28 April 2016
EMA/CHMP/345935/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gazyvaro

International non-proprietary name: obinutuzumab

Procedure No. EMEA/H/C/002799/II/0007

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AEPI	adverse event of particular interest
benda	bendamustine
BOR	best overall response
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRu	unconfirmed complete response
CSR	clinical study report
CVP	cyclophosphamide, vincristine, and prednisone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
iDMC	independent Data Monitoring Committee
DoR	duration of response
EOI	end of induction
EQ-5D	Euro–Quality-of-Life-5D Questionnaire
ESMO	European Society for Medical Oncology
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drugs Administration
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G-benda	obinutuzumab plus bendamustine
GI	gastrointestinal
HACA	human anti-chimeric antibodies
HAHA	human anti-human antibodies
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
iNHL	indolent non-Hodgkin lymphoma
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MALT	mucosa associated lymphoid tissue
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NE	not estimable
IRR	infusion-related reaction
ORR	objective response rate
OS	overall survival
PD	progressive disease or pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PSP	Paediatric Study Plan
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SLL	small lymphocytic lymphoma
SOC	system organ class
TLS	tumour lysis syndrome
TOI	trial outcome index
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 28 August 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. Consequently, updates to sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC, the Package Leaflet and RMP have been proposed. Furthermore, the MAH took the opportunity to make minor editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Gazyvaro was designated as an orphan medicinal product (EU/3/15/1504) in the following indication: treatment of follicular lymphoma on 19 June 2015.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions CW/0001/2015 and CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 21 October 2010 (EMEA/H/SA/1269/2/FU/1/2010/II) and 29 May 2009 (EMEA/H/SA/1269/2/2009/II). The Protocol Assistance pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	28 August 2015
Start of procedure:	19 September 2015
CHMP Rapporteur Assessment Report	19 November 2015
CHMP Co-Rapporteur Assessment Report	20 November 2015
PRAC Rapporteur Assessment Report	20 November 2015
PRAC members comments	25 November 2015
PRAC Outcome	3 December 2015
CHMP members comments	7 December 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 December 2015
Request for supplementary information (RSI)	17 December 2015
CHMP Rapporteur(s) Joint Assessment Report	5 April 2016
PRAC Rapporteur Assessment Report	5 April 2016
PRAC members comments	6 April 2016
PRAC Outcome	14 April 2016
CHMP members comments	21 April 2016
Opinion	28 April 2016

2. Scientific discussion

2.1. Introduction

Gazyvaro (Obinutuzumab) is a glyco-engineered, Type II mAb of the immunoglobulin (Ig) IgG1 subclass, recognizing an epitope of the CD20 molecule found on B cells (Beers et al, 2008; Herter et al, 2013). It was approved in the EU for use in combination with chlorambucil in the first-line treatment of patients with CLL in November 2013.

B-cell lymphomas, including iNHLs, are characterized by the expression of a membrane antigen, CD20. Non-Hodgkin lymphoma are B-lymphoproliferative disorders that include a heterogeneous group of malignancies, ranging from slow-growing, indolent non-Hodgkin lymphomas (iNHLs), which comprise about a third of all NHLs, to more aggressive forms of NHL. Subtypes of iNHL are follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia [LPL/WM] and small lymphocytic lymphoma (SLL). FL accounts for approximately 20%-25% of all new NHLs and 70% of iNHLs (The Non-Hodgkin Lymphoma Classification Project 1997). SLL is an uncommon disorder, comprising 6% of iNHLs and 15% of cases of the CLL/SLL entity (Tsimberidou et al. 2007; Nola et al. 2004), classified as same biological entity with CLL according to

WHO. Follicular lymphoma (FL) is the second most common lymphoma diagnosed in the United States and Western Europe, representing approximately 22% of all NHLs and 70% of iNHL. The median age at diagnosis is 59 years and median survival is 8-10 years.

Follicular lymphoma is defined as a mature B-cell neoplasm in the 2008 World Health Organization (WHO) classification of tumours of hematopoietic and lymphoid tissues. Follicular lymphoma cells are malignant counterparts of normal germinal center B cells. Approximately 85% of patients with FL have a genomic translocation t(14;18)(q32;q21), which results in the overexpression of the BCL-2 protein, a member of a family of proteins that blocks programmed cell death or apoptosis. FL is chemo-sensitive and with a generally good prognosis at diagnosis, however in resistant and refractory stages the current treatment alternatives are limited.

Rituximab (Mabthera) a monoclonal antibody (mAb) directed against CD20, has been authorised in the EU as monotherapy for patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy; improved progression-free survival (PFS) or event-free survival (EFS) and overall survival (OS) in patients with FL (Hiddemann et al, 2005; Herold et al, 2007; Marcus et al, 2008; Salles et al, 2008) has been shown. Improved efficacy has also been demonstrated with rituximab in patients with MZL and SLL (McLaughlin et al. 1998; Foran et al. 2000; Hainsworth et al. 2003; Rummel et al. 2013).

Data from a range of clinical trials suggest that the quality and duration of response to induction therapy are factors that predict survival in patients with previously untreated and relapsed FL; patients who achieve a complete response that is maintained for a prolonged period of time tend to survive longer than other patients. As a result, there has been much interest in post-induction therapy for patients with FL. Two main approaches have been evaluated: consolidation, consisting of a single or short course of therapy; and maintenance, in which treatment is continued for a prolonged period of time (theoretically until relapse, but in practice, usually limited to around 2 years).

In the European Union, rituximab maintenance for up to 2 years is approved for patients with previously untreated FL and for patients with relapsed/refractory FL, after induction therapy. This has been shown to have an acceptable safety profile in patients with newly diagnosed disease and in patients with relapsed/refractory disease. Based on a systematic meta-analysis, rituximab maintenance has been shown to substantially prolong PFS and OS even after antibody containing induction (although the OS benefit was only shown in relapsed patients who did not receive rituximab during first-line induction treatment). Both ESMO and the NCCN guidelines indicate that the efficacy of maintenance rituximab in the second-line setting is likely to be influenced by the efficacy of maintenance rituximab in the first-line setting. The NCCN guidelines state that if a patient progressed during or within 6 months of first line maintenance rituximab, the clinical benefit of maintenance rituximab in the second-line setting is likely to be very minimal and ESMO guidelines state that second-line maintenance rituximab probably should not be used for patients who had relapsed during their first maintenance period.

Radioimmunotherapy, chemotherapy and immunotherapy have all been investigated as potential forms of post-induction therapy in patients with FL in the first-line and/or relapsed/refractory setting; ^{90}Y-ibritutomab tiuxetan is approved as consolidation therapy for patients with FL in first remission but not in the relapsed/refractory setting. Interferon-alpha (for 18 months) is licensed as an adjunct to induction combination chemotherapy such as a CHOP-like regimen, for patients with FL and a high tumour burden, but its use is limited by toxicity and inconvenience of administration. Relatively few studies have been conducted with maintenance chemotherapy and this is not established in FL.

As the disease becomes increasingly resistant to chemotherapy and to rituximab as well as histologic transformation to high-grade NHL can occur which are more aggressive than the original iNHL and has a poor outcome. Overall, about 50% of patients with FL die within 5 years of first relapse/progression

(Montoto et al. 2004; Causoli et al, 2015), but the median OS of patients with FL who develop histological transformation is estimated to 1-2 years (Al-Tourah et al. 2008).

The alkylating agent bendamustine has been shown to be effective in the treatment of patients with rituximab-refractory iNHL, demonstrating an overall response rate (ORR) of approximately 75%, a complete response (CR) rate of approximately 15%, a median DoR of 6.7-9.2 months, and a median PFS of 7.1-9.3 months (Friedberg et al. 2008; Kahl et al. 2010). As disease remissions are relatively short with bendamustine, there is still a medical need for new therapeutic options for patients with iNHL after failure of rituximab-based therapy.

The MAH applied to extend the indication as follows:

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

The recommended dose of Gazyvaro (Obinutuzumab) when used in combination with Bendamustine is 1000 mg as an intravenous infusion on day 1, 8 and 15 of cycle 1, on day 1 of cycles 2-6, and then every 2 months thereafter until progression or for up to 2 years (whichever was earlier).

The proposed indication, falls within the orphan designation: treatment of follicular lymphoma (EU/3/15/1504, granted on 19 June 2015).

2.2. Non-clinical aspects

All relevant pharmacology studies, multiple dose PK and TK studies as well as toxicology studies conducted in support of obinutuzumab development were included in the initial license application. Two additional toxicology studies contributing to the overall evaluation of the obinutuzumab safety profile and relevant to this application were completed since submission of the initial license application in CLL and are discussed here in the context of the overall toxicology program.

2.2.1. Introduction

Two supplemental in vitro studies were performed post-approval.

To exclude that the unexpected staining of endothelial cells observed in human and monkey tissue cross-reactivity studies could indicate a direct binding of obinutuzumab to endothelial cells leading to vasculitis in macaques, an additional study was submitted (Report No. 1061540) using different tissue donors (see toxicology section). In addition, another in vitro toxicology study (Report No. 1062523) was designed to explore the role of cytokine release in the increased infusion-related reactions (IRR) incidence and severity observed in obinutuzumab-treated versus rituximab-treated patients.

2.2.2. Pharmacology

No new pharmacology studies were included in this submission.

2.2.3. Pharmacokinetics

No new PK studies were included in this submission.

2.2.4. Toxicology

Other toxicity studies

Report No. 1061540: A Tissue cross-reactivity study of obinutuzumab in normal human and cynomolgus monkey tissues

The objective of this study was to determine the potential cross reactivity of RO5072759 with cryosections of human and non-human primate (cynomolgus monkey) tissues.

Tissues were collected as surgical or autopsy specimens from humans (Table 1) and necropsy specimens from cynomolgus monkeys. Unfixed tissues as received from the tissue suppliers were considered essentially normal. Tissues were from a different set of human and cynomolgus donors (at least 3 different donors per tissue) and the secondary labelled antibody used was different than in the previous studies; all other assay procedures were similar to the earlier studies.

Table 1 Human tissue (normal) from three separate donors.

Adrenal	Heart	Salivary Gland
Bladder (urinary)	Kidney (glomerulus, tubule)	Skin
Blood Cells [a]	Liver	Spinal Cord
Blood Vessels (endothelium) [b]	Lung	Spleen
Bone Marrow	Lymph Node	Striated Muscle (skeletal)
Brain – cerebellum	Ovary	Testis
Brain – cerebrum (cerebral cortex)	Pancreas	Thymus
Breast	Parathyroid	Thyroid
Colon (large intestine)	Peripheral Nerve	Tonsil
Eye	Pituitary	Ureter
Fallopian Tube	Placenta	Uterus – cervix
Gastrointestinal (GI) Tract [c]	Prostate	Uterus – endometrium

[a] Evaluated from peripheral blood smears.
[b] Evaluated from all tissues where present.
[c] Includes esophagus, small intestine, and stomach (including underlying smooth muscle).

Table 2 Cynomolgus monkey tissue (normal) from three separate animals

Adrenal	Heart	Salivary Gland
Bladder (urinary)	Kidney (glomerulus, tubule)	Skin
Blood Cells [a]	Liver	Spinal Cord
Blood Vessels (endothelium) [b]	Lung	Spleen
Bone Marrow	Lymph Node	Striated Muscle (skeletal)
Brain – cerebellum	Ovary	Testis
Brain – cerebrum (cerebral cortex)	Pancreas	Thymus
Breast	Parathyroid	Thyroid
Colon (large intestine)	Peripheral Nerve	Tonsil
Eye	Pituitary	Ureter
Fallopian Tube	Placenta	Uterus – cervix
Gastrointestinal Tract [c]	Prostate	Uterus – endometrium

[a] Evaluated from all tissues where present.
[b] Evaluated from all tissues where present.
[c] Includes esophagus, small intestine, and stomach (including underlying smooth muscle).

After pathology review, it was determined that some of the tissue samples did not contain a sufficient amount of the required tissue for evaluation or were determined to be unsuitable for evaluation due to tissue morphology. Therefore, additional samples of the tissue were stained and evaluated to obtain the

required three samples of each tissue; however, there were only two viable donors of cervix evaluated within the study timeframe.

In the human tissue panel, obinutuzumab showed membrane and cytoplasmic staining of mononuclear leukocytes (B lymphocytes) and cytoplasmic staining was seen in endothelium, epithelium/myoepithelium, and platelets. In cynomolgus monkey tissues, cytoplasmic staining was observed in endothelium, epithelium, cerebellar granular layer cells and neural processes, and skin follicular root sheaths.

The cytoplasmic staining of endothelial cells was observed in a similar range of tissues between human and monkey tissues, with no membranous endothelial staining being observed in either species. In contrast to the previous TCR studies performed with RO5072759, there was no membrane staining observed, in neither human nor cynomolgus monkey tissues, except for B lymphocytes.

In conclusion, data from the new TCR study demonstrated lack of membranous staining of endothelial cells and, according to the MAH, provided additional data to confirm the inherent variability of the unexpected staining and to support the lack of any direct effect of obinutuzumab on endothelial cells in vivo.

The results of this study may support that the unexpected staining of endothelial cells observed in previous human and monkey tissue cross-reactivity studies, may not indicate a direct binding of obinutuzumab to endothelial cells leading to vasculitis in macaques.

Report No. 1062523: Obinutuzumab Rituximab- and Ofatumumab-induced cytokine release in human whole blood)

This additional whole blood cell assay was designed to explore the role of cytokine release in the increased IRR rate and severity observed in obinutuzumab-treated versus rituximab-treated patients. Whole blood from 13 healthy donors was incubated with 0.1, 1, 10 and 100 ug/mL obinutuzumab, and other CD20 antibodies rituximab and ofatumumab, as well as the comparators alemtuzumab and cetuximab. After 24 hours IL6, IL8, TNFα, IFNγ, interleutkin-2 (IL2), interleukin-12p70 (IL12p70), interleukin-1 beta (IL1β), interleukin-1 alpha (IL1α) and interleukin-10 (IL10) released into the plasma was measured. In addition, immunophenotyping was performed to identify changes in the numbers of B cells, T cells and NK cells. Additionally expression of the activation marker CD11b on neutrophils was monitored. Obinutuzumab induced stronger cytokine release, increased up-regulation of CD11b and stronger B cell depletion than rituximab and ofatumumab in this assay.

2.2.5. Ecotoxicity/environmental risk assessment

No environmental risk assessement was submitted (See discussion on non-clinical aspects).

2.2.6. Discussion on non-clinical aspects

The active substance in Gazyvaro, obinutuzumab, is a monoclonal antibody that has been designed using recombinant DNA technology to recognise and attach to the protein CD20, which is found on the surface of all B-lymphocytes. In the current indication, CLL, cancerous B- lymphocytes multiply too quickly and replace the normal cells in the bone marrow, and are unable to function properly. By attaching to CD20 on B-lymphocytes of patients with CLL, obinutuzumab causes the death of these abnormal lymphocytes.

All relevant pharmacology studies, multiple dose PK and TK studies as well as toxicology studies conducted in support of obinutuzumab development were included in the initial license application. Two additional toxicology studies contributing to the overall evaluation of the obinutuzumab safety profile and relevant to this application were completed since submission of the initial license application in CLL and

are discussed here in the context of the overall toxicology program.

