

NAME OF THE MEDICINE

GAZYVA[®]

obinutuzumab

CAS: 949142-50-1

WARNING

Progressive Multifocal Leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML) including fatal PML can occur in patients receiving GAZYVA. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of GAZYVA should be immediately suspended until a diagnosis of PML has been excluded. If a diagnosis of PML is confirmed GAZYVA must be permanently discontinued (see PRECAUTIONS).

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

DESCRIPTION

GAZYVA is supplied in a single-dose vial containing 40 mL of preservative-free concentrate solution for infusion. Each vial contains 1000 mg of obinutuzumab (25 mg/mL) with the following excipients: histidine, histidine hydrochloride monohydrate, trehalose dehydrate and poloxamer 188. The pH of the concentrate solution is approximately 6, with an osmolality of approximately 300 mOsmol/kg.

PHARMACOLOGY

Pharmacodynamics

Obinutuzumab specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre B and mature B lymphocytes. CD20 is not expressed on haemopoietic stem cells, pro B cells, or normal plasma cells. Glycoengineering of the Fc part of *obinutuzumab* results in higher affinity for Fc γ RIII receptors on immune effector cells such as natural killer (NK) cells and macrophages and monocytes as compared to non-glycoengineered antibodies.

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

SCID mice showed no difference in tumour growth inhibition between *obinutuzumab* and non-glycoengineered wild type *obinutuzumab*.

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

Pharmacokinetics

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

Absorption

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

Distribution

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

Metabolism

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

Excretion

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 $t_{1/2}$ 26.4 days in CLL patients and 36.8 days in iNHL patients.

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

Pharmacokinetics in special populations

In the population PK analyses, gender was found to be a covariate which explains some of the inter-patient variability, with a 18% greater steady state clearance (CL_{ss}) and a 19%

greater volume of distribution (V) in males. However, results from the population analyses have shown that the differences in exposure between genders are not clinically important (with an estimated median AUC and C_{max} in CLL patients of 11,282 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 578.9 $\mu\text{g}/\text{mL}$ in females and 8,451 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 432.5 $\mu\text{g}/\text{mL}$ in males, respectively at Cycle 6, and AUC and C_{max} in iNHL patients of 13,172 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 635.7 $\mu\text{g}/\text{mL}$ in females and 9,769 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 481.3 $\mu\text{g}/\text{mL}$ in males, respectively), indicating that there is no need to dose adjust based on gender.

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

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

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

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

CLINICAL TRIALS

Chronic Lymphocytic Leukaemia (CLL)

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

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

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

In the majority of patients, GAZYVA was given intravenously as a 1000 mg initial dose administered on Day 1, Day 8 and Day 15 of the first treatment cycle. In order to reduce the

rate of infusion related reactions in patients, an amendment was implemented and 140 patients received the first GAZYVA dose administered over 2 days (Day 1 (100mg) and Day 2 (900mg), see DOSAGE AND ADMINISTRATION). For each subsequent treatment cycle (Cycles 2 to 6), patients received GAZYVA 1000 mg on Day 1 only. Chlorambucil was given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients enrolled were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% 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%.

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

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

Table 1 Summary of efficacy from BO21004 (CLL11) study

| | Stage 1 | | Stage 2 | |
|--|--|-----------------------------------|--|-----------------------------------|
| | Chlorambucil n=118 | GAZYVA + Chlorambucil n=238 | Rituximab + Chlorambucil n=330 | GAZYVA + Chlorambucil n=333 |
| | 22.8 months median observation time | | 18.7 months median observation time | |
| <i>Investigator-assessed PFS (PFS-INV)*</i> | | | | |
| Number (%) of patients with event | 96 (81.4%) | 93 (39.1%) | 199 (60.3%) | 104 (31.2%) |
| Median duration of PFS (months) | 11.1 | 26.7 | 15.2 | 26.7 |
| HR (95% CI) | 0.18 [0.13; 0.24] | | 0.39 [0.31; 0.49] | |
| p-value (Log-Rank test, stratified [†]) | < 0.0001 | | < 0.0001 | |
| <i>IRC-assessed PFS (PFS-IRC)*</i> | | | | |
| Number (%) of patients with | 90 (76.3%) | 89 (37.4%) | 183 (55.5%) | 103 (30.9%) |

| | | | | |
|---|--------------------|-------------|---------------------|-------------|
| event | | | | |
| Median duration of PFS (months) | 11.2 | 27.2 | 14.9 | 26.7 |
| HR (95% CI) | 0.19 [0.14; 0.27] | | 0.42 [0.33; 0.54] | |
| p-value (Log-Rank test, stratified [†]) | < 0.0001 | | < 0.0001 | |
| <i>End of Treatment Response</i> | | | | |
| 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 (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 [‡] (%) | 0 (0.0%) | 53 (22.3%) | 23 (7.0%) | 69 (20.7%) |
| <i>Molecular Remission at end of treatment[§]</i> | | | | |
| No. of patients included in the analysis | 90 | 168 | 244 | 239 |
| MRD negative [¶] (%) | 0 (0%) | 45 (26.8%) | 6 (2.5%) | 61 (25.5%) |
| MRD positive (%) | 90 (100%) | 123 (73.2%) | 238 (97.5%) | 178 (74.5%) |
| Difference in MRD (95% CI) | 26.79 [19.5; 34.1] | | 23.06 [17.0; 29.1] | |
| <i>Event Free Survival</i> | | | | |
| No. (%) of patients with event | 103 (87.3%) | 104 (43.7%) | 208 (63.0%) | 118 (35.4%) |
| Median time to event (months) | 10.8 | 26.1 | 14.3 | 26.1 |
| HR (95% CI) | 0.19 [0.14; 0.25] | | 0.43 [0.34; 0.54] | |
| p-value (Log-Rank test, stratified [†]) | <0.0001 | | < 0.0001 | |
| <i>Time to new anti-leukaemic therapy</i> | | | | |
| No. (%) of patients with event | 65 (55.1%) | 51 (21.4%) | 86 (26.1%) | 55 (16.5%) |
| Median duration of event (months) | 14.8 | - | 30.8 | - |
| HR (95% CI) | 0.24 [0.16; 0.35] | | 0.59 [0.42; 0.82] | |
| p-value (Log-Rank test, stratified [†]) | <0.0001 | | < 0.0018 | |
| <i>Overall Survival</i> | | | | |
| No. (%) of patients with event | 24 (20.3%) | 22 (9.2%) | 41 (12.4%) | 28 (8.4%) |
| Median time to event (months) | NR | NR | NR** | NR** |
| HR (95% CI) | 0.41 [0.23; 0.74] | | 0.66 [0.41; 1.06]** | |
| p-value (Log-Rank test, stratified [†]) | 0.0022 | | 0.0849** | |

