Day 1	100 mg	4 mL	100 mL
Cycle 1 Day 1 (continued) or Day 2	900 mg	36 mL	250 mL
Cycle 1 Day 8 and beyond	1 000 mg	40 mL	250 mL

Do not use other diluents such as glucose (5%) solution (see section 6.2).

The bag should be gently inverted to mix the solution in order to avoid excessive foaming. The diluted solution should not be shaken or frozen.

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

No incompatibilities have been observed between Gazyvaro, in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Gazyvaro with sodium chloride 9 mg/mL (0.9%) solution for injection, and:

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

<u>Disposal</u>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/937/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2014
Date of latest renewal: 02 April 2019

10. DATE OF REVISION OF THE TEXT

05 March 2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.