Obinutuzumab was evaluated in repeat-dose studies in cynomolgus monkeys up to 26 weeks in duration. Cynomolgus monkey was selected as the species of choice in the safety assessment of obinutuzumab on the basis of its high target sequence homology and comparable target binding affinities to human, Fc-mediated effector function, and tissue cross-reactivity results.

Toxicology studies were conducted in monkeys at dose levels ranging from 5 to 100 mg/kg body weight i.v. Treatment-related findings across all toxicology studies were related to the pharmacological action of obinutuzumab, to secondary opportunistic infections and/or to hypersensitivity reactions.

An enhanced pre- and postnatal development study revealed a complete depletion of B-lymphocytes in all infants with a return to almost normal levels by 168 days postpartum, indicating that a long-lasting effect of treatment on immune function is unlikely. There was no evidence of any treatment-related effects on embryo-fetal development, parturition, postnatal survival, and growth and development of infants.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has the propensity to cause first infusion-related cytokine release in patients.

Immunohistochemical staining in frozen cynomolgus monkey and human tissue sections was in general comparable with the reported tissue expression of CD20. However, cross reactivity of obinutuzumab was also present in human bile duct epithelia, salivary glands, and endothelium of the lung as well as on membrane and cytoplasm of monkey endothelium in the following tissues: small intestine, heart, kidney, lung, ovary, pancreas, pituitary, prostate, salivary gland, testis, and endometrium.

Two supplementary toxicology studies (ex vivo and in vitro) were submitted for this extension application.

To exclude that the unexpected staining of endothelial cells observed in human and monkey tissue cross-reactivity studies could indicate a direct binding of obinutuzumab to endothelial cells leading to vasculitis in macaques. One study investigated the potential cross reactivity of obinutuzumab with cryosections of human and non-human primate (cynomolgus monkey) tissues. The objective was to exclude that the unexpected staining of endothelial cells observed in previous human and monkey tissue cross-reactivity studies could indicate a direct binding of obinutuzumab to endothelial cells and that this in turn could lead to vasculitis in macaques.

The results of the new study demonstrated obinutuzumab staining of membrane and cytoplasmic elements in mononuclear leukocytes in B cell regions of lymphoid tissues, in hematopoietic cells and in individual mononuclear leukocytes in multiple tissues in both human and cynomolgus monkey tissue panels. In addition, cytoplasmic staining with obinutuzumab was seen in endothelium, epithelium/myoepithelium, and platelets in the human tissue panel. In cynomolgus monkey tissues, cytoplasmic staining was observed in endothelium, epithelium, cerebellar granular layer cells and neural processes, and skin follicular root sheaths.

According to ICH S6, binding to areas not typically accessible to the antibody in vivo i.e. cytoplasm, is generally not toxicologically relevant. This is also underscored by the MAH regarding the results from this study, and this assumption may be endorsed. Thus, the results may support that the unexpected staining of endothelial cells observed in previous human and monkey tissue cross-reactivity studies, may not indicate a direct binding of obinutuzumab to endothelial cells leading to vasculitis in macaques.

The mechanism by which infusion-related reactions (IRRs) are triggered is not clearly understood, however, evidence suggests that IRRs may be linked to the release of cytokines and/or other chemical mediators from immune effector cells such as NK cells, macrophages/monocytes and/or neutrophils; potentially also from B-cells targeted by obinutuzumab. Cytokine release can occur as a consequence of the antibody-antigen interaction between obinutuzumab and the CD20 antigen on B lymphocytes,

resulting in Fc receptor crosslinking of FcγRIII on immune effector cells such as natural killer cells and macrophages/monocytes and subsequent cytokine release from these cells. An in vitro study was designed to explore the role of cytokine release in the increased infusion-related reactions (IRR) incidence and severity observed in obinutuzumab-treated versus rituximab-treated patients. Obinutuzumab induced stronger cytokine release, increased up-regulation of CD11b and stronger B cell depletion than rituximab and ofatumumab, when incubated with whole blood from healthy donors. These data are in alignment with the clinical trial CLL11/BO21004 in CLL patients where obinutuzumab was found to have greater efficacy than Rituximab, albeit with more severe and increased incidence of IRR.

In accordance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use", EMEA/CHMP/SWP/4447/00 corr 2*, an environmental risk assessment (ERA) is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure, including extensions to already marketed products. In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment. The active ingredient in GAZYVARO, Obinutuzumab, is a glyco-engineered Type II humanised anti-CD20 monoclonal antibody of the IgG1 subclass, therefore it is exempted. The justification is that as a protein, Obinutuzumab is categorically exempt from the necessity of an ERA. This is agreed.

2.2.7. Conclusion on the non-clinical aspects

The non-clinical aspects of obinutuzumab are sufficiently covered in the original submission for the MA and by the updated data submitted in this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Table 1:** Tabular overview of clinical studies

Study	Study Design	Study Population	Number of Subjects	Treatment arms
BO20999	Phase I/II, open-label multicentre, dose escalating	Relapsed/refract. iNHL,aNHL,CLL	iNHL: 56 FL: 47	Obimutuzumab (G) monotherapy
BO21003	Phase I/II, open-label multicentre, dose escalating	Relapsed/refract. iNHL/CLL	iNHL: 188 FL: 159	G monoth. G vs R
BO21000	Phase Ib, open-label multicentre, randomized	1)Relapsed/refractory FL 2) First-line FL	1) 56 2) 81	1) G-CHOP, G-FC 2) G-CHOP, G-benda
GA04753g	Phase III, open-label, multicentre, randomized G-benda vs. benda	Refractory iNHL	396	G-benda vs. benda

CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisolone; CLL – chronic lymphocytic leukemia; FL – follicular lymphoma; G-benda – obinutuzumab in combination with bendamustine; G-FC – obinutuzumab in combination with fludarabine and cyclophosphamide; aNHL – aggressive non-Hodgkin lymphoma; iNHL – indolent non-Hodgkin lymphoma.

[a] Date first patient screened or enrolled in the study

[b] At the time of the primary analysis, with a clinical cutoff date of 1 September 2014, a total of 396 patients were randomized in the study, with 413 randomized by the time of the Independent Data Monitoring Committee analysis review and assessment.

[c] Included only patients with FL.

2.3.2. Pharmacokinetics

PK investigations in patients with iNHL in order to support dose / posology and to explore DDI interactions with bendamustine have been included in study GAO4753g. A drug –drug interaction sub-study is part of study GAO4753g. This sub-study included 20 patients with intensive sampling operated in day 2 of cycle one in order to. A formal non compartment analysis (NCA) of plasma/serum concentrations of bendamustine was followed in this portion of the study.

Absorption

N / A

Distribution

N / A

Elimination

No new data are submitted.

Dose proportionality and time dependencies

Samples were collected and analysed using population-PK approach.

Methods

Analytical Methods

The ELISA technique for the quantification of obinutuzumab in human serum was the same as used in the original application. Bendamustine concentrations were measured in human Li-heparin plasma samples using a validated LC-MS/MS method. Briefly, human plasma samples were analyzed using deuterated bendamustine (bendamustine-d8-HCL) as an internal standard, and performing protein precipitation. Analysis was performed by high performance liquid chromatography with tandem mass spectrometric detection (API 3000, PE Sciex) operated in the positive ion mode. Separation was performed on a reversed phase (C18, 50 - 2.1 mm, 3.0 µm particle size) analytical column using methanol/acetonitrile/water/formic acid as the mobile phase. The retention time of bendamustine was approximately 1.15 minutes.

PK and statistical analysis

Obinutuzumab

PK of Obinutuzumab has been characterized in earlier development using basically population-PK modelling approach.

The population PK analysis was conducted via nonlinear mixed-effects modeling with software NONMEM 7.3.0. The PK data from studies BO20999, BO21000, BO21003, and BO21004 were assessed previously as this analysis was part of the documentation submitted in the CLL application.

In this application, the base model developed in the original report was used as a starting point but refined by the inclusion of data collected in studies GAO4753g and also study GAO4915g for the current analysis. The structured model was first established then followed by the development of the covariate model. Model evaluation was performed using informative graphics and various predictive check simulations.

The final population PK model was used to calculate (using Bayesian posthoc parameters) and summarize the individual derived PK parameters (terminal half-life [t1/2,term], effective half-life [t1/2,eff], CLinf, central volume [V1], and volume of steady-state [VSS]). Terminal and effective half-life were computed at steady-state when time-dependent clearance has already decreased to zero [Lötsch et al. 2002].

For all patients in the analysis dataset, the individual concentration-time courses were simulated using patients' individual PK parameters estimated from the model. For each time point, median concentration and 90% prediction interval were computed and illustrated graphically. Two dosing regimens were simulated: iNHL dosing regimen implemented in Study GAO4753g (1000 mg IV dosing every 4 weeks for 24 weeks, with the additional 1000 mg IV doses at days 8 and 15, and then 1000 mg every 2 months) and DLBCL dosing regimen implemented in Study GAO4915g (1000 mg IV dosing every 3 weeks for 24 weeks, with the additional 1000 mg IV doses at days 8 and 15). For important covariates, the effect of covariates was illustrated by comparison of concentrations over time for subsets of patients with the respective covariate values (or categories). The predicted individual exposure measures (Cmax, Ctrough, and AUC_{τ} with τ =21, 28, or 60 days, depending on the dosing regimen) at the last dosing cycle (separately for Induction and Maintenance periods for iNHL regimen) were computed and summarized by important covariates.

For the FL indication and similarly to the sensitivity analysis performed for patients with CLL in the original report, sensitivity analyses were performed for patients with iNHL, FL, or DLBCL by refitting the model to the data associated to those diseases only, separately for each, and comparison of model parameters and predictions with the final model. Individual predicted PK parameters were summarized by disease types and iNHL subtypes. Individual concentrations and exposure measures were simulated for the iNHL and DLBCL dosing regimens, and summarized by disease types, iNHL subtypes, and covariates as described above.

Bendamustine

The study included a DDI sub-study to explore the impact of obinutuzumab on the PK of bendamustine. This sub-study included 20 patients who underwent intensive PK sampling on Day 2 of Cycle 1 at the following times: pre-bendamustine infusion, immediately after the end of the infusion, and then 15, 30 and 45 minutes, and 1, 2, 3 and 6 hours after the end of the bendamustine infusion. Bendamustine PK was assessed in 10 patients who received bendamustine in combination with obinutuzumab and a comparison was made to bendamustine PK in 10 patients who received bendamustine alone. The impact of bendamustine on obinutuzumab PK was not assessed. Due to the different dose regimens for bendamustine in the 2 treatment arms, AUCinf and Cmax were dose-normalized to enable comparison.

Results

Obinutuzumab

Initial model (003imp)

Brief description of the model structure

The pharmacokinetics of monoclonal antibodies is usually described by a two-compartment model, either linear or with target-mediated disposition. The original population PK model of obinutuzumab was a two-compartment linear model with time-dependent clearance. In this model, clearance was the sum of non-specific time-independent clearance (CLinf) and time-dependent clearance (CLt) that exponentially decreased with time. The base model developed in the original analysis was a starting point for the model development. The model included body-size dependences for all model parameters using allometric scaling with the estimated power coefficients.

Model parameters

The parameters and the precision of their estimation are tabulated below.

Table 2 Parameter Estimates for Base Model 003imp

		Estimate	%RSE	95%CI		
k_{des} (day^{-1})	$exp(\theta_1)$	0.0607	6.47	0.0535-0.0689		
CL_T (L/day)	$exp(\theta_2)$	0.223	6.24	0.198 - 0.253		
CL_{inf} (L/day)	$exp(\theta_3)$	0.0894	1.66	0.0866-0.0924		
V_1 (L)	$exp(\theta_4)$	3.01	0.966	2.95 - 3.07		
V_2 (L)	$exp(\theta_5)$	1.24	3.87	1.15 - 1.34		
Q (L/day)	$exp(\theta_6)$	1.34	10.7	1.09 - 1.65		
$CL_{T,WT}$	θ_7	0.403	59.1	-0.0637 - 0.869		
$CL_{inf,WT}$	θ_8	0.837	9.75	0.677 - 0.997		
$V_{1,WT}$	θ_9	0.552	6.64	0.48 - 0.624		
$V_{2,WT}$	θ_{10}	1.06	14.7	0.754 - 1.37		
σ_L	θ_{11}	1.71	8.91	1.41 - 2.01		
σ_H	θ_{12}	0.11	3.87	0.102 - 0.119		
σ_{50}	θ_{13}	8.81	13.5	6.47 - 11.1		
Parameter		**Estimate**	**%RSE**	**95%CI**	**Variability**	**Shrinkage**
ω^2_{kdes}	Ω(1,1)	1.39	8.03	1.17 - 1.6	CV=118%	20.9%
ω^2_{CLT}	Ω(2,2)	1.31	17	0.872 - 1.75	CV=114%	25.2%
ω^2_{CLinf}	Ω(3,3)	0.191	6.73	0.166 - 0.216	CV=43.7%	9.5%
ω^2_{V1}	Ω(4,4)	0.0427	7.32	0.0366 - 0.0488	CV=20.7%	9.1%
ω^2_{V2}	Ω(5,5)	0.227	12.9	0.17 - 0.284	CV=47.7%	38.7%
ω^2_{Q}	Ω(6,6)	0.941	19.2	0.588 - 1.3	CV=97.0%	51.3%
ω^2_{EPS}	Ω(7,7)	0.226	8.4	0.189 - 0.263	CV=47.6%	3.1%
σ^2	Σ(1,1)	1	Fixed			2.2%

SE: Standard Error: %RSE: Relative Standard Error, RSE=100·SE/PE, where PE is parameter estimate. 95% CI: 95% confidence interval. CV: coefficient of variation computes as 100% multiplied by the square root of the variance.

Source: 003ParEst.csv, 003ParEstExp.csv

The suitability of the model was evaluated using graphical evaluation and statistics and precision of parameters estimates.

The full model 171imp (including all available data) was refined by the re-estimation of the model parameters using a larger dataset including all available data (see Table 1 for details on datasets). The final population PK model was used to calculate (using Bayesian posthoc parameters) for each patients the individual derived PK parameters. The data obtained are summarized below for each patients group.

Table 4. Summary of Conditional Predictions for Cmax, Ctrough, and AUCτ following iNHL Dosing Regimen, by Disease Type

The covariate factors and patients' individual random effects were used to compute PK parameters in each group following iNHL dosing regimen (1000 mg on Days 1, 8, and 15 of cycle 1, and on Day 1 of cycles 2-6, cycle duration 28 days; then every two months). Residual variability was not included in the simulations. CV was computed as standard deviation of the log-transformed data. CLL: chronic lymphocytic leukemia; iNHL: indolent non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma.