IRC: Independent Review Committee; PFS: progression-free survival; HR: hazard ratio; CI: confidence intervals; MRD: minimal residual disease; NR: not reached

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

** Data not yet mature

† stratified by Binet stage at baseline

‡ includes 11 patients in the GClb arm with a complete response with incomplete marrow recovery

§ blood and bone marrow combined

¶ Minimal Residual Disease (MRD) negativity is defined as <1 CLL cell in 10,000 leucocytes

\\ includes MRD positive patients and patients who progressed or died before the end of treatment

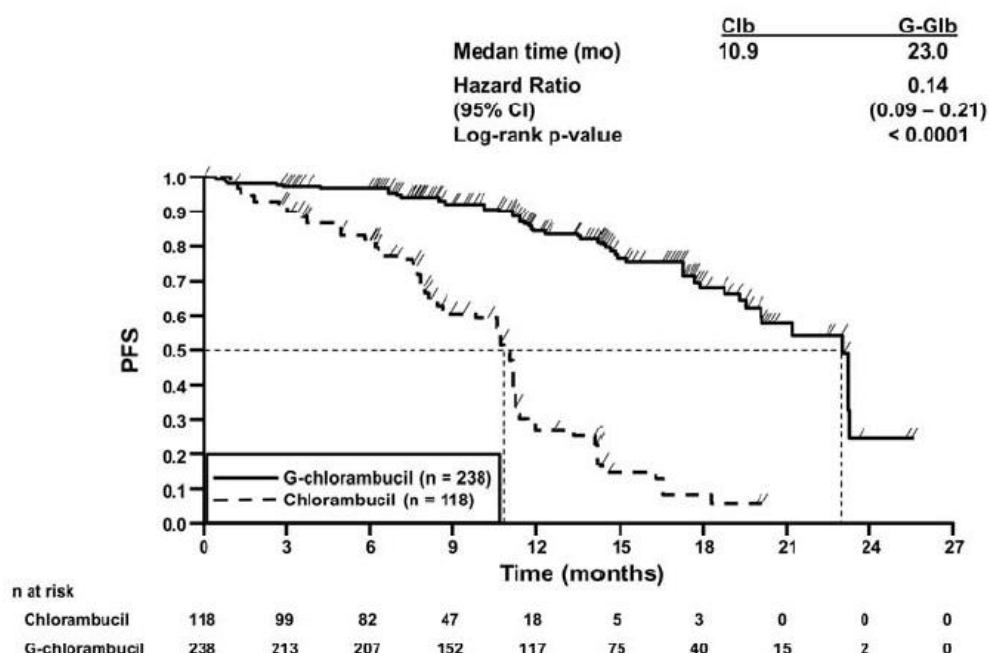
Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in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

Patient Reported Outcomes

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

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

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



CI, confidence interval; PFS, progression-free survival.

Figure 2 Kaplan-Meier curve of Overall Survival from Stage 1

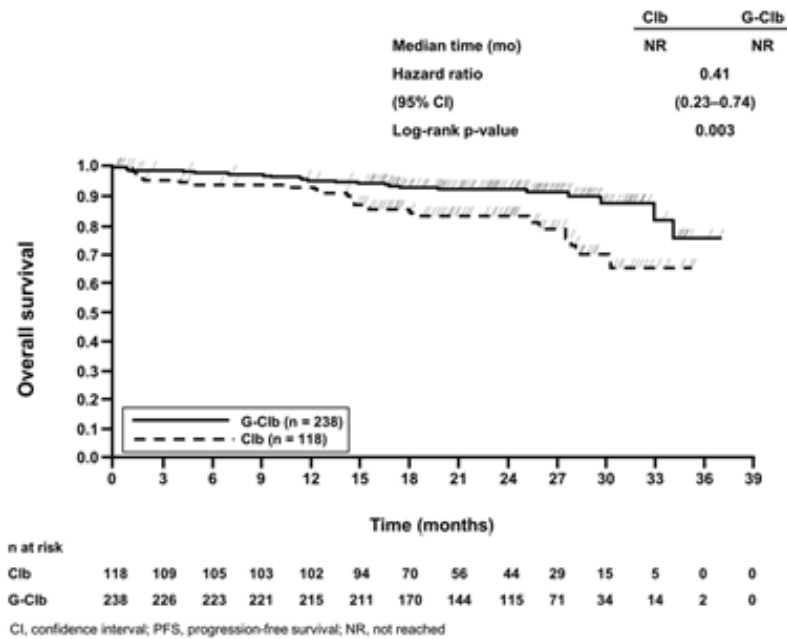
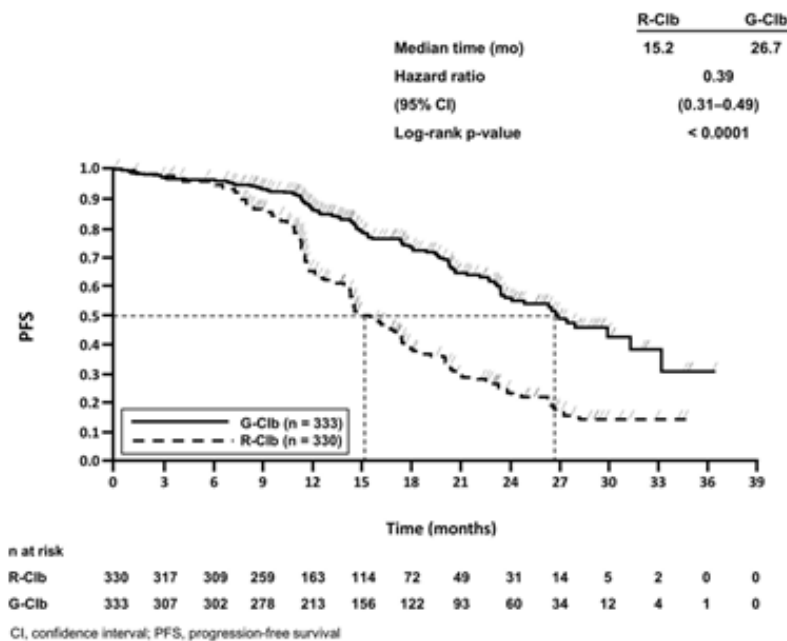


Figure 3 Kaplan-Meier curve of Investigator-assessed PFS from Stage 2



Follicular Lymphoma

In a phase III, open-label, multicenter, randomised study (GAO4753g/GADOLIN), 396 patients with indolent NHL (iNHL) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen were evaluated. Patients were randomised 1:1 to receive either bendamustine (B) alone (n=202) or GAZYVA in combination with bendamustine (G+B) (n=194) for 6 cycles, each of 28 days duration. Patients in the G+B arm who did not have disease progression [i.e. patients with a complete

response (CR), partial response (PR) or stable disease (SD)] at the end of induction continued receiving GAZYVA maintenance until disease progression or for up to two years (whichever occurred first).