	Statistic	Disease Type			
		CLL	iNHL	DLBCL	MCL
Number of patients		342	469	130	20
Induction (Cycle 6, Day 140 to 168)					
C_{max} (µg/mL)	Mean (SD)	496.3 (179.8)	568.9 (189)	490.2 (179)	368 (153)
	Median (Range)	465.7 (171.5-1445.7)	539.3 (117-1331.6)	460.2 (234.4-1441.3)	345.2 (169.5-776.1)
	G. Mean (CV)	466.3 (0.35)	539.1 (0.33)	463.4 (0.33)	340.5 (0.41)
C_{trough} (µg/mL)	Mean (SD)	245 (159.9)	323.5 (165.4)	260.6 (155.9)	132.4 (126.8)
	Median (Range)	215.7 (7-1226.2)	288.8 (0.1-992.7)	218.8 (26.1-1152.3)	98.7 (2-497.3)
	G. Mean (CV)	192.5 (0.78)	276.9 (0.69)	223.8 (0.57)	73.4 (1.38)
AUC_τ (µg/mL* day)	Mean (SD)	9828 (4840)	11955 (4998)	9809 (4741)	6213 (4075)
	Median (Range)	8961 (1652-37410)	10956 (565-32470)	8780 (2486-36290)	5652 (1230-17573)
	G. Mean (CV)	8701 (0.51)	10927 (0.45)	8904 (0.44)	5069 (0.68)
Maintenance (Cycle 4 of Maintenance, Day 380 to 440)					
C_{max} (µg/mL)	Mean (SD)	343.7 (105.8)	384.3 (113.6)	355.3 (117.5)	279 (80.6)
	Median (Range)	324.2 (142-1080.4)	363.4 (116.9-842.7)	336.3 (171.3-990)	281.5 (146.9-467.5)
	G. Mean (CV)	329.8 (0.28)	368.9 (0.28)	339.2 (0.3)	268.1 (0.29)
C_{trough} (µg/mL)	Mean (SD)	82.1 (79.8)	123.7 (82.1)	107 (84.1)	37.2 (46.5)
	Median (Range)	65.5 (0.1-754.6)	106 (0-449.5)	88.9 (3.8-607.2)	19.7 (0-178.2)
	G. Mean (CV)	50.6 (1.2)	95 (1.05)	82.9 (0.76)	11.8 (2.37)
AUC_τ (µg/mL* day)	Mean (SD)	10396 (5839)	13161 (5961)	11491 (6105)	6440 (4081)
	Median (Range)	9328 (1652-54590)	12140 (565-37520)	10426 (2489-47170)	5720 (1229-17920)
	G. Mean (CV)	9061 (0.53)	11927 (0.46)	10268 (0.47)	5349 (0.65)

Source File: 171imp_NHL_Q4W_Cond_by_DIS.csv, 171imp_NHL_Q2M_Cond_by_DIS.csv
G.=geometric

Table 5. Summary of Conditional Predictions for Cmax, Ctrough, and AUCτ following iNHL Dosing Regimen, for iNHL patients by iNHL subtype

The covariate factors and patients' individual random effects were used to compute PK parameters in each group following the induction part of iNHL dosing regimen (1000 mg on Days 1, 8, and 15 of cycle 1, and on Day 1 of cycles 2-6, cycle duration 28 days; then every two months). Residual variability was not included in the simulations. CV was computed as standard deviation of the log-transformed data. WM: Waldenstrom macroglobulinemia, MZL: marginal zone lymphoma ; FL: follicular lymphoma , SLL: small lymphocytic lymphoma.

Statistic		iNHL subtype			
		WM	MZL	FL	SLL
Number of patients		5	35	406	22
Induction (Cycle 6, Day 140 to 168)					
C_{max} (µg/mL)	Mean (SD)	374.7 (203.2)	511.4 (189.7)	581.8 (187.6)	467.3 (150.6)
	Median (Range)	329.6 (117-670.5)	511.1 (227.6-1094.8)	550.2 (134.7-1331.6)	437.8 (221.1-840.2)
	G. Mean (CV)	324.1 (0.65)	481 (0.35)	553.5 (0.32)	444.4 (0.33)
C_{trough} (µg/mL)	Mean (SD)	185 (142.4)	274.4 (169.1)	335.5 (164.3)	214.2 (122.9)
	Median (Range)	171.8 (0.1-389.7)	236 (41.4-793.1)	306.1 (4.7-992.7)	205.6 (28.1-449.9)
	G. Mean (CV)	44.9 (3.5)	232.4 (0.6)	295 (0.56)	171.1 (0.78)
AUC_{τ} (µg/mL* day)	Mean (SD)	7308 (5072)	10432 (5064)	12308 (4959)	8959 (3906)
	Median (Range)	6770 (565-14452)	10047 (2919-26140)	11512 (1134-32470)	8188 (2767-17701)
	G. Mean (CV)	4905 (1.26)	9418 (0.46)	11362 (0.41)	8072 (0.49)

The final model was refitted with only FL data (called FL model, Model 171impD6). These data included 8545 samples from 406 patients with FL. Comparison of the predictions (PRED and IPRED) and goodness-of-fit between the final and FL models show that the population predictions are very similar, and individual predictions are nearly identical.

Obinutuzumab PKs in FL patients could be considered elucidated. The drug exhibits typical "Target Mediated Drug Disposition" (TMDD) PK behavior of anti-tumoural antibodies. The concentration-time course of obinutuzumab is adequately described by a two-compartment PK model with non-linear time-dependent clearance and steady-state PK parameters typical for a mAb. Obinutuzumab clearance was described as the sum of steady-state (time-independent) clearance and time-dependent clearance that decreased exponentially with time on treatment.

The original population PK analysis of obinutuzumab that was based on CLL and NHL data accurately described the PK of obinutuzumab. The parameters of the updated population PK model (model imp171 and imp171D) and the precision of their estimation, which included the data from studies GAO4753g and GAO4915g, were basically similar between the three models. Despite slight differences sensitivity analysis showed that the PK characteristics of obinutuzumab in patients with iNHL were similar to the PK findings in the combined population.

Special populations

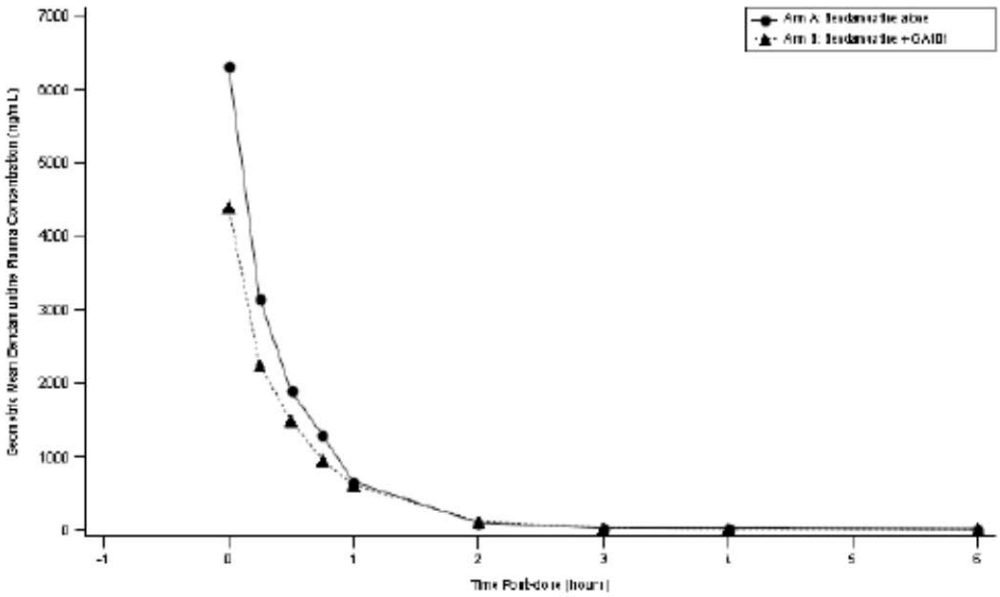
N/A

Pharmacokinetic interaction studies

Bendamustine

The mean Plasma/serum concentrations as a function of time, obtained in each arm (120 mg/m^2 of bendamustine versus 90 mg/m^2 of bendamustine in combination with obinutuzumab) is shown below (figure 7).

Figure 7 Plot of Geometric Mean Plasma Bendamustine Concetrations (ng/mL) versus Time on a Linear Scale:



A summary of the PK parameters for bendamustine is presented below in Tables 8 & 9.

Table 8 Summary of Plasma Bendamustine Pharmacokinetics (GAO4753g)

	Bendamustine	Bendamustine + GA101	Bendamustine/ Bendamustine + GA101	
	Geometric Mean (%CV)	Geometric Mean (%CV)	Ratio of Geometric Mean	95% CI for Ratio of Geometric Mean
Cmax (ng/mL)	7774.0 (59.0)	5255.0 (70.4)	1.44	(0.76, 2.71)
AUC(INF) (min*ng/mL)	508128.6 (66.2)	368794.0 (85.5)	1.42	(0.71, 2.83)
AUC(0-T) (min*ng/mL)	507794.4 (66.2)	368517.9 (85.5)	1.42	(0.71, 2.83)

*Median and range presented for Tmax

Treatment Arm A: Bendamustine

Treatment Arm B: Bendamustine + GA101

Table 9 Summary of dose-normalized Plasma Bendamustine Pharmacokinetics (GAO4753g)

		Bendamustine	Bendamustine + GA101	Bendamustine/ Bendamustine + GA101	
	n	Geometric Mean (%CV)	Geometric Mean (%CV)	Ratio of Geometric Mean	95% CI for Ratio of Geometric Mean
Cmax (ng/mL/mg)	10	26.39 (65.3)	23.78 (72.5)	1.11	(0.57, 2.16)
AUC(INF) (min*ng/mL/mg)	10	1684.07 (72.6)	1537.35 (87.7)	1.10	(0.53, 2.26)

Following IV administration of bendamustine, plasma data indicated a rapid elimination with a half-life (t1/2) of 24.6 minutes and 28.6 minutes, when bendamustine was given alone and in combination, respectively. There were no meaningful differences observed for bendamustine AUCinf and Cmax (dose-normalized) between the 2 treatment arms (the 95% CI for the ratio of geometric means includes 1). In addition, there were no meaningful differences in bendamustine t1/2, clearance or volume of distribution between the 2 treatment arms. Inter-subject variability was high with coefficients of variation (CV) ranging between 65.3–87.7% for Cmax and AUCinf (Table 9).

The DDI sub-study is insufficiently powered to allow any reliable conclusions regarding the influence of obinutuzumab co-administration on the bendamustine PKs. This is clearly illustrated by the 95% CI of Cmax and AUCinf ratios shown above. However, it is recognized that the occurrence of such PK interaction is not plausible.

Pharmacokinetics using human biomaterials

N/A

2.3.3. Pharmacodynamics

Mechanism of action

The primary pharmacodynamic effect of obinutuzumab is depletion of B cells and their subsequent recovery in the peripheral blood. In all studies, a rapid depletion of B cells was observed following the first obinutuzumab administration, which was maintained over the treatment cycles and follow-up. Human Anti-Human Antibodies (HAHA) for obinutuzumab and Human Anti-Chimeric Antibodies (HACA) for rituximab were evaluated in the G-Benda arm of the study.

B- Cell depletion

In Study GAO4753g, blood samples for immunophenotyping of B-cells were only assessed in patients in the G-benda arm (N =194).

B-cell depletion was defined as CD19-positive B-cell counts $<0.07x10^9$/L occurring after at least one dose of obinutuzumab had been administered. Time to depletion was defined as the number of days between the first intake of obinutuzumab and the date of the first CD19-positive B-cell count of $<0.07x10^9$/L. The extent of $CD19^+$B-cell depletion was defined as the lowest absolute counts for the individual (i.e., the nadir) across all visits.

B-cell recovery was defined as a CD19-positive B-cell count >0.07x10^9/L, in a patient whose previous CD19-positive B-cell count measurement revealed B-cell depletion. B-cell recovery was considered possible only after the patient had completed study treatment.

The time to B-cell recovery was defined as the time from B-cell depletion until B-cell recovery.

Of the 121 patients who had a CD19-positive B-cell result, 116 (96%) patients had B-cell depletion at the last obinutuzumab administration. B-cell recovery could not be assessed because of the low number of patients who have been followed for a sufficient length of time. At 6-12 months after the last obinutuzumab administration, only 26 patients had a B-cell assessment, and the B-cells had recovered in 1 of the 26 patients. Very few patients were available for B-cell assessment after 12 months. Considering only patients with documented recovery at the time of the data cutoff, the median time from the last antibody administration (LAA) to B-cell recovery was 660 days (~1.8 years) (range: 1- 746 days).

In study GAO4753g immunophenotyping of B-cells was performed in G-benda arm patients only. As bendamustine is expected to cause T-cell suppression, immunophenotyping of B-cells was not performed in the benda arm of the GAO4753g study.

Immunogenicity

HAHA (anti obinutuzumab antibody)

Among the 175 patients validly tested for HAHA at baseline (day-1, cycle-1) two patients were positive, in the G-benda arm (both at 1:10 titre) and both patients had an IRR the same day.

No patients had a positive HAHA result for anti-obinutuzumab antibodies after Cycle 1, Day 1.

The observed concentration time courses for the one patient with HAHA who continued to receive study treatment was similar to that of patients without detected HAHA.

The occurrence of HAHA evidenced in study GAO4753g (2 patients among 175) is unexpectedly much lower than that observed in study BO21004 (17 patients among 286).

HACA: (Anti-rituxumab antibodies)

As all patients participating in the trial had previously been exposed to rituximab, human anti-chimeric antibodies (HACA) for rituximab were also assessed. At baseline, 13 patients (7.4%) in the G-benda arm had a positive HACA result, including one of the patients described above. Two of these patients experienced Grade 3-4 IRRs on Cycle 1, Day 1.

Table 3: HACA positivity in study GAO4753g study.

Visit	HACA Positivity	G-B (N=194)
Baseline	NEGATIVE	162 (92.6%)
	POSITIVE	13 (7.4%)
	n	175
Cycle 1 Day 1	NEGATIVE	10 (90.9%)
	POSITIVE	1 (9.1%)
	n	11

Percentages are based on number of valid values.

13 patients (7.4%) were positive for HACA. Among them, 2 patients experienced grade 3-4 IRRs. The current EU SmPC includes the appropriate special warning and precautions with regards to IRR risk as well as the appropriate recommendations for dosing, premedication, prophylaxis monitoring and

management of patients experiencing IRRs. Therefore, no additional prophylaxis and premedication is proposed.

Primary and secondary pharmacology

2.3.4. PK/PD modelling

Exposure-Efficacy relationships

An attempt to characterize the exposure-Efficacy relationship in the pivotal GAO4753g study was made in the population PK analysis detailed above. The analyses, similar to the analysis performed for patients with CLL in study BO21004, were conducted separately for iNHL patients from Study GAO4753g and for DLBCL patients from Study GAO4915g. The objectives of the graphical analysis of the exposure-efficacy relationships of obinutuzumab for patients with iNHL (Study GAO4753g) were:

- To assess the relationships between the drug exposure and efficacy measures such as BOR, PFS, and OS and
- To assess the relationships between the drug exposure and pharmacodynamics parameters of the drug effect such as the observed tumour size and B-cell counts.

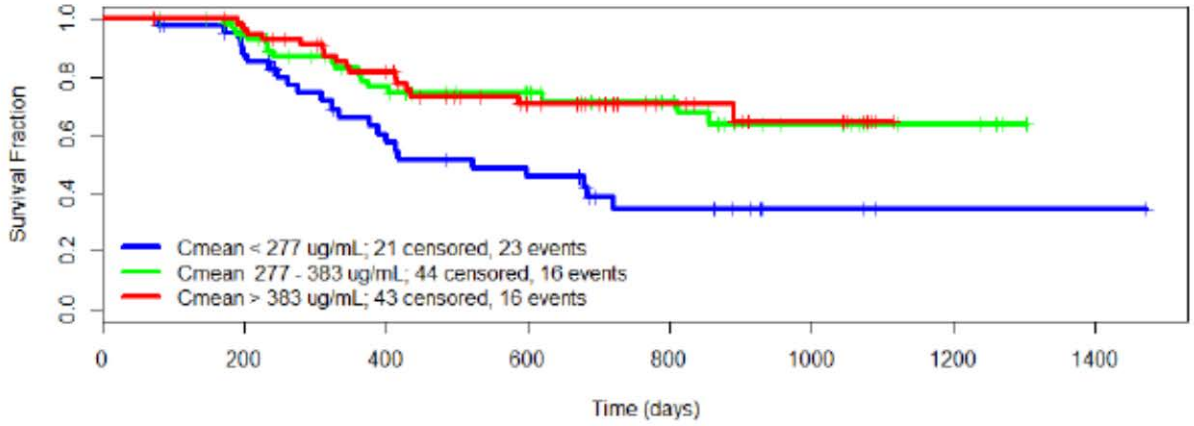
Exposure – efficacy relationships

There was high variability in time of achieving the complete response (CR), and median time to CR was close to 200 days. Median Cmean appeared to be higher in subjects with CR, compared to subjects in other response groups, both overall and in subjects with low baseline tumour size.

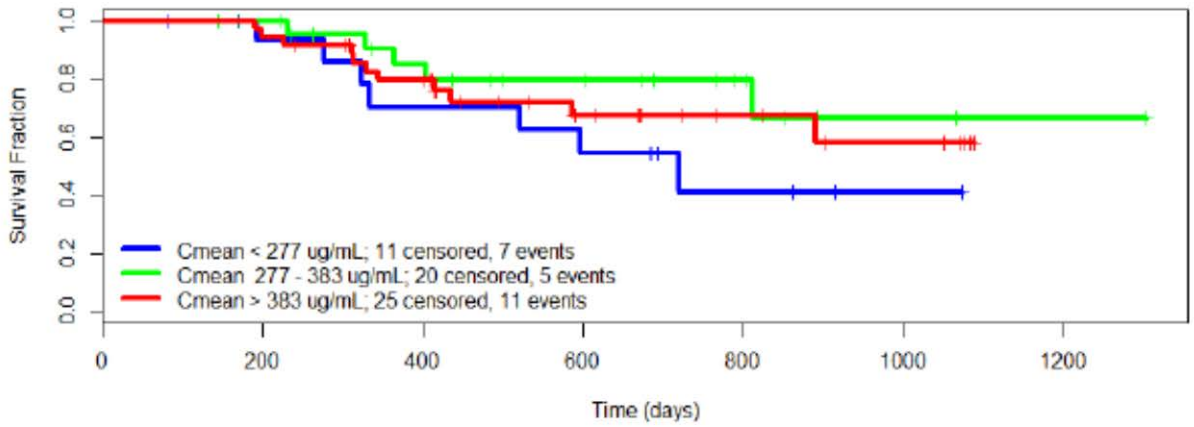
For PFS, subjects with events had a slightly lower median Cmean compared to subjects without events, overall and for subjects with high baseline tumour size; the distributions of Cmean were similar for subjects with low baseline tumour size. Among subjects with events, there were no differences in event times for subjects in different exposure tertiles (Figure 3). Kaplan-Meier plots (Figure 4) suggested that PFS was similar in medium and high exposure groups, and was lower in the low tertile of exposure. The effect was mostly due to the lower survival in the lowest exposure category for patients with high baseline tumour size.

For progression-free (PFS) and overall survival (OS), patients in higher exposure categories (medium and high tertiles of exposure) had longer survival compared to patients in lowest exposure tertile; the effect was mostly due to shorter survival in the lowest exposure tertile in patients with high baseline tumour size (figures 5 & 6).

Figure 4: Kaplan-Meier Plot for Progression-Free Survival, by Exposure Group (Cmean) in Study GAO4753g (iNHL)



Baseline Tumor size < 3067 mm^2



Baseline Tumor size >= 3067 mm^2

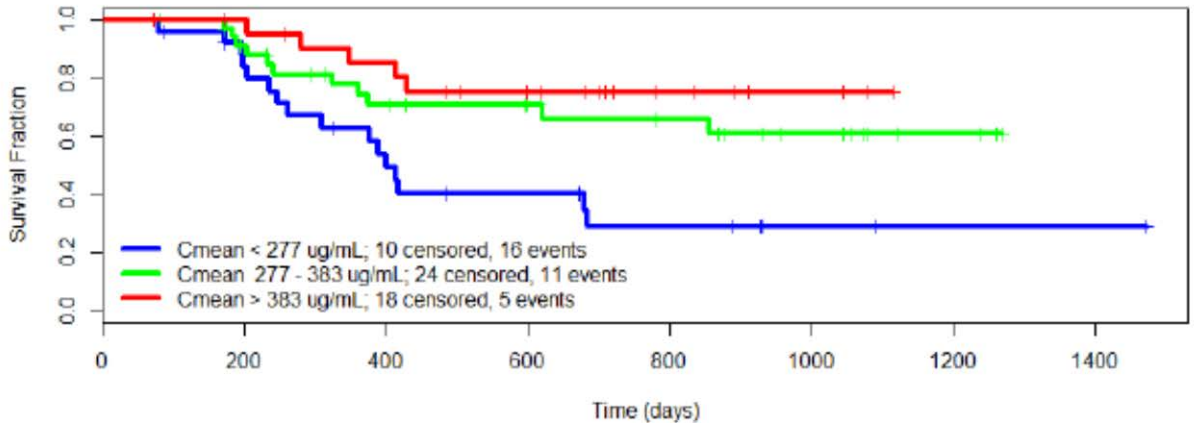
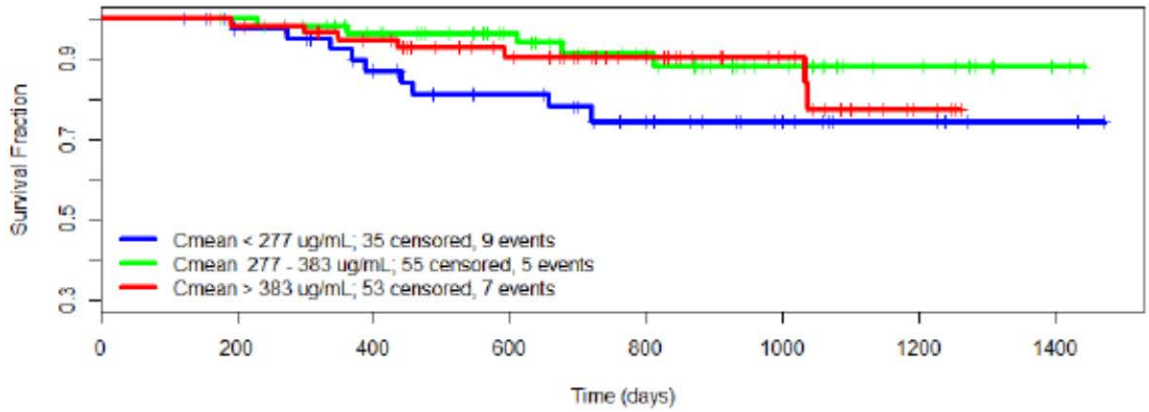
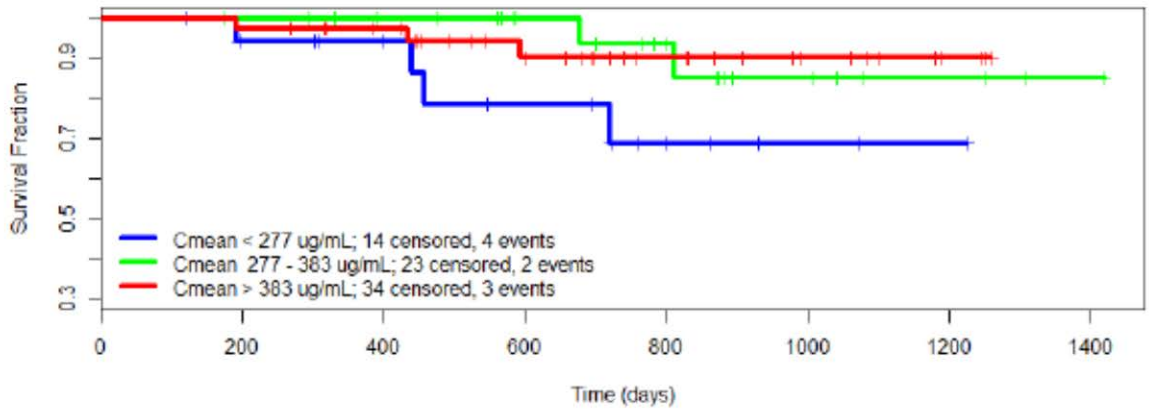


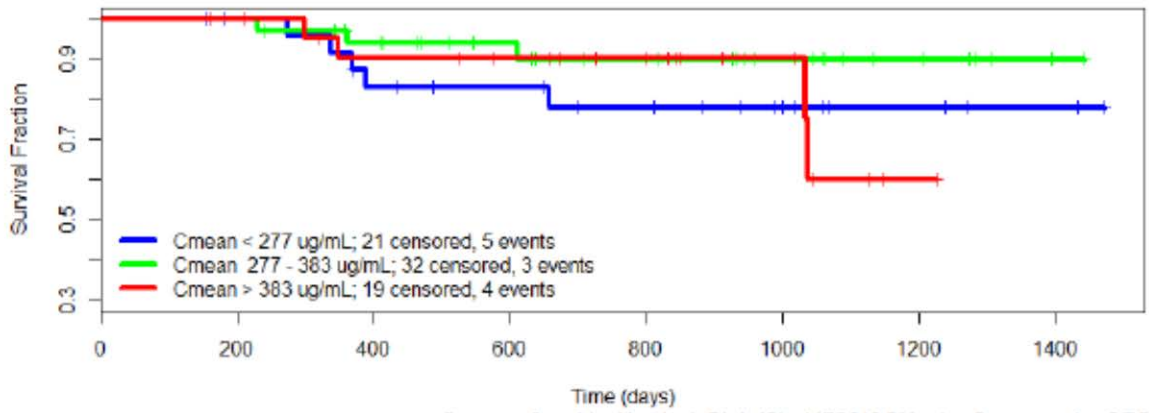
Figure 6: Kaplan-Meier Plot of overall Survival, by Exposure Group (Cmean) in Study GAO4753g (iNHL)



Baseline Tumor size < 3067 mm^2



Baseline Tumor size >= 3067 mm^2



Tumour size reduction compared to baseline was slightly greater in patients showing higher obinutuzumab exposure (80%, 85%, and 90% in the 1st, 2nd, and 3rd tertiles, respectively) (figure 7); however this result is confounded with slightly higher baseline tumour size in the lower categories of exposure.

Patients with complete response appeared to have higher exposure compared to patients in other response categories, overall and in patients with low (below median value) baseline tumour size.

The finding of a potential trend of increased efficacy parameters (change of tumour size, BOR, and PFS) in the medium and high exposure groups is similar to the results of the previous analysis for patients with CLL. It is important to note that for both iNHL and CLL patients this trend was observed for relationships unadjusted for key baseline prognostic factors. Thus, it could be due to potential confounding of exposure and prognosis of patients. The performed graphical analysis stratified patients only by baseline tumour size and not by other prognostic factors. This could represent a limitation of the methodology used in the analysis.

Similar graphical Exposure-Efficacy analyses have been conducted for the subpopulation of patients with FL in the GAO4753g study.

As seen in the overall population of patients with iNHL, the efficacy (PFS) of obinutuzumab-containing therapy in patients with FL appeared to be greater in patients with highest exposure to obinutuzumab than in patients with lower exposure to obinutuzumab. This finding was consistent with expectations since patients with FL made up the majority (almost 90%) of patients in the iNHL population in the GAO4753g study which were included in the exposure-PFS analysis. It is important to note that those Exposure-Efficacy graphical analyses were not adjusted for prognostic factors at baseline other than baseline tumour size. Therefore, the apparent association between higher exposure to obinutuzumab and better PFS could be due to confounding factors, such as differences in tumour burden, body weight, and other baseline demographic and prognostic factors. Further analyses of PFS/OS and exposure in patients with FL (i.e., Cox regression analyses), has been conducted. Overall the results of the exposure efficacy analyses in the FL population are consistent with the ones obtained in the iNHL population.

Exposure-Safety relationships

Exposure-safety relationship has been extensively investigated using the population-PK modelled analysis. Data from all patients enrolled in the G-benda arm receiving at least one dose has included in the analysis. No clear relationship between exposure level and the occurrence of any SAE has been evidenced.

2.3.5. Discussion on clinical pharmacology

Obinutuzumab exhibits typical “Target Mediated Drug Disposition” (TMDD) PK behavior of anti-tumoural antibodies. The concentration-time course of obinutuzumab is adequately described by a two-compartment PK model with non-linear time-dependent clearance and steady-state PK parameters typical for a mAb. Obinutuzumab clearance was described as the sum of steady-state (time-independent) clearance and time-dependent clearance that decreased exponentially with time on treatment.

The original population PK analysis of obinutuzumab that was based on CLL and NHL data accurately described the PK of obinutuzumab. The parameters of the updated population PK model (model imp171 and imp171D) and the precision of their estimation, which included the data from studies GAO4753g and GAO4915g, were similar between the three models. Despite slight differences sensitivity analysis showed that the PK characteristics of obinutuzumab in patients with iNHL were similar to the PK findings in the combined population.

Interference with other co-administered medication has been tested in the intitial submission. No significant interference of these medications (chlorambucil, bendamustine, cyclophosphamide, prednisone, vincristine doxorubicine, and fludarabine) with the method performances has been detected. The DDI sub-study included in this submission is insufficiently powered to allow any reliable conclusion regarding the influence of obinutuzumab co-administration on the bendamustine PKs. This is clearly illustrated by the 95% CI of Cmax and AUCinf ratios shown above. However, it is recognized that the occurrence of such PK interaction is not plausible.

Occurrence of HAHA in the GAO4753g study is low, however it is medically/scientifically plausible that the lower incidence of HAHA could be due to the fact that these patients had all been heavily treated with immunosuppressive medication or to inherent differences between iNHL and CLL in immunological reactivity. However, it is also possible that the difference in incidence of HAHAs with the supportive study is simply due to differences in the frequency and timing of HAHA sampling relative to completion of obinutuzumab therapy, and to the difference in number of patients sampled post-obinutuzumab treatment. Data to date do not suggest a correlation between HAHAs and disease progression in the GAO4753g study but these data need to be interpreted with care because most patients progressed on or soon after receiving obinutuzumab, and detection of HAHAs may be unreliable in this context.