The demographic data and baseline characteristics were well balanced [median age was 63 years; the majority of patients were Caucasian (88%) and male (58%)]. The median time from initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10); 44% of patients had received 1 prior therapy and 34% of patients had received 2 prior therapies. The majority of the patients had follicular lymphoma (FL) (81.1%). Of the non-follicular patients, 11.6% had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL).

GAZYVA was given intravenously as a 1000 mg dose on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2-6, and in patients who did not have disease progression, every 2 months for up to 2 years or until disease progression. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m²/day when given in combination with GAZYVA or 120 mg/m²/day when given alone.

The primary analysis demonstrated a statistically significant and clinically meaningful 52% reduction in the risk of disease progression (PD) or death, based on IRC assessment, in patients with FL receiving G+B followed by G maintenance vs B alone (stratified log-rank test p value <=0.0001). IRC-assessed response rates at the end of induction treatment and IRC-assessed best overall response within 12 months of start of treatment were similar in the two treatment arms. At the time of the primary analysis, the median time to event in the B arm was 13.8 months (95% CI: 11.4, 16.2) and the median was not reached in the G+B arm (95% CI: 22.5, NR). Overall survival is not yet mature and will continue to be followed.

Table 2 Summary of efficacy in FL patients from GAO4753g (GADOLIN) study

| | Bendamustine n=166 | G+B followed by GAZYVA 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 duration of PFS (months) | 13.8 | NR |
| 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 duration of PFS (months) | 13.7 | 29.2 |
| HR [95% CI] | 0.48 [0.35, 0.67] | |
| p-value (Log-Rank test, stratified*) | <0.0001 | |

| | Bendamustine n=166 | G+B followed by GAZYVA maintenance n=155 |
|---|--------------------------------|---|
| 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 [¶] | |
| Duration of response (IRC-assessed) | | |
| No. of patients included in the analysis | 127 | 122 |
| No. (%) of patients with event | 74 (58.3%) | 36 (29.5%) |
| Median duration of response (months) | 11.9 | NR |
| HR [95% CI] | 0.36 [0.24, 0.54] | |
| 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 ^{¶†} | |
| Overall Response Rate at End of Induction[‡] (IRC-assessed) | | |
| Patients assessed at end of treatment | 155 | 149 |
| Responders (%) (CR, PR) | 97 (62.6%) | 105 (70.5%) |
| Difference in response rate (%) [95% CI] | 7.89 [-3.05, 18.83] | |
| p-value (Cochran-Mantel-Haenszel test) | 0.1713 | |
| Complete response (CR) | 21 (13.5%) | 14 (9.4%) |
| Partial response (PR) | 76 (49.0%) | 91 (61.1%) |
| Stable disease (SD) | 15 (9.7%) | 12 (8.1%) |
| Progressive disease (PD) | 15 (9.7%) | 15 (10.1%) |
| Unable to evaluate (UE) | 4 (2.6%) | 3 (2.0%) |
| Missing (NA) | 24 (15.5%) | 14 (9.4%) |

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

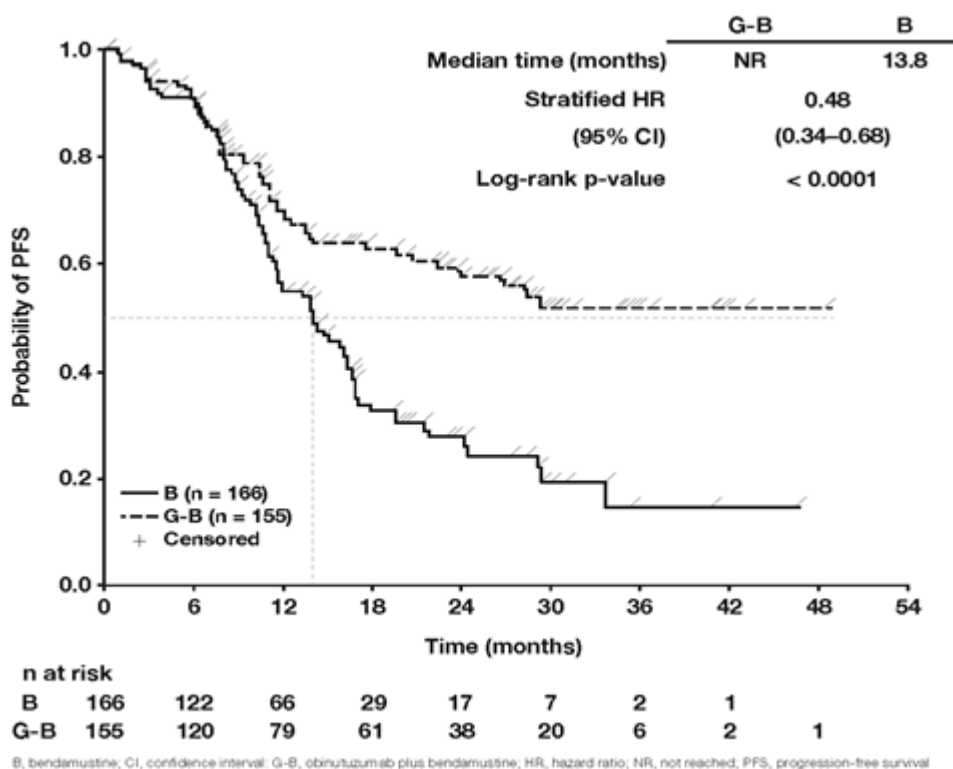
* Stratification factors were iNHL subtype (follicular vs. non-follicular: not used in analysis of patients with FL), refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2)

[§] Best response within 12 months of start of treatment

[¶] Data Not Yet Mature

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

Figure 4 Kaplan-Meier curve of IRC-assessed PFS in FL patients from GAO4753g (GADOLIN) study



Results of subgroup analyses

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

Patient Reported Outcomes

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

Immunogenicity

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

In the pivotal iNHL trial, GAO4753g, two patients in the G+B arm had a positive HAHA assessment at baseline and experienced IRRs. No patient developed HAHA to GAZYVA during or following GAZYVA treatment.

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

medications and underlying disease. For these reasons, comparison of incidence of antibodies to GAZYVA with the incidence of antibodies to other products may be misleading.

INDICATIONS

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

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

CONTRAINDICATIONS

GAZYVA is contraindicated in patients with a known hypersensitivity (IgE mediated) to *obinutuzumab*, murine proteins or to any of the excipients.

PRECAUTIONS

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

Infusion Related Reactions (IRRs)

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

In CLL patients who received the combined measures for prevention of IRRs (corticosteroid; oral analgesic/anti-histamine (H1 histamine receptor blockade); omission of antihypertensive medication in the morning of the first infusion; Cycle 1 Day 1 dose administered over 1 or 2 days; see DOSAGE AND ADMINISTRATION) decreased incidence of IRRs of all Grades was observed. The incidence of IRRs was independent of the corticosteroid pre-medication given (prednisone/prednisolone or methylprednisolone/ dexamethasone). The incidence 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 DOSAGE AND ADMINISTRATION). The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of GAZYVA (see ADVERSE EFFECTS).

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

If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction. For Grade 4 IRR, the infusion must be stopped and permanently discontinued.

For Grade 3 IRR, the infusion should be temporarily interrupted and appropriate medication administered to treat the symptoms. For Grade 1-2 IRR, the infusion should be slowed down and symptoms treated as appropriate. Upon resolution of symptoms, infusion can be restarted, except following Grade 4 IRR, at no more than half the previous rate and, if the patient does not experience the same adverse event with the same severity, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. In CLL patients, if the previous infusion rate was not well tolerated, instructions for the Cycle 1, Day 1 and Day 2 infusion rate should be used for subsequent cycles (see Table 9 DOSAGE AND ADMINISTRATION).

Patients should not receive further GAZYVA infusions if they experience:

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

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

Hypersensitivity reactions including anaphylaxis

Hypersensitivity may be difficult to distinguish from IRRs; however, anaphylaxis has been reported in patients treated with GAZYVA. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped, appropriate treatment of the hypersensitivity reaction should be commenced, and GAZYVA treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to GAZYVA must not be treated (see CONTRAINDICATIONS).

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys [C_{max} and AUC_{0-168h} at steady state (Day 176) after weekly administration of 5, 25, and 50 mg/kg, were 377, 1,530, and 2,920 $\mu\text{g/mL}$ and 39,800, 183,000, and 344,000 ($\mu\text{g}\cdot\text{h}$)/mL, respectively]. Findings included acute anaphylactic or anaphylactoid reactions and an increased prevalence of systemic inflammation and infiltrates consistent with immune-complex mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation. These reactions led to unscheduled termination of 6/36 animals treated with GAZYVA during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to GAZYVA has been observed in humans.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) has been reported with GAZYVA. Patients who are considered to be at risk of TLS [e.g. patients with a high tumour burden and/or a high circulating

lymphocyte count ($> 25 \times 10^9/L$) and/or renal impairment ($CrCl < 70 \text{ mL/min}$)] should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase), prior to the infusion of GAZYVA as described under DOSAGE AND ADMINISTRATION. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines should also be followed, according to standard practice. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated (see PRECAUTIONS, *Worsening of Pre-existing Cardiac Conditions*).

Neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with GAZYVA. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. 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. If treatment is necessary, it should be administered in accordance with local guidelines, and administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Cases of 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) have also been reported. Patients with renal impairment ($CrCl < 50 \text{ mL/min}$) are more at risk of neutropenia.

Thrombocytopenia

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

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe 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.

Worsening of Pre-existing Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with GAZYVA (see ADVERSE EFFECTS). These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Infections

GAZYVA should not be administered in the presence of an active infection and caution should be exercised when considering the use of GAZYVA in patients with a history of recurring or chronic infections. Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of GAZYVA therapy. Fatal infections have been reported. Patients with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections.

Hepatitis B reactivation

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

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

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for at least 12 months following treatment with GAZYVA. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

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

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with GAZYVA (see BOXED WARNING, ADVERSE EFFECTS). The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are non-specific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (CSF testing for JC viral DNA). Therapy with GAZYVA should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive

therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

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

Exposure in utero to GAZYVA and vaccination of infants with live virus vaccines: Due to the potential depletion of B cells in infants of mothers who have been exposed to GAZYVA during pregnancy, the safety and timing of vaccinations with live virus vaccines should be discussed with the child's healthcare provider. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to GAZYVA during pregnancy until the infants' B cell levels are within normal ranges (see PRECAUTIONS *Use in pregnancy*).

Use in renal impairment

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 27% (90 out of 336) of patients treated with GAZYVA plus chlorambucil had moderate renal impairment ($\text{CrCl} < 50 \text{ mL/min}$). These patients experienced more serious adverse events and adverse events leading to death than those associated with $\text{CrCl} \geq 50 \text{ mL/min}$ (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY *Pharmacokinetics in special populations*). No significant differences in efficacy were observed between patients with $\text{CrCl} < 50 \text{ mL/min}$ and those with $\text{CrCl} \geq 50 \text{ mL/min}$. Patients with $\text{CrCl} < 30 \text{ mL/min}$ were excluded from the study (see CLINICAL TRIALS).

Non-Hodgkin Lymphoma

In the pivotal study in iNHL, 8% (15 out of 194) of patients treated with GAZYVA plus bendamustine had moderate renal impairment ($\text{CrCl} < 50 \text{ mL/min}$). These patients experienced more serious adverse events and adverse events leading to death than those associated with $\text{CrCl} \geq 50 \text{ mL/min}$ (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY *Pharmacokinetics in special populations*). Patients with $\text{CrCl} < 40 \text{ mL/min}$ were excluded from the study (see CLINICAL TRIALS).

Use in hepatic impairment

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

Effects on fertility

No specific studies in animals have been performed to evaluate the effect of GAZYVA on fertility. No adverse effects on male and female reproductive organs were observed in repeat dose toxicity studies in cynomolgus monkeys at up to 100 mg/kg/day for 3 months (8 times the clinical exposure based on AUC at the clinical dose of 1000 mg/kg, 3 doses per 28 day cycle) and 50 mg/kg/day for 6 months (6 times the clinical exposure based on AUC).