As seen in the overall population of patients with iNHL, the efficacy (PFS) of obinutuzumab-containing therapy in patients with FL appeared to be greater in patients with highest exposure to obinutuzumab than in patients with lower exposure to obinutuzumab. This finding was consistent with expectations since patients with FL made up the majority (almost 90%) of patients in the iNHL population in the GAO4753g study which were included in the exposure-PFS analysis. It is important to note that those Exposure-Efficacy graphical analyses were not adjusted for prognostic factors at baseline other than baseline tumour size. Therefore, the apparent association between higher exposure to obinutuzumab and better PFS could be due to confounding factors, such as differences in tumour burden, body weight, and other baseline demographic and prognostic factors. Further analyses of PFS/OS and exposure in patients with FL (i.e., Cox regression analyses) conducted and are consistent with the ones obtained in the iNHL population. No clear relationship between exposure level and the occurrence of any SAE has been evidenced.

2.3.6. Conclusions on clinical pharmacology

Obinutuzumab pharmacokinetics in FL patients could be considered elucidated and in line with the knowledge of obinutuzumab PK in CLL.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose response study was submitted. The obinutuzumab dose selection was based on safety, efficacy and PK data in phase I studies (BO20999/BO21003), which indicated that an obinutuzumab dose of 1000 mg was the dose most likely to be well tolerated and efficacious in a majority of NHL patients regardless of their initial tumour burden. PK modelling also suggested that additional doses of obinutuzumab on day 8 and 15 of cycle 1 and then every 2 months beyond 6 months were needed in patients with iNHL to saturate target-mediated clearance thought to be indicative of clearance of CD19+ cells, and achieve and maintain a steady state of drug levels early, and throughout treatment (Gibarsky et al. 2014).

The preliminary data from phase I/II monotherapy studies showed a favourable safe profile of obinutuzumab treatment beyond 6 months to improve the clinical outcomes of patients otherwise treated with bendamustine alone. The dose of bendamustine was given according to the recommendations of the consensus conference for relapsed/refractory iNHL patients for bendamustine monotherapy and in combination with rituximab (Cheson et al. 2010).

2.4.2. Main study

GAO4753g

Study GAO4753g is an ongoing, open-label, multicentre, randomized Phase III study to investigate the efficacy and safety of bendamustine (benda) compared with bendamustine plus obinutuzumab (G-benda) in patients with rituximab-refractory, iNHL those patients who had no response to or who progressed within 6 months of treatment with rituximab or a rituximab-containing regimen.

Methods

Study participants

Patients were eligible to participate if they would fulfil all of the following inclusion criteria:

- History of histologically documented, CD20-positive, indolent NHL (including follicular lymphoma, Grades 1-3a; marginal zone lymphoma [including splenic, nodal, and extranodal] and small lymphocytic lymphoma with an absolute lymphocyte count < 5000 * 10^9/L).
- For each patient, a prior lymph node biopsy demonstrating CD20 positivity of tumour cells had to be available locally at the investigator site prior to dosing; this was to be further confirmed retrospectively following central pathology review.
- A bone marrow biopsy was insufficient for confirming pathology or CD20 positivity.
- A lymph-node biopsy to rule out transformation was required in patients for whom there was clinical suspicion of transformation.
- Refractory to a regimen containing rituximab, defined as no response to or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:
- Patients with progressive disease while receiving rituximab monotherapy (after at least one full cycle), rituximab + chemotherapy (after at least one full cycle), or rituximab maintenance treatment (after having received at least one full dose [375 mg/m2] of rituximab)
- Patients with no clinical response (PR or better) to a rituximab-containing regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Patients with disease relapse (after having achieved a clinical response) within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Rituximab-refractory as defined included patients who were refractory to any prior rituximab-containing regimen, not just the most recent regimen containing rituximab (Rituxan®, MabThera®).
- Previously treated with a maximum of four unique chemotherapy-containing treatment regimens ("unique treatment regimen" was defined as at least two cycles of treatment of a planned multidose regimen containing chemotherapy with or without antibody-based therapy).
- Prior autologous stem-cell transplant or radioimmunotherapy was permitted if it was completed more than 6 months prior to study entry.

- All patients had to have at least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan).
- Tumour response was based on the status of all areas of disease and assessed according to the modified response criteria for NHL (Cheson et al. 2007).
- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.

Patients were excluded from participation to the study if they met one of the following exclusion criteria:

- Prior use of any mAb (with the exception of anti-CD20 mAb within 3 months of the start of Cycle 1); prior treatment with obinutuzumab was not allowed
- Chemotherapy or other investigational therapy within 28 days prior to the start of Cycle 1
- Radiation therapy within 42 days prior to the start of Cycle 1
- Prior treatment with bendamustine within 2 years of the start of Cycle 1
- Patients with prior bendamustine treatment (i.e., > 2 years prior to the start of Cycle 1) were eligible if they met both of the following criteria:
- Achieved either a partial or complete response to the bendamustine regimen of at least 12 months in duration prior to relapse/progression and
- Experienced progression following a regimen containing an alkylating agent (e.g., cyclophosphamide, vincristine, prednisolone [CVP]) or an anthracycline (e.g., CHOP or etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin [EPOCH])
- Prior allogeneic stem-cell transplant
- History of severe allergic or anaphylactic reactions to mAb therapy (e.g., patients in whom re-dosing with rituximab would be contraindicated for safety reasons)
- History of sensitivity to mannitol
- Central nervous system (CNS) lymphoma, prior DLBCL, or histological evidence of transformation to a high-grade or diffuse large B-cell lymphoma
- History of other malignancy that could affect compliance with the protocol or interpretation of results
- Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix were generally eligible. Patients with a malignancy that had been treated, but not with curative intent, were also z excluded, unless the malignancy had been in remission without treatment for ≥ 2 years prior to enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or

hospitalization (relating to the completion of the course of antibiotics) within 4 weeks of the start of Cycle 1

- Patients with a history of confirmed PML
- Vaccination with a live vaccine less than 28 days prior to randomization
- Recent major surgery (within 4 weeks prior to the start of Cycle 1) other than for diagnosis
- Any of the following abnormal laboratory values:
- Creatinine > 1.5 * the upper limit of normal (ULN) (unless creatinine clearance normal) or creatinine clearance < 40 mL/min
- AST or ALT > 2.5 * ULN
- Total bilirubin ≥ 3 * ULN
- Platelet count< 100 * 10^9/L (unless due to underlying disease, as established by extensive bone marrow involvement)
- Neutrophil count < 1.5 * 10^9/L (unless due to underlying disease, as established by extensive bone marrow involvement)
- Hemoglobin < 9 g/dL (unless due to underlying disease, as established by extensive bone marrow involvement)
- Presence of positive test results for hepatitis B surface antigen (HBsAg); antibody to hepatitis B core antigen [anti-HBc]) with detectable viral load (i.e., positive hepatitis B virus [HBV] DNA); or hepatitis C (hepatitis C virus [HCV] antibody serology testing)
- Patients with chronic hepatitis B or seropositive occult (HBV) infection were excluded.
- Patients with seronegative occult HBV infection or past HBV infection (defined as anti-HBc positive and HBV DNA negative) could be eligible if they were willing to be followed according to the protocol for HBV DNA testing (limited to 20 patients). For HBV DNA testing see Section 4.5.1 of the protocol.
- Patients positive for HCV antibody were eligible only if polymerase chain reaction (PCR) was negative for HCV RNA.
- Known history of human immunodeficiency virus (HIV) seropositive status
- Positive test results for human T-Lymphotropic virus Type 1 (HTLV-1) virus in endemic countries (endemic countries included Japan, the Caribbean basin, South America, sub-Saharan Africa, and Melanesia)
- Women who were pregnant or lactating
- Fertile men or women of childbearing potential unless 1) surgically sterile or 2) using an adequate measure of contraception such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly
- Effective contraception was required while receiving obinutuzumab or bendamustine. For women, effective contraception was required to continue for ≥ 12 months after the last dose of obinutuzumab. For men, effective contraception was required to continue for ≥ 3 months after the last dose of obinutuzumab. For both men and women receiving bendamustine alone, effective contraception was required to continue for ≥ 3 months after the last dose of bendamustine.
- Ongoing corticosteroid use > 30 mg/day prednisone or equivalent

- Patients receiving corticosteroid treatment ≤ 30 mg/day prednisone or equivalent had to be documented to be on a stable dose 1 week prior to the baseline CT/MRI scans obtained during screening.

Treatments

A total of 413 patients were randomly assigned in a 1:1 ratio to the two study treatment arms to receive bendamustine alone (benda arm) or obinutuzumab in combination with bendamustine (G-benda arm).

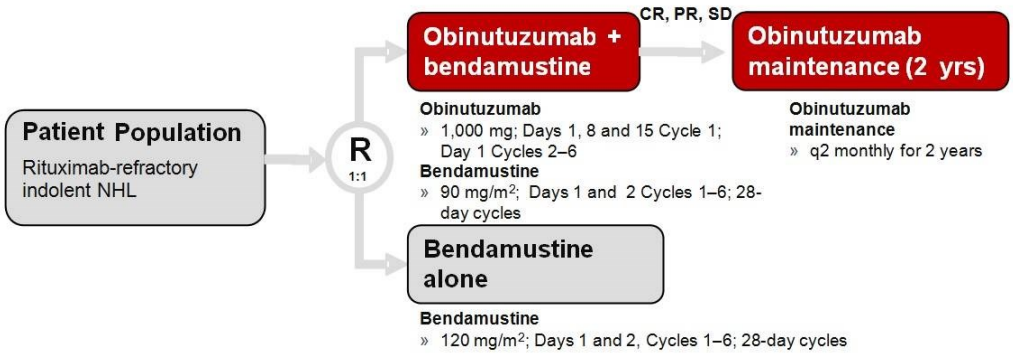


Figure 1. Overview of study design

Objectives

The primary objective of this study was to evaluate clinical benefit in terms of PFS, as assessed by an Independent Radiology Facility (IRF), for obinutuzumab when used in combination with bendamustine compared with bendamustine alone in patients with indolent NHL refractory to prior rituximab-containing therapy.

The secondary objectives were:

- To compare PFS as assessed by the investigator
- To compare OS between study arms
- To evaluate in each study arm and compare between study arms the following:
    1. ORR (rate of CR + PR) and CR rate at the study treatment completion/early study treatment termination visit;
    2. Best ORR achieved during treatment or within 12 months of the start of treatment;
    3. DFS in CR patients;
    4. Duration of response (DoR) in patients with CR and PR
- To compare EFS between the two study arms
- To evaluate and compare the safety profiles of patients treated with the combination of bendamustine + obinutuzumab and bendamustine alone
- To characterize the pharmacokinetics (PK) of obinutuzumab in combination with bendamustine and evaluate for drug-drug interactions by comparing the pharmacokinetics of the combination with the PK of bendamustine alone.
- To analyze pharmacoeconomics (medical resource utilization) in both arms of the study
- To assess patient-reported outcomes (PROs) in both treatment arms

Outcomes/endpoints

The primary efficacy endpoint was IRC-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse as assessed by an IRC according to the modified response criteria for NHL (Cheson et al, 2007), or to death from any cause.

The secondary efficacy endpoints were:

- PFS as assessed by investigator

- Best overall response (BOR) and best response of CR during treatment and up to 12 months after the start of treatment, as assessed by the IRC and by the investigator

- Complete response (CR) and overall response (CR or PR) rate at the end-of-induction (EOI)/early study treatment termination visit, as assessed by the IRC and by the investigator

- OS, defined as the time between the date of randomization and the date of death from any cause. Patients who were not reported as having died at the time of the analysis were censored at the date when they were last known to be alive, as documented by the investigator.

- Disease-free survival (DFS), defined for patients with a best overall response of CR, as the time from the first occurrence of a documented CR, as assessed by the IRC, until relapse defined on the basis of the IRC assessments or death from any cause on study.

- Duration of response (DoR), defined as the time from a best overall response of CR or PR to the first occurrence of progression/relapse (based on the IRC assessment) or death from any cause on study.

- Event-free survival (EFS), defined as the time between the date of randomization and the date of disease progression/relapse based on IRC assessments, death from any cause on study, or start of a new anti-lymphoma therapy (NALT).

- Medical resource utilization, which included the number of hospitalizations related to AEs (as captured in the electronic Case Report Form [eCRF] SAE section), types of subsequent drug therapies, and medical and surgical procedures (i.e., blood transfusions, bone marrow transplantation, or stem-cell transplantation). Analysis of data on medical resource utilization will be summarized in a separate report.

- Change in health-related patient-reported outcomes (PROs) from baseline, by visit, as assessed by the Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT-Lym) instrument.

- EuroQol-5 Dimension (EQ-5D) Health Index Scale summary scores at baseline, during treatment, and following treatment discontinuation or completion (both progression-free and after disease progression)

Sample size

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based upon the hypothesis with use of a two-sided stratified log-rank test at an overall 5% significance level. Two-sided level 0.05 log-rank test, 80% power to detect a hazard ratio (HR) of G-benda versus benda alone of 0.70 corresponding to a 43% improvement in median PFS from 9.3 to 13.3 months.

Two interim analyses of PFS were performed, one for futility when approximately 34% of PFS events had occurred and another for efficacy and futility when approximately 65% of the total PFS events had occurred (interim boundary is described in the study protocol). The futility boundary was non-binding with respect to the overall type I error and no adjustment was made for the early 20-patient, safety-only interim analysis.

Efficacy boundaries for PFS were computed with the use of the Lan-DeMets approximation to the O'Brien-Fleming boundary shape. The futility boundary was chosen so that a 95% confidence interval (CI) excluded the alternative hazard ratio of 0.7 when the observed monitoring statistic matched the futility boundary exactly.

Thereby a total of 260 PFS events, as assessed by the IRC were required for the final analysis of the trial.

With an initial accrual rate of 8.5 patients per month, and a 9-month ramp-up, then reducing to a revised assumed accrual rate after 44 months of 5 patients per month and 5% loss to follow-up per year, 410

patients enrolled over 54 months and followed for an additional 23 months were required to observe 260 IRC-assessed PFS events, with a total duration of approximately 77 months. For OS, under the assumption of a hazard ratio of 0.73, a total of approximately 96 months (i.e., 3.5 years after the last patient enrollment) were required to observe 226 deaths for 55%-65% power.

Randomisation

Eligible subjects were randomly assigned to the benda alone or G-benda arm at a ratio of 1:1 using the dynamic allocation method, based on the following stratification factors:

1. Indolent NHL subtype (follicular versus other)

2. Refractory type (rituximab monotherapy vs. rituximab + chemotherapy)

3. Number of prior therapies (≤2 vs. >2)

4. Geographic region.

Blinding (masking)

This was an open-label study.

The IDMC was responsible for reviewing the data at pre-specified timepoints per the statistical plan, while the Sponsor remained blinded to treatment arm allocation of the study data.