Use in pregnancy – Category C

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

No studies in pregnant women have been performed. A reproduction study in 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-lymphocytes, opportunistic infections and immune-complex mediated hypersensitivity reactions in infants at weekly intravenous *obinutuzumab* doses of 25 and 50 mg/kg (2-5 times the clinical exposure based on C_{max} and AUC). Offspring exposures on day 28 postpartum (mean C_{max} 80-240 µg/mL, in the range of concentrations in maternal serum) and very low concentrations in milk (less than 0.5% of the corresponding maternal serum levels) suggest in utero exposure. B-cell counts returned to normal levels in the infants, and immunologic function was restored within 6 months of birth. Furthermore, the serum concentrations of GAZYVA in offspring were similar to those in the mothers on day 28 post-partum, whereas concentrations in milk on the same day were very low, suggesting that GAZYVA crosses the placenta.

Use in lactation

As human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue breast-feeding during GAZYVA therapy and for 18 months after the last dose of GAZYVA (see PHARMACOLOGY, Excretion). Animal studies have shown excretion of GAZYVA in breast milk (see PRECAUTIONS *Use in pregnancy*).

Paediatric use

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

Use in the elderly

Chronic Lymphocytic Leukaemia

In the pivotal study in CLL, 46% (156 out of 336) of patients treated with GAZYVA plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than patients < 75 years of age. No significant differences in efficacy were observed between patients ≥ 75 years of age and those < 75 years of age (see CLINICAL TRIALS).

Non-Hodgkin Lymphoma

In the pivotal study in iNHL, 44% (85 out of 194) of patients treated with GAZYVA plus bendamustine were 65 years of age or older. No clinically meaningful differences in safety and efficacy were observed between these patients and younger patients.

Genotoxicity

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

Carcinogenicity

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

Effect on laboratory tests

See PRECAUTIONS.

Ability to Drive and Use Machines

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

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

Chronic Lymphocytic Leukaemia

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up from the pivotal clinical trial, BO21004/CLL11, in which GAZYVA was given in combination with chlorambucil compared to chlorambucil alone (Stage 1) or rituximab plus chlorambucil (Stage 2). In patients treated with GAZYVA in combination with chlorambucil, 81% received all 6 treatment cycles compared to 89% of patients in the rituximab plus chlorambucil arm and 67% of patients in the chlorambucil alone arm.

Tables 3 and 4 summarise the ADRs that occurred at a higher incidence (difference of $\geq 2\%$) in patients receiving GAZYVA plus chlorambucil as compared to chlorambucil alone or rituximab plus chlorambucil, respectively.

Table 3 Adverse Reactions reported with a higher incidence (difference of $\geq 2\%$) in patients receiving GAZYVA plus chlorambucil vs chlorambucil alone (Stage 1)*

| ADR (MedDRA) System Organ Class | All Grades % | | Grades 3-5 [†] % | |
|---|-----------------------|-----------------------------------|---------------------------|-----------------------------------|
| | chlorambucil n=116 | GAZYVA + chlorambucil n=241 | chlorambucil n=116 | GAZYVA + chlorambucil n=241 |
| Injury, Poisoning and Procedural Complications | | | | |
| Infusion related reactions | N/A | 68.9 | N/A | 21.2 |

| | | | | |
|--|------|------|------|------|
| Blood and lymphatic system disorders | | | | |
| Neutropenia | 18.1 | 40.7 | 15.5 | 34.9 |
| Thrombocytopenia | 7.8 | 15.4 | 4.3 | 11.2 |
| Anaemia | 10.3 | 12.4 | 4.3 | 4.6 |
| Leucopenia | 0 | 7.1 | 0 | 5.4 |
| Infections and Infestations | | | | |
| Urinary tract infection | 2.6 | 6.2 | < 1 | 1.7 |
| Oral herpes | < 1 | 3.7 | 0 | 0 |
| Rhinitis‡ | < 1 | 2.1 | 0 | 0 |
| Pharyngitis | 0 | 2.1 | 0 | 0 |
| General disorders and administration site conditions | | | | |
| Pyrexia | 6.9 | 10.4 | 0 | < 1 |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 6.9 | 9.5 | < 1 | 0 |
| Metabolism and nutrition disorders | | | | |
| Tumour lysis syndrome | < 1 | 4.1 | 0 | 1.7 |
| Hyperuricaemia | 0 | 3.3 | 0 | < 1 |
| Musculoskeletal and connective tissue disorders | | | | |
| Arthralgia | 2.6 | 4.6 | < 1 | < 1 |
| Back pain | 1.7 | 5.0 | 0 | < 1 |
| Musculoskeletal chest pain | 0 | 2.5 | 0 | < 1 |
| Vascular disorders | | | | |
| Hypertension | 1.7 | 3.7 | 1.7 | 1.7 |
| Investigations | | | | |
| White blood cell count decreased‡ | < 1 | 2.1 | 0 | 2.1 |
| Neutrophil count decreased | 0 | 2.1 | 0 | 2.1 |
| Weight increased | 0 | 2.1 | 0 | 0 |
| Cardiac disorders | | | | |
| Atrial fibrillation | 0 | 2.1 | 0 | < 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | |
| Squamous cell carcinoma of skin | 0 | 2.1 | 0 | 1.2 |
| Gastrointestinal disorders | | | | |
| Diarrhoea‡ | 11.2 | 10.4 | < 1 | 2.5 |
| Skin and subcutaneous tissue disorders | | | | |
| Alopecia | 0 | 2.1 | 0 | 0 |

* In all Grades or Grade 3-5

† No Grade 5 adverse reactions have been observed with a difference of $\geq 2\%$ between the treatment arms

‡ With Stage 1 update and Stage 2 data, this event was no longer reported with a difference of $\geq 2\%$ between the treatment arms

Table 4 Adverse Reactions reported with a higher incidence (difference of $\geq 2\%$) in patients receiving GAZYVA plus chlorambucil vs rituximab plus chlorambucil (Stage 2)*

| ADR (MedDRA) System Organ Class | All Grades % | | Grades 3-5† % | |
|------------------------------------|-----------------------------|--------------------------|-----------------------------|--------------------------|
| | rituximab + chlorambucil | GAZYVA + chlorambucil | rituximab + chlorambucil | GAZYVA + chlorambucil |
| | | | | |

| | n=321 | n=336 | n=321 | n=336 |
|--|-------|-------|-------|-------|
| Injury, Poisoning and Procedural Complications | | | | |
| Infusion related reactions | 37.7 | 65.8 | 3.7 | 19.9 |
| Blood and lymphatic system disorders | | | | |
| Neutropenia | 32.1 | 38.1 | 28.3 | 33.0 |
| Thrombocytopenia | 6.5 | 14.3 | 3.1 | 10.4 |
| Leucopenia | 1.9 | 6.3 | < 1 | 4.5 |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 7.5 | 10.1 | 0 | 2.1 |
| Constipation | 5.0 | 8.3 | 0 | 0 |
| Infections and Infestations | | | | |
| Nasopharyngitis | 3.1 | 5.7 | 0 | < 1 |
| Urinary tract infection | 1.6 | 5.4 | < 1 | 1.5 |
| Musculoskeletal and connective tissue disorders | | | | |
| Back pain | 2.8 | 4.8 | < 1 | < 1 |
| Arthralgia | 2.5 | 4.8 | 0 | < 1 |
| Metabolism and nutrition disorders | | | | |
| Tumour lysis syndrome | 0 | 4.2 | 0 | 1.8 |

* In all Grades or Grade 3-5

† No Grade 5 adverse reactions have been observed with a difference of $\geq 2\%$ between the treatment arms

Non-Hodgkin Lymphoma

The adverse drug reactions (ADRs) described in this section (based on a safety population of 392 patients with indolent NHL) were identified during induction, maintenance, and follow-up from study GAO4753g, in which GAZYVA was given in combination with bendamustine during induction (G+B), and as GAZYVA monotherapy in maintenance and compared to bendamustine during induction alone (B). In patients treated with G+B, 79.4% received all 6 treatment cycles of GAZYVA and 75.6% received all 6 cycles of B compared to 66.7% of patients in the B arm.

Table 5 summarises the ADRs that occurred at a higher incidence (difference of $\geq 2\%$) in patients receiving G+B during induction followed by GAZYVA maintenance as compared to B during induction alone.

Table 5 Adverse Reactions reported with a higher incidence (difference of $\geq 2\%$) in patients receiving GAZYVA plus bendamustine (induction) followed by GAZYVA maintenance vs bendamustine (induction) alone

| ADR (MedDRA ^a) System Organ Class | All Grades % | | Grades 3-5 [†] % | |
|---|-----------------------|------------------------------------|---------------------------|------------------------------------|
| | bendamustine n=198 | GAZYVA + bendamustine* n=194 | bendamustine n=198 | GAZYVA + bendamustine* n=194 |
| Injury, Poisoning and Procedural Complications | | | | |
| Infusion related reactions [‡] | 63.1 | 68.6 | 5.6 | 10.8 |
| Blood and Lymphatic System Disorders | | | | |
| Neutropenia | 28.3 | 35.1 | 26.3 | 33.0 |

| ADR (MedDRA ^a) System Organ Class | All Grades % | | Grades 3-5 [†] % | |
|---|-----------------------|------------------------------------|---------------------------|------------------------------------|
| | bendamustine n=198 | GAZYVA + bendamustine* n=194 | bendamustine n=198 | GAZYVA + bendamustine* n=194 |
| Lymph node pain | 0 | 2.1 | 0 | 0 |
| Cardiac Disorders | | | | |
| Cardiac failure | 0 | 2.1 | 0 | 1.0 |
| Eye Disorders | | | | |
| Ocular hyperaemia | 0 | 2.1 | 0 | 0 |
| Gastrointestinal Disorders | | | | |
| Constipation | 15.7 | 18.6 | 0 | 0 |
| Dyspepsia | 2.5 | 5.2 | 0 | 0 |
| Colitis | 0 | 2.1 | 0 | 1.0 |
| Haemorrhoids | 0 | 2.1 | 0 | 0 |
| General Disorders And Administration Site Conditions | | | | |
| Pyrexia | 13.6 | 18.0 | 0 | 1.0 |
| Asthenia | 8.1 | 11.3 | 0 | 1.0 |
| Chest Pain | 2.0 | 4.6 | 0.5 | 0 |
| Infections And Infestations | | | | |
| Upper Respiratory Tract Infection | 8.1 | 12.9 | 0.5 | 2.1 |
| Sinusitis | 5.1 | 11.9 | 0 | 1.0 |
| Urinary Tract Infection | 5.6 | 9.8 | 0 | 3.1 |
| Nasopharyngitis | 4.0 | 8.8 | 0 | 0 |
| Pharyngitis | 0.5 | 4.1 | 0 | 0 |
| Lung Infection | 1.0 | 3.1 | 0.5 | 1.0 |
| Influenza | 0 | 3.1 | 0 | 0 |
| Musculoskeletal and Connective Tissue Disorders | | | | |
| Arthralgia | 4.5 | 11.9 | 0 | 0 |
| Pain In Extremity | 3.5 | 8.8 | 0 | 1.0 |
| Bone Pain | 1.0 | 3.6 | 0 | 0 |
| Psychiatric Disorders | | | | |
| Depression | 1.5 | 3.6 | 0 | 0 |
| Renal and Urinary Disorders | | | | |
| Dysuria | 0.5 | 2.6 | 0 | 0.5 |
| Urinary incontinence | 0 | 2.6 | 0 | 0.5 |
| Respiratory, Thoracic and Mediastinal Disorders | | | | |
| Cough | 16.7 | 26.3 | 0 | 0 |
| Nasal Congestion | 1.5 | 7.2 | 0 | 0 |
| Rhinorrhoea | 1.0 | 4.1 | 0 | 0 |
| Skin and Subcutaneous Tissue Disorders | | | | |
| Pruritus | 5.6 | 8.8 | 0 | 0 |

| ADR (MedDRA ^a) System Organ Class | All Grades % | | Grades 3-5 [†] % | |
|--|-----------------------|------------------------------------|---------------------------|------------------------------------|
| | bendamustine n=198 | GAZYVA + bendamustine* n=194 | bendamustine n=198 | GAZYVA + bendamustine* n=194 |
| Night sweats | 2.0 | 4.1 | 0 | 0 |
| Eczema | 0.5 | 2.6 | 0 | 0 |

*followed by GAZYVA maintenance

^aMedDRA coded adverse reactions as reported by investigators (excluding IRRs).

[†]No Grade 5 adverse reactions have been observed with a difference of $\geq 2\%$ between the treatment arms

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

Patients in the B arm received 6 months of induction treatment only, whereas after the induction period, patients in the G+B arm continued on with GAZYVA maintenance treatment. During the maintenance period with GAZYVA, the most common adverse reactions were cough (14.7%), upper respiratory tract infections (11.9%), neutropenia (10.5%), sinusitis (9.8%), diarrhoea (8.4%), IRRs (8.4%), nausea (7.7%), fatigue (7.7%), bronchitis (7.0%), arthralgia (7.0%), nasopharyngitis (6.3%), urinary tract infections (6.3%) and pyrexia (5.6%). The most common grade 3-5 adverse reactions were neutropenia (9.8%), and anaemia, febrile neutropenia, thrombocytopenia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1.4%).