Statistical methods

PFS for patients without disease progression or death was censored at the time of the last IRC tumour assessment. If no IRC tumour assessments were performed after the baseline visit, PFS was censored at the time of randomization plus 1 day.

A two-sided stratified Log-Rank test at an overall 5% significance level was done to confirm the primary analysis. Estimates of the treatment effect are expressed as hazard ratios, estimated with the use of a stratified Cox model, including 95% confidence limits. Median PFS and the 95% confidence limits were estimated using Kaplan-Meier methodology using Greenwood's formula. An unstratified log-rank test was also performed as a sensitivity analysis.

Response rates were compared using a chi-square test. In addition, 95% confidence limits for the difference were calculated using Cochran-Mantel Haenszel.

To control the overall type 1 error rate at two-sided 5%, the fixed sequence testing procedure (Westfall and Krishen, 2001) was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. If the primary endpoint was positive, the key secondary endpoints were to be tested in the following order:

- PFS as assessed by the investigator
- BOR within 12 months of start of treatment as assessed by the IRC
- Best response of CR within 12 months of start of treatment as assessed by the IRC
- OS

Disease response measures (BOR, CR and overall response rates) were compared between the two treatment arms using stratified Cochran-Mantel-Haenszel tests.

Patients with no response assessments (for whatever reason) were considered non-responders. A non-stratified analysis calculating a X^2 test result is provided as a sensitivity analysis. In addition, response

rates and 95% confidence limits are given for each treatment group, and 95% confidence limits for the difference are calculated.

Analysis methods for OS and other time-to-event analyses were the same as those described for the primary efficacy. At the time of the primary analysis, an interim OS analysis was performed. Group sequential methods with the use of alpha-spending function with an O'Brien-Fleming boundary were used to control the type I error at the 0.05 level. A final OS analysis will take place after approximately 226 deaths have occurred.

Table 1. Planned analyses (Study GAO4753g)

			Efficacy			Futility		
No.	Time (Months)	IRC Events (%)	One-Sided Critical p-Value	HR	Cumulative Two-Sided Type I Error Spent	One-Sided Critical p-Value	HR	Cumulative One-Sided Type II Error Spent
1 (safety)	8	NA	NA	NA	NA	NA	NA	NA
2 (interim futility) [a]	40	100/ ~290 (34)	NA	NA	0.0009	>0.9164	1.338	0.001
3 (interim)	51	170 (65)	≤0.0075	0.68	0.015	>0.3715	0.951	0.023
4 (final)	77	260 (100)	≤0.0221	0.779	0.050	>0.0221	0.779	0.189

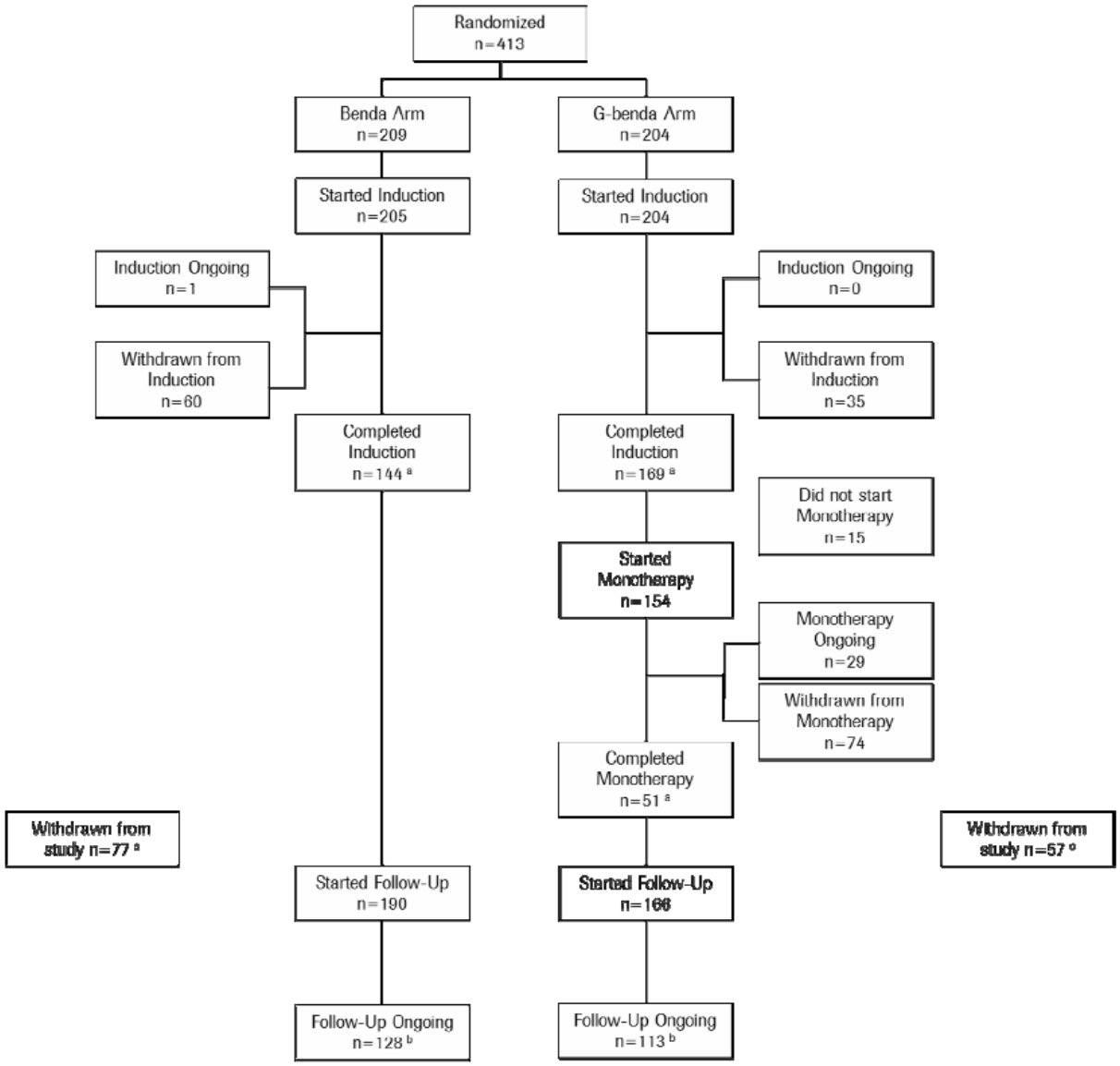
HR = hazard ratio; IRC = Independent Review Committee; NA = not applicable; PFS = progression-free survival.

[a] The early futility analysis was based on investigator-assessed PFS. All other analyses were based on IRC-assessed PFS.

Results

Participant flow

Figure 2 Participant flow (Study GAO4753g; Cut-off date: 1 May 2015)



Benda = bendamustine; G-benda = obinutuzumab + bendamustine.

[a] Six additional patients (2 in the benda arm and 4 in the G-benda arm) received their last dose of treatment before the clinical cutoff date for the updated analysis (1 May 2015), but their eCRF treatment completion page was completed after the clinical cutoff date.
A further 2 patients (1 patient in each treatment arm) had completed the eCRF treatment page but had not started Follow-up before the clinical cutoff date.

[b] Follow-up ongoing: patients have received their last treatment and are still being followed in the study.

[c] Withdrawn from study: withdrawal from study can be reported at any period of the study.

Recruitment

Patients were recruited from 82 investigational sites in 14 countries, the highest recruiting countries being Canada (24.0%), France (19.7%), USA (17.4%), Czech Republic (7.6%), and United Kingdom (7.3%). The first patient was randomized on 15 April 2010 and the last patient on 07 January 2015. The

data cut-off was 1 September 2014. The applicant submitted updated results with a cut-off date of 1 May 2015.

Conduct of the study

Main protocol amendments were:

In version 2 the bendamustine control arm regimen was modified from 90 mg/m2 to 120 mg/m2 - given on days 1 and 2 of a 28 day cycle; rituximab refractoriness was more clearly defined in the inclusion criteria. In version 3 exclusion criteria were modified to also exclude patients who had received bendamustine; rituximab – refractory iNHL was clarified to mean any prior line and not just the most recent; an early interim analysis for futility was added; the analysis of the FACT-Lym questionnaire was modified to capture changes in HRQoL based on minimally important differences. In Version 4 a number of changes were made to the eligibility criteria, clarifying parameters. In version 5 eligibility criteria were modified to allow the enrolment of patients previously treated with a bendamustine - containing regimen to reflect clinical practice. A country- specific amendment was made in version 6 to exclude patients with a history of PML; revised information about PML was included in version 7. In version 8 the protocol was amended to allow for an increase in the number of patients enrolled from 360 to 410 and to extend AE reporting period in the comparator arm; revised response criteria for malignant lymphoma were amended in appendix E.

Protocol violations occured by the cut-off of 1st September 2014 are listed in table 3

Table 2. Summary of protocol violations (Study GAO4753g; Data cut-off: 1 September 2014)

	B (N=198)	G-B (N=194)	No Treatment Given (N=4)
Number of Patients Enrolled	198	194	4
Number of Patients with at least one Protocol Deviation	8 (4.0%)	16 (8.2%)	3 (75.0%)
Protocol Deviations			
Number of Deviations	8	17	8
Number of Patients with each Deviation			
No documented history of CD20+ malignant disease	0	0	0
No bi-dimensionally measurable lesion (>1.5 cm in its largest dimension)	0	1	3
ECOG performance status > 2 at baseline	0	0	0
Evidence of significant, uncontrolled concomitant diseases	0	0	0
Not rituximab-refractory as defined in the protocol	1	7	0
Previously treated with > 4 unique chemotherapies	0	0	0
Prior treatment with bendamustine within 2 years of start of cycle 1	0	0	0
Positive HBsAg or HBV-DNA	0	1	0
Age < 18 years	0	0	0
Pregnancy or lactation	0	0	0
Missing lesion assessment at baseline	0	0	3
No test done for HBcAb and/or HBsAg	4	7	2
Indadequate HBV-DNA monitoring for patients with positive HBcAb result at baseline	3	1	0
Incorrect protocol treatment given versus randomized treatment arm	0	0	0
ICF not signed by patient prior to any study-related procedure being undertaken	0	0	0

Baseline data

Table 3. Demographic characteristics – Follicular lymphoma patients (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=171)	G-B (N=164)	Total (N=335)
Age (yr) at Baseline			
Mean	62.4	61.8	62.1
SD	11.0	11.2	11.1
Median	64.0	63.0	63.0
Min - Max	35 - 87	34 - 87	34 - 87
n	171	164	335
Age Group I (yr) at Baseline			
< 40	5 (2.9%)	7 (4.3%)	12 (3.6%)
>= 70	56 (32.7%)	39 (23.8%)	95 (28.4%)
40 - 59	58 (33.9%)	55 (33.5%)	113 (33.7%)
n	171	164	335
60 - 69	52 (30.4%)	63 (38.4%)	115 (34.3%)
Age Group II (yr) at Baseline			
< 60	63 (36.8%)	62 (37.8%)	125 (37.3%)
>= 60	108 (63.2%)	102 (62.2%)	210 (62.7%)
n	171	164	335
Age Group III (yr) at Baseline			
< 65	91 (53.2%)	92 (56.1%)	183 (54.6%)
>= 65	80 (46.8%)	72 (43.9%)	152 (45.4%)
n	171	164	335
Sex			
Male	98 (57.3%)	91 (55.5%)	189 (56.4%)
Female	73 (42.7%)	73 (44.5%)	146 (43.6%)
n	171	164	335
Ethnicity			
Hispanic or Latino	5 (2.9%)	5 (3.0%)	10 (3.0%)
Not Hispanic or Latino	139 (81.3%)	144 (87.8%)	283 (84.5%)
Not Reported	27 (15.8%)	15 (9.1%)	42 (12.5%)
n	171	164	335
Race			
American Indian or Alaska Native	2 (1.2%)	1 (0.6%)	3 (0.9%)
Asian	2 (1.2%)	4 (2.4%)	6 (1.8%)
Black or African American	3 (1.8%)	3 (1.8%)	6 (1.8%)
White	148 (86.5%)	144 (87.8%)	292 (87.2%)
Multiple	1 (0.6%)	0	1 (0.3%)
Unknown	15 (8.8%)	12 (7.3%)	27 (8.1%)
n	171	164	335

Height (cm) at Baseline			
Mean	169.56	169.76	169.66
SD	9.62	9.20	9.40
Median	170.00	170.00	170.00
Min - Max	149.0 - 193.5	150.0 - 188.0	149.0 - 193.5
n	168	162	330
Weight (kg) at Baseline			
Mean	82.06	80.12	81.10
SD	20.02	17.01	18.59
Median	80.00	80.00	80.00
Min - Max	38.2 - 155.9	46.0 - 126.0	38.2 - 155.9
n	165	161	326
Baseline Body Surface Area (m2)			
Mean	1.92	1.91	1.92
SD	0.25	0.22	0.24
Median	1.92	1.91	1.92
Min - Max	1.3 - 2.6	1.4 - 2.4	1.3 - 2.6
n	165	161	326
Baseline Body Mass Index (kg/m2)			
Mean	28.35	27.71	28.03
SD	5.75	4.98	5.39
Median	27.23	26.84	27.11
Min - Max	17.0 - 50.3	19.4 - 42.3	17.0 - 50.3
n	165	161	326
Geographic Region			
Eastern Europe	18 (10.5%)	19 (11.6%)	37 (11.0%)
North America	74 (43.3%)	67 (40.9%)	141 (42.1%)
Western Europe	79 (46.2%)	78 (47.6%)	157 (46.9%)
n	171	164	335

Table 4. Baseline disease characteristics – iNHL subtype (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=209)	G-B (N=204)	Total (N=413)
Diagnosis - iNHL Subtype			
Extranodal (MALT) marginal zone lymphoma	13 (6.2%)	13 (6.4%)	26 (6.3%)
Follicular non-Hodgkins lymphoma	171 (81.8%)	164 (80.4%)	335 (81.1%)
Nodal marginal zone lymphoma	5 (2.4%)	12 (5.9%)	17 (4.1%)
Small lymphocytic lymphoma	18 (8.6%)	12 (5.9%)	30 (7.3%)
Splenic marginal zone	1 (0.5%)	3 (1.5%)	4 (1.0%)
Other	1 (0.5%)	0	1 (0.2%)
n	209	204	413
iNHL Subtype			
Follicular	171 (81.8%)	164 (80.4%)	335 (81.1%)
Non-Follicular	38 (18.2%)	40 (19.6%)	78 (18.9%)
n	209	204	413

Table 5. Baseline disease characteristics – Follicular lymphoma patients (ITT population - Study GAO4753g; Data cut-off: 1 September 2014)