Further information on selected adverse reactions

Infusion related reactions

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

Chronic Lymphocytic Leukaemia

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

In patients who received the combined measures for prevention of IRRs (corticosteroid; oral analgesic/anti-histamine (H1 histamine receptor blockade); omission of antihypertensive medication in the morning of the first infusion; Cycle 1 Day 1 dose administered over 2 days) as described under DOSAGE AND ADMINISTRATION, decreased incidence of all Grades IRRs was observed. The incidence of Grade 3-4 IRRs (which are based on a relatively low number of patients) were similar before and after mitigation measures were implemented.

Non-Hodgkin Lymphoma

In Cycle 1, the overall incidence of IRRs was higher in patients receiving G+B (55%) compared to patients receiving B alone (42%) (with Grade 3-5 IRR reported in 9% and 2%, respectively and no fatal events reported). In patients receiving G+B the incidence of IRRs was highest on Day 1 (38%) and gradually decreased on Days 2, 8 and 15 of cycle 1 (25%, 7% and 4%, respectively).

During Cycle 2, the incidence of IRRs was lower in patients receiving G+B (24%) compared to patients receiving B alone (32%). The incidence of IRRs in subsequent infusions was comparable in both arms and decreased with each cycle. IRRs were also observed in 8% of patients during the GAZYVA maintenance period. Overall, 3% of patients experienced an IRR leading to discontinuation of GAZYVA.

Neutropenia and infections

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the GAZYVA plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte colony-stimulating factors. The incidence of infection was 38% in the GAZYVA plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the GAZYVA plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the GAZYVA plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see PRECAUTIONS).

Non-Hodgkin Lymphoma

The incidence of neutropenia was higher in the G+B arm compared to the arm treated with B alone. The incidence of infection was 66% in the G+B arm and 57% in the B arm (with Grade 3-5 events reported in 18% and 17%, respectively, and fatal events reported in 3% and 4%, respectively). Cases of prolonged neutropenia (3% in the G+B arm) and late onset neutropenia (7% in the G+B arm) were also reported (See PRECAUTIONS).

Thrombocytopenia

Chronic Lymphocytic Leukaemia

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

Non-Hodgkin Lymphoma

The incidence of thrombocytopenia was lower in the G+B arm (15%) compared to the arm treated with B alone (24%). The incidence of haemorrhagic events (11% G+B, 10% B) and Grade 3-5 haemorrhagic events (5% G+B, 3% B) was similar in both treatment arms with no fatal events reported.

Progressive multifocal leukoencephalopathy (PML)

PML has been reported in patients treated with GAZYVA (see BOXED WARNING, PRECAUTIONS).

Hepatitis B Reactivation

Cases of hepatitis B reactivation have been reported in patients treated with GAZYVA (see PRECAUTIONS).

Worsening of Pre-existing Cardiac Conditions

Cases of fatal cardiac events have been reported in patients treated with GAZYVA (see PRECAUTIONS).

Gastro-Intestinal Perforation

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

Malignancies

There is an increased incidence of second malignancies in patients with CLL. Data from the pivotal study in CLL does not demonstrate an increased risk of second malignancies following GAZYVA therapy.

Laboratory Abnormalities

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

For additional information see *Further information on selected adverse reactions*, Neutropenia and infections; Thrombocytopenia.

DOSAGE AND ADMINISTRATION

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

General

GAZYVA should be administered as an intravenous infusion through a dedicated line in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced physician. GAZYVA infusions should not be administered as an intravenous push or bolus. Isotonic 0.9% sodium chloride solution should be used as the infusion vehicle (see *Disposal of unused/expired medicines*).

Prophylaxis and Premedication for Tumour Lysis Syndrome (TLS)

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

Prophylaxis and Premedication for Infusion Related Reactions (IRR)

Premedication to reduce the risk of IRRs (see PRECAUTIONS) is outlined in Table 6. Corticosteroid premedication is recommended for FL patients and mandatory for CLL patients for the first infusion. Premedication for subsequent infusions and other premedication should be administered as described below. Patients with a high tumour burden and/or (i.e. high peripheral circulating lymphocyte count in CLL ($> 25 \times 10^9/L$)) may be at increased risk of severe IRR.

Hypotension as a symptom of IRR may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each infusion, and for the first hour after administration (see PRECAUTIONS).

Table 6 Premedication to be administered before GAZYVA infusion to reduce the risk of infusion-related reactions

| Day of Treatment Cycle | Patients requiring premedication | Premedication | Administration |
|--|---|--|--|
| Cycle 1 CLL: Day 1* , Day 2 FL: Day 1 | All patients | Intravenous corticosteroid ¹ | Completed at least 1 hour prior to GAZYVA infusion |
| | | Oral analgesic/anti-pyretic ² | At least 30 minutes before GAZYVA infusion |
| | | Anti-histaminic drug ³ | |
| All subsequent infusions: CLL and FL | Patients with no IRR during the previous infusion | Oral analgesic/anti-pyretic ² | At least 30 minutes before GAZYVA infusion |
| | Patients with an IRR (Grade 1 or 2) with the previous infusion | Oral analgesic/anti-pyretic ² | At least 30 minutes before GAZYVA infusion |
| | | Anti-histaminic drug 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 | Completed at least 1 hour prior to GAZYVA infusion |
| | | Oral analgesic/anti-pyretic ² | At least 30 minutes before GAZYVA infusion |
| | | Anti-histaminic drug ³ | |

*If the 100 mg dose of GAZYVA is administered without interruption or modification of the infusion rate the subsequent 900 mg dose may also be administered on the same day (see Table 7). In the event the 900 mg dose is given on the same day no additional premedication is required prior to commencement of the 900 mg dose.

¹ 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions

² e.g. 1000 mg paracetamol

³ H1 histamine receptor blockade

Standard Dosage

Chronic Lymphocytic Leukaemia (in combination with chlorambucil)*

Cycle 1

The recommended dosage of GAZYVA is 1000 mg administered over Day 1 and 2, and on Day 8 and Day 15 of the first 28 day treatment cycle as shown in Table 7.

Two infusion bags should be prepared; one for the first infusion of 100 mg and one for the second infusion of 900 mg. If the 100 mg dose is completed without modifications of the infusion rate or interruptions, the 900 mg dose can be administered on the same day (no dose delay necessary) provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or

interruptions during the first 100 mg the 900 mg infusion must be administered the following day (see Table 7).

Cycles 2-6

The recommended dosage of GAZYVA is 1000 mg administered on Day 1 for each 28 day treatment cycle as shown in Table 7.

Table 7 Dose and infusion rate of GAZYVA for patients with CLL

| Day of Treatment Cycle | | Dose of GAZYVA | Rate of infusion If an IRR occurs, adjust infusion rate as outlined in Table 9 |
|------------------------|----------------------------------|----------------|---|
| Cycle 1 | Day 1 | 100 mg | Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate. |
| | Day 2 or Day 1 (continued) | 900 mg | 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. |
| | Day 8 | 1000 mg | If no IRR occurred during the previous infusion where the final infusion rate was \geq 100 mg/hr, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. |
| | Day 15 | 1000 mg | |
| Cycles 2 – 6 | Day 1 | 1000 mg | |

* see CLINICAL TRIALS for information on chlorambucil dose.

Delayed or missed doses

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

Follicular Lymphoma

Induction Treatment (in combination with bendamustine**)

The recommended dosage of GAZYVA is 1000 mg administered on Day 1, Day 8 and Day 15 of the first 28 day treatment cycle followed by 1000 mg administered on Day 1 only for each subsequent 28 day treatment cycle (Cycles 2 to 6) as shown in Table 8.

Maintenance Treatment

Patients who respond to induction treatment (i.e. the initial 6 treatment cycles) or have stable disease should continue to receive GAZYVA 1000 mg alone as maintenance therapy once every 2 months until disease progression or for up to two years (whichever occurs first).

Table 8 Dose and infusion rate of GAZYVA for patients with FL

| Day of Treatment Cycle | | Dose of GAZYVA | Rate of infusion If an IRR occurs, adjust infusion rate as outlined in Table 9. |
|------------------------|-------|----------------|--|
| Cycle 1 | Day 1 | 1000 mg | Administer at 50 mg/hr. The rate of |

| | | | |
|-------------|---|---------|---|
| | | | infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. |
| | Day 8 | 1000 mg | If no IRR occurred during the previous infusion where the final infusion rate was ≥ 100 mg/hr, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. |
| | Day 15 | 1000 mg | |
| Cycles 2-6 | Day 1 | 1000 mg | |
| Maintenance | Every two months until progression or up to two years | 1000 mg | |

** see CLINICAL TRIALS for information on bendamustine dose.

Delayed or missed doses

If a planned dose of GAZYVA is missed, it should be administered as soon as possible; do not wait until the next planned dose. During induction, the planned treatment interval for GAZYVA should be maintained between doses. During maintenance, maintain the original dosing schedule for subsequent doses.

Dosage modifications during treatment (all indications)

No dose reductions of GAZYVA are recommended.

For management of symptomatic adverse events (including IRRs), see Table 9 and PRECAUTIONS.

Table 9 Infusion Rate Modification Guidelines for Infusion Related Reactions (see PRECAUTIONS, Infusion Related Reactions)

| | |
|--------------------------------------|---|
| Grade 4 (life-threatening) | Stop infusion and permanently discontinue therapy. |
| Grade 3 (severe) | <p>Temporarily interrupt infusion and treat symptoms.</p> <p>Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred).</p> <p>If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 7 and 8).</p> <ul style="list-style-type: none"> • <u>For CLL patients</u> receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back to 25 mg/hr after 60 minutes, but not increased further. <p>If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.</p> |
| Grade 1-2 (mild and moderate) | <p>Reduce infusion rate and treat symptoms.</p> <p>Upon resolution of symptoms, continue infusion.</p> <p>If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 7 and 8).</p> <ul style="list-style-type: none"> • <u>For CLL patients</u> receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased |

| | |
|--|----------|
| | further. |
|--|----------|

Dosage modifications in Special Populations

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

Elderly: No dose adjustment is required in elderly patients (see PRECAUTIONS, Use in the elderly).

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment. GAZYVA has not been studied in patients with a CrCl < 30mL/min (see PRECAUTIONS, Use in renal impairment; PHARMACOLOGY *Pharmacokinetics in special populations*).

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

Instructions for dilution

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

For all FL cycles and CLL cycles 2-6

Withdraw the required amount of GAZYVA liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see *Incompatibilities*).

For CLL cycle 1, Day 1 only: Preparation of infusion bags for dose administered over 2 days

The table below provides guidance on the volume of GAZYVA liquid concentrate to be diluted and the volume of sterile 0.9% sodium chloride solution it is to be diluted in. Withdraw the required amount of GAZYVA liquid concentrate from the vial and dilute in a PVC or non-PVC polyolefin infusion bag containing the appropriate volume of sterile, non-pyrogenic 0.9% aqueous sodium chloride solution. Do not use dextrose-containing solutions or other diluents (see *Incompatibilities*).

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

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

| Dose of GAZYVA to be administered | Required amount of GAZYVA liquid concentrate | Volume of PVC or non-PVC polyolefin infusion bag |
|--|---|---|
| 100 mg | 4 mL | 100 mL |
| 900 mg | 36 mL | 250 mL |

| | | |
|---------|-------|--------|
| 1000 mg | 40 mL | 250 mL |
|---------|-------|--------|

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

GAZYVA is for single use in one patient only. Once the infusion is prepared it should be administered immediately (see PRESENTATION AND STORAGE CONDITIONS).

Incompatibilities

No incompatibilities between GAZYVA and polyvinyl chloride, polyethylene, polypropylene or polyolefine bags, polyvinyl chloride, polyurethane, or polyethylene infusion sets, as well as optional inline filters with product contact surfaces of polyethersulfon, a 3-way stopcock infusion aid made from polycarbonate, and catheters made from polyetherurethane have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of GAZYVA with 0.9% sodium chloride.

Diluted product should not be shaken or frozen. Do not use other diluents such as dextrose (5%) solution to dilute GAZYVA since their use has not been tested.

OVERDOSAGE

No experience with overdosage is available from human clinical trials. In clinical trials with GAZYVA, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent. Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. Patients should be closely monitored with regular blood cell counts, and for increased risk of infections, while B cell-depleted.

Treatment of overdose should consist of general supportive measures.

Contact the Poison Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

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

Storage conditions

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

Shelf-life of reconstituted solution

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

Physical and chemical stability of the prepared infusion solution of GAZYVA has been demonstrated for 24 hours at 2°C - 8°C followed by 24 hours at ambient temperature ($\leq 30^{\circ}\text{C}$)

followed by an infusion taking no longer than 24 hours. To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, hold at 2°C - 8°C for not more than 24 hours.

Disposal of unused/expired medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4. Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

15 May 2014

DATE OF MOST RECENT AMENDMENT

26 August 2016