	B (N=166)	G-B (N=155)	Total (N=321)
Diagnosis - iNHL Subtype			
Follicular non-Hodgkins lymphoma	166 (100.0%)	155 (100.0%)	321 (100.0%)
n	166	155	321
ECOG at Baseline			
0-1	157 (95.7%)	147 (94.8%)	304 (95.3%)
2	7 (4.3%)	8 (5.2%)	15 (4.7%)
n	164	155	319
Ann Arbor Stage at Diagnosis			
I	9 (5.5%)	9 (5.8%)	18 (5.6%)
II	19 (11.5%)	15 (9.7%)	34 (10.6%)
III	45 (27.3%)	31 (20.0%)	76 (23.8%)
IV	82 (49.7%)	90 (58.1%)	172 (53.8%)
Unknown	10 (6.1%)	10 (6.5%)	20 (6.3%)
n	165	155	320
FLIPI No. of Adverse Factors Categories 1			
Low (0,1)	34 (20.6%)	42 (27.1%)	76 (23.8%)
Intermediate (2)	58 (35.2%)	47 (30.3%)	105 (32.8%)
High (>=3)	67 (40.6%)	60 (38.7%)	127 (39.7%)
Unknown	6 (3.6%)	6 (3.9%)	12 (3.8%)
n	165	155	320
FLIPI No. of Adverse Factors Categories 2			
Low (0)	10 (6.1%)	8 (5.2%)	18 (5.6%)
Intermediate (1-2)	82 (49.7%)	81 (52.3%)	163 (50.9%)
High (>=3)	67 (40.6%)	60 (38.7%)	127 (39.7%)
Unknown	6 (3.6%)	6 (3.9%)	12 (3.8%)
n	165	155	320
Bone Marrow Involvement at Baseline			
Yes	50 (32.3%)	42 (28.0%)	92 (30.2%)
No	100 (64.5%)	97 (64.7%)	197 (64.6%)
Indeterminate by morphology but negative by immunohistochemistry (IHC)	4 (2.6%)	1 (0.7%)	5 (1.6%)
Sample insufficient for evaluation	0	7 (4.7%)	7 (2.3%)
Other	1 (0.6%)	3 (2.0%)	4 (1.3%)
n	155	150	305
Extranodal Involvement			
Yes	76 (46.1%)	82 (52.9%)	158 (49.4%)
No	77 (46.7%)	63 (40.6%)	140 (43.8%)
Unknown	12 (7.3%)	10 (6.5%)	22 (6.9%)
n	165	155	320
Time from Initial Diagnosis to Randomization (years)			
Mean	4.24	4.37	4.30
SD	4.19	4.41	4.29
Median	2.96	3.07	3.04
Min - Max	0.3 - 29.9	0.3 - 32.1	0.3 - 32.1
n	166	155	321

Time from Initial Diagnosis to Randomization (years)			
< 1	24 (14.5%)	17 (11.0%)	41 (12.8%)
1-5	95 (57.2%)	95 (61.3%)	190 (59.2%)
> 5	47 (28.3%)	43 (27.7%)	90 (28.0%)
n	166	155	321
Bulky Disease at Baseline (6cm threshold)			
Yes	58 (35.4%)	49 (31.6%)	107 (33.5%)
No	106 (64.6%)	106 (68.4%)	212 (66.5%)
n	164	155	319
Serum LDH at Baseline			
Normal	108 (65.9%)	101 (65.6%)	209 (65.7%)
Elevated	56 (34.1%)	53 (34.4%)	109 (34.3%)
n	164	154	318
CD20 Positivity (Local Result)			
Positive	158 (95.8%)	146 (94.2%)	304 (95.0%)
Negative	5 (3.0%)	4 (2.6%)	9 (2.8%)
Unknown	2 (1.2%)	5 (3.2%)	7 (2.2%)
n	165	155	320
B2 Microglobulin (mg/L)			
< 3.5	118 (77.1%)	121 (81.2%)	239 (79.1%)
>= 3.5	35 (22.9%)	28 (18.8%)	63 (20.9%)
n	153	149	302

Table 6. Summary of the Rituximab Refractory Status (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

Stratified to:	B (N=209)	G-B (N=204)
Refractory to Rituximab Monotherapy	48 (23.0%)	38 (18.6%)
PD prior to last rituximab dose	4 (8.3%)	3 (7.9%)
Best response of SD	16 (33.3%)	8 (21.1%)
PD within 6 months of last rituximab dose	28 (58.3%)	27 (71.1%)
Refractory to Rituximab + Chemotherapy	161 (77.0%)	166 (81.4%)
PD prior to last rituximab induction dose	2 (1.2%)	5 (3.0%)
Best response of SD	27 (16.8%)	39 (23.5%)
PD within 6 months after last rituximab induction dose	60 (37.3%)	33 (19.9%)
PD during or within 6 months after last rituximab maintenance dose	70 (43.5%)	82 (49.4%)
PD within 6 months of last maintenance dose (no induction rituximab or last rituximab induction dose unknown)	1 (0.6%)	3 (1.8%)
PD more than 6 months after last rituximab dose but within 6 months after best response*	1 (0.6%)	1 (0.6%)
Not refractory	0 (0.0%)	3 (1.8%)

*Considered as refractory for purposes of stratification.

Numbers analysed

The intent-to-treat (ITT) population included all patients randomized in the study and is the primary population for analysis of efficacy: 194 patients in the G-benda arm and 202 patients in the benda arm.

The PK-evaluable population included all patients with the required PK data for the analyses: 183 patients (173 in the G-benda arm and 10 patients in the benda arm).

The safety population included all patients who received any amount of obinutuzumab or bendamustine therapy: 194 patients in the G-benda arm and 198 patients in the benda arm.

Outcomes and estimation

Primary endpoint – PFS assessed by IRC

Table 7. Summary of PFS by IRC assessment - all patients (ITT population - Study GAO4753g; Cut-off date: 1 May 2015)

	B (N=209)	G-B (N=204)
Patients included in analysis	209 (100.0%)	204 (100.0%)
Patients with event (%)	125 (59.8%)	87 (42.6%)
Earliest contributing event		
Death	10	13
Disease Progression	115	74
Patients without event (%)*	84 (40.2%)	117 (57.4%)
Time to event(months)		
Median	14.1	29.2
95% CI for Median	(11.7, 16.6)	(20.5, NE)
25% and 75%-ile	8.5, 29.3	10.7, NE
Range	0.0 to 53.4	0.0 to 54.1
Time Point Analysis		
0.5 year		
Patients remaining at risk	166	168
Event free proportion	88.41	91.76
95% CI	(83.06, 92.14)	(86.90, 94.87)
1 year		
Patients remaining at risk	94	119
Event free proportion	57.53	70.81
95% CI	(49.90, 64.42)	(63.56, 76.88)
1.5 years		
Patients remaining at risk	54	91
Event free proportion	38.46	60.34
95% CI	(30.97, 45.88)	(52.63, 67.19)
2 years		
Patients remaining at risk	35	66
Event free proportion	31.41	55.23
95% CI	(24.17, 38.89)	(47.29, 62.45)
2.5 years		
Patients remaining at risk	19	44
Event free proportion	24.03	48.80
95% CI	(16.99, 31.77)	(40.50, 56.58)
3 years		
Patients remaining at risk	12	27
Event free proportion	21.03	47.27
95% CI	(14.00, 29.04)	(38.71, 55.34)
4 years		
Patients remaining at risk	1	4
Event free proportion	15.77	40.18
95% CI	(7.02, 27.69)	(28.39, 51.67)

Stratified Analysis	
p-value (log-rank)	<.0001
Hazard Ratio	0.53
95% CI	(0.40, 0.70)
Unstratified Analysis	
p-value (log-rank)	<.0001
Hazard Ratio	0.55
95% CI	(0.42, 0.73)

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: iNHL Subtype, Prior Therapies, Refractory Type.

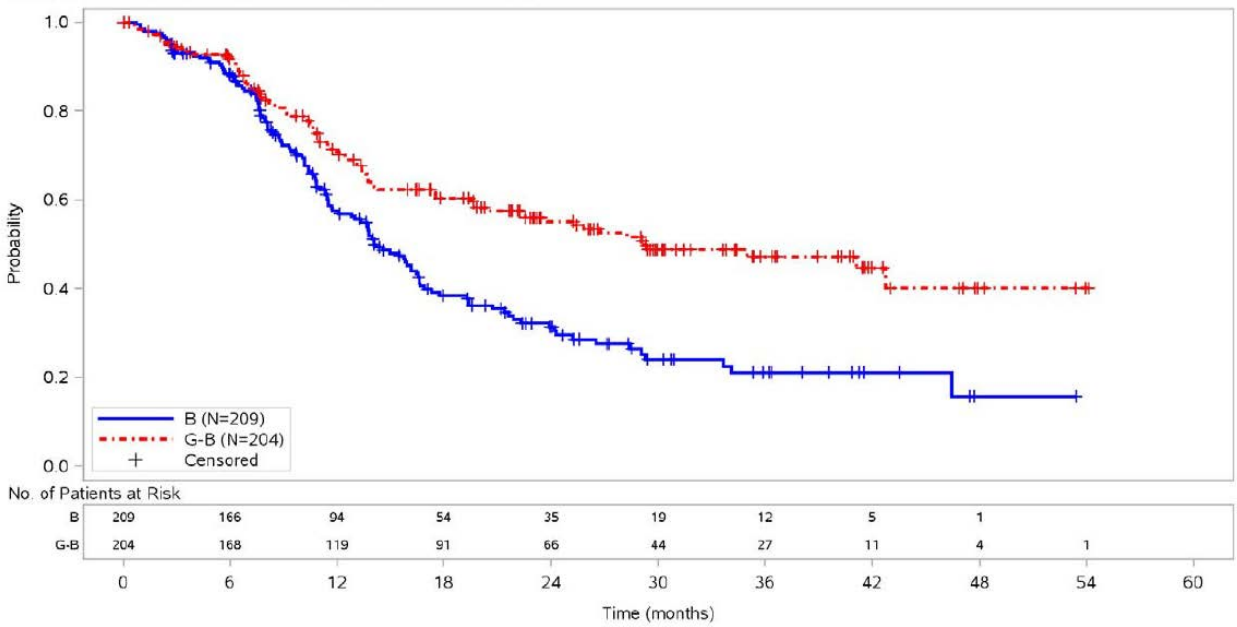


Figure 3. Kaplan-Meier plot of PFS by IRC assessment - all patients (ITT population - study GAO4753g; Cut-off date: 1 May 2015)

Secondary endpoint – PFS by investigator

Table 8. PFS by investigator (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=209)	G-B (N=204)
Patients included in analysis	209 (100.0%)	204 (100.0%)
Patients with event (%)	133 (63.6%)	95 (46.6%)
Earliest contributing event		
Death	9	13
Disease Progression	124	82
Patients without event (%)*	76 (36.4%)	109 (53.4%)
Time to event(months)		
Median	14.0	25.8
95% CI for Median	(11.5, 16.0)	(20.2, 42.7)
25% and 75%-ile	8.5, 25.6	10.5, NE
Range	0.0 to 53.4	0.0 to 54.1
Time Point Analysis		
0.5 year		
Patients remaining at risk	166	170
Event free proportion	88.34	89.83
95% CI	(82.97, 92.10)	(84.68, 93.32)
1 year		
Patients remaining at risk	94	124
Event free proportion	56.19	70.23
95% CI	(48.60, 63.09)	(63.11, 76.24)
1.5 years		
Patients remaining at risk	55	96
Event free proportion	35.87	59.16
95% CI	(28.70, 43.08)	(51.62, 65.93)
2 years		
Patients remaining at risk	38	69
Event free proportion	30.17	52.32
95% CI	(23.27, 37.35)	(44.56, 59.50)
2.5 years		
Patients remaining at risk	22	47
Event free proportion	22.61	47.49
95% CI	(16.17, 29.71)	(39.57, 54.98)
3 years		
Patients remaining at risk	15	28
Event free proportion	21.42	44.89
95% CI	(15.01, 28.59)	(36.64, 52.78)
4 years		
Patients remaining at risk	1	5
Event free proportion	17.31	38.27
95% CI	(10.54, 25.47)	(27.12, 49.31)
Stratified Analysis		
p-value (log-rank)	<.0001 (SIGNIFICANT)	
Hazard Ratio	0.52	
95% CI	(0.40, 0.68)	
Unstratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.55	
95% CI	(0.42, 0.72)	

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: iNHL Subtype, Prior Therapies, Refractory Type.

Secondary endpoint – Best Overall response (IRC-assessed)

Table 9. Best Overall response based on IRC assessment - all patients (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=209)		G-B (N=204)
n	209		204
Objective Response (CR,PR)	162 (77.5%)		154 (75.5%)
95% CI (Clopper-Pearson)	(71.24, 82.98)		(69.00, 81.23)
Difference (G-B vs. B)		-2.02	
95% CI (Hauck-Anderson)		(-10.46, 6.42)	
P-Value* (Cochran-Mantel-Haenszel)		0.5240 (NOT SIGNIFICANT)	
Odds Ratio (G-B vs. B)		0.86	
95% CI		(0.54, 1.36)	
Complete Response (CR)	36 (17.2%)		33 (16.2%)
95% CI (Clopper-Pearson)	(12.37, 23.04)		(11.40, 21.96)
Partial Response (PR)	126 (60.3%)		121 (59.3%)
95% CI (Clopper-Pearson)	(53.31, 66.97)		(52.23, 66.12)
Stable Disease (SD)	25 (12.0%)		28 (13.7%)
95% CI (Clopper-Pearson)	(7.89, 17.15)		(9.32, 19.22)
Progressive Disease (PD)	12 (5.7%)		10 (4.9%)
95% CI (Clopper-Pearson)	(3.00, 9.81)		(2.38, 8.83)
Unable to Evaluate (NE)	2 (1.0%)		2 (1.0%)
95% CI (Clopper-Pearson)	(0.12, 3.41)		(0.12, 3.50)
Missing (NA)	8 (3.8%)		10 (4.9%)
95% CI (Clopper-Pearson)	(1.67, 7.40)		(2.38, 8.83)

n is based on the number of patients who have at least one post-baseline assessment, or have withdrawn from study prior to the first response assessment. * P-Values based on stratified Cochran-Mantel-Haenszel. Stratification factors: iNHL Subtype, Prior Therapies, Refractory Type.

Secondary endpoint – Disease-free survival (IRC-assessed)

Table 10. Summary of Disease-Free Survival in patients with CR assessed by IRC - all patients (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=37)	G-B (N=46)
Patients included in analysis	37 (100.0%)	46 (100.0%)
Patients with event (%)	17 (45.9%)	4 (8.7%)
Earliest contributing event		
Death	1	0
Disease Progression	16	4
Patients without event (%)*	20 (54.1%)	42 (91.3%)
Time to event (months)		
Median	13.2	NE
95% CI for Median	(8.5, NE)	NE
25% and 75%-ile	6.9, NE	NE
Range	0.0 to 40.7	0.0 to 44.6
Time Point Analysis		
0.5 year		
Patients remaining at risk	24	37
Event free proportion	80.11	97.67
95% CI	(62.72, 89.99)	(84.62, 99.67)
1 year		
Patients remaining at risk	15	27
Event free proportion	55.54	91.26
95% CI	(36.30, 71.08)	(74.99, 97.14)
1.5 years		
Patients remaining at risk	12	22
Event free proportion	48.13	87.75
95% CI	(29.41, 64.60)	(70.23, 95.29)
2 years		
Patients remaining at risk	8	12
Event free proportion	43.76	87.75
95% CI	(25.30, 60.83)	(70.23, 95.29)
2.5 years		
Patients remaining at risk	5	7
Event free proportion	43.76	87.75
95% CI	(25.30, 60.83)	(70.23, 95.29)
3 years		
Patients remaining at risk	1	2
Event free proportion	43.76	87.75
95% CI	(25.30, 60.83)	(70.23, 95.29)
4 years		
Patients remaining at risk	NE	NE
Event free proportion	NE	NE
95% CI	NE	NE
Stratified Analysis		
Hazard Ratio	0.13	
95% CI	(0.04, 0.45)	
Unstratified Analysis		
Hazard Ratio	0.15	
95% CI	(0.05, 0.45)	

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: iNHL Subtype, Prior Therapies, Refractory Type.

Secondary endpoint – Overall Survival

At the time of the efficacy update (1 May 2015), a total of 98 patients had died, 56 patients (26.8%) in the benda arm and 42 patients (20.6%) in the G-benda arm. OS data for the ITT population remain immature; further follow-up of OS will be performed.

Table 11. Summary of OS - all patients (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=209)	G-B (N=204)
Patients included in analysis	209 (100.0%)	204 (100.0%)
Patients with event (%)	56 (26.8%)	42 (20.6%)
Earliest contributing event		
Death	56	42
Patients without event (%)*	153 (73.2%)	162 (79.4%)
Time to event(months)		
Median	NE	NE
95% CI for Median	NE	NE
25% and 75%-ile	25.3, NE	34.9, NE
Range	0.0 to 58.0	0.4 to 55.2
Time Point Analysis		
0.5 year		
Patients remaining at risk	187	182
Event free proportion	94.58	94.50
95% CI	(90.43, 96.96)	(90.28, 96.91)
1 year		
Patients remaining at risk	151	164
Event free proportion	86.08	89.66
95% CI	(80.33, 90.24)	(84.42, 93.21)
1.5 years		
Patients remaining at risk	131	142
Event free proportion	81.27	85.71
95% CI	(74.85, 86.21)	(79.83, 89.98)
2 years		
Patients remaining at risk	106	108
Event free proportion	76.67	80.39
95% CI	(69.67, 82.26)	(73.66, 85.56)
2.5 years		
Patients remaining at risk	76	85
Event free proportion	71.89	78.77
95% CI	(64.26, 78.18)	(71.75, 84.23)
3 years		
Patients remaining at risk	49	57
Event free proportion	66.57	74.40
95% CI	(58.06, 73.76)	(66.37, 80.79)
4 years		
Patients remaining at risk	11	16
Event free proportion	60.65	72.45
95% CI	(50.17, 69.59)	(63.56, 79.51)

Stratified Analysis	
p-value (log-rank)	0.1137 (NON-SIGNIFICANT)
Hazard Ratio	0.72
95% CI	(0.48, 1.08)
Unstratified Analysis	
p-value (log-rank)	0.1018
Hazard Ratio	0.72
95% CI	(0.48, 1.07)

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: iNHL Subtype, Prior Therapies, Refractory Type.

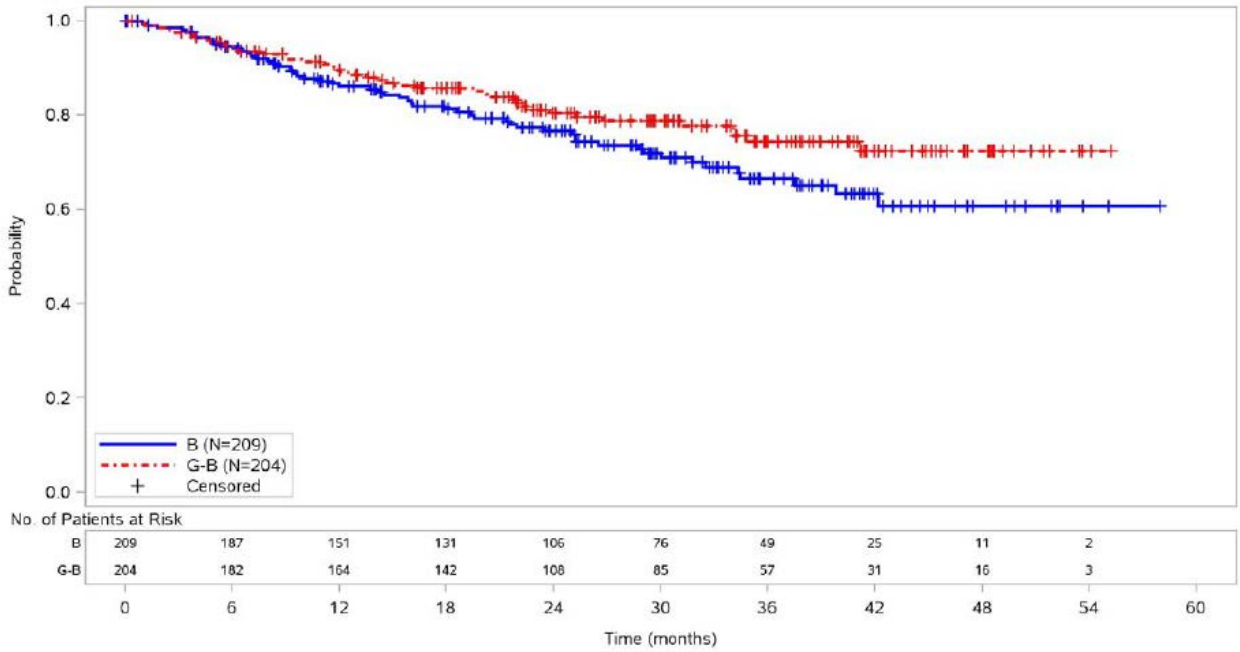


Figure 4. Kaplan-Meier plot of OS (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

Ancillary analyses

PFS in subgroups

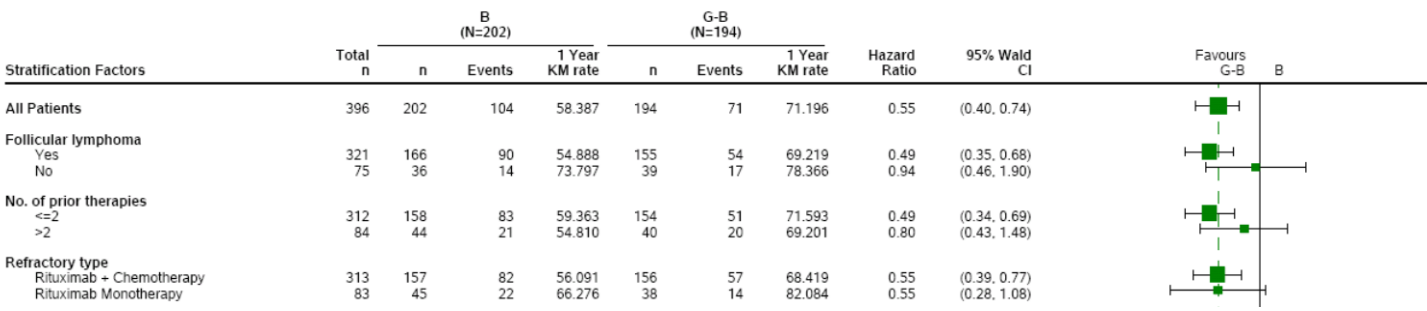
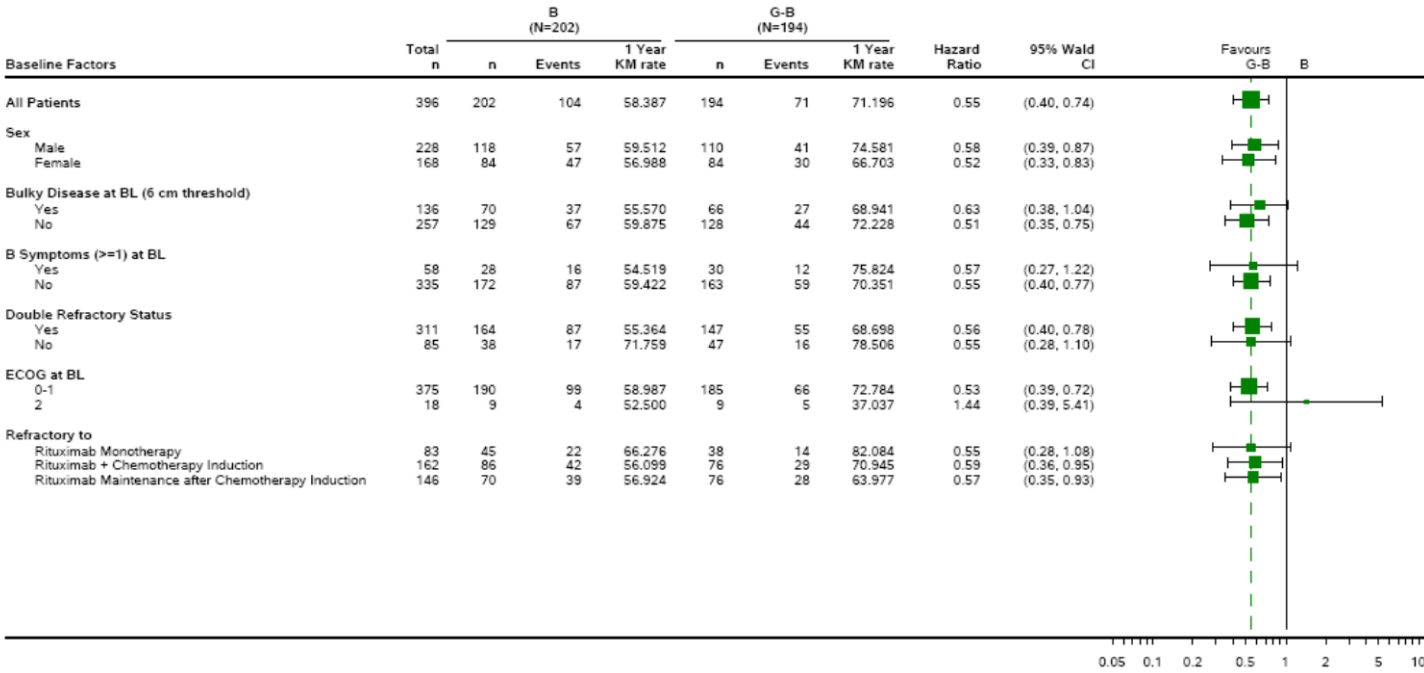


Figure 5. Forest Plot of Hazard Ratios for PFS Assessed by IRC by Subgroup: Randomization Stratification Factors (ITT population - Study GAO4753g; Data cut-off: 1 September 2014)



Unstratified hazard ratio is displayed. x-axis with logarithmic scale.
CI = confidence interval, NE = not evaluable.

Figure 6. Forest Plot of Hazard Ratios for PFS Assessed by IRC by Subgroup: Demographic and Baseline Disease Characteristics (ITT population - Study GAO4753g; Data cut-off: 1 September 2014)

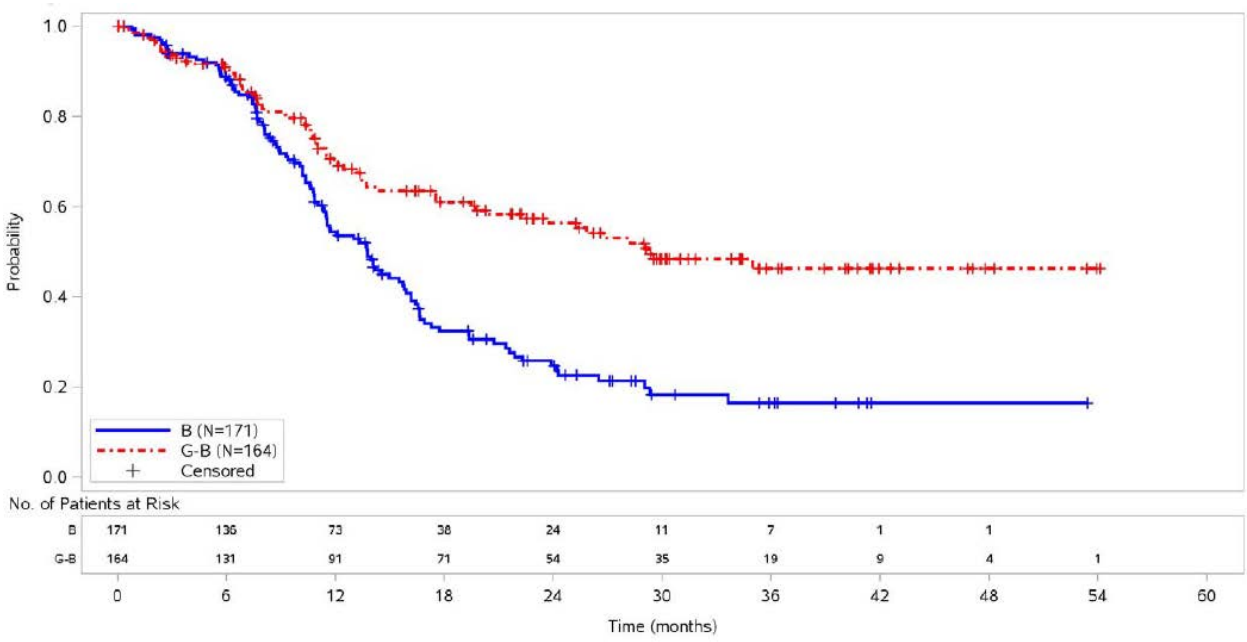
PFS by IRC assessment in patients with follicular lymphoma

Table 12. Summary of PFS by IRC Assessment in Patients with FL (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)

	B (N=171)	G-B (N=164)
Patients included in analysis	171 (100.0%)	164 (100.0%)
Patients with event (%)	108 (63.2%)	67 (40.9%)
Earliest contributing event		
Death	8	9
Disease Progression	100	58
Patients without event (%)*	63 (36.8%)	97 (59.1%)
Time to event(months)		
Median	13.8	29.2
95% CI for Median	(11.5, 15.8)	(20.5, NE)
25% and 75%-ile	8.5, 23.9	11.0, NE
Range	0.0 to 53.4	0.0 to 54.1
Time Point Analysis		
0.5 year		
Patients remaining at risk	136	131
Event free proportion	88.89	91.01
95% CI	(82.93, 92.85)	(85.28, 94.58)
1 year		
Patients remaining at risk	73	91
Event free proportion	54.43	69.92
95% CI	(45.93, 62.16)	(61.60, 76.77)
1.5 years		
Patients remaining at risk	38	71
Event free proportion	32.43	61.06
95% CI	(24.55, 40.55)	(52.29, 68.71)
2 years		
Patients remaining at risk	24	54
Event free proportion	24.81	56.38
95% CI	(17.51, 32.79)	(47.37, 64.43)
2.5 years		
Patients remaining at risk	11	35
Event free proportion	18.39	48.42
95% CI	(11.54, 26.52)	(38.99, 57.21)
3 years		
Patients remaining at risk	7	19
Event free proportion	16.55	46.40
95% CI	(9.79, 24.86)	(36.59, 55.64)
4 years		
Patients remaining at risk	1	4
Event free proportion	16.55	46.40
95% CI	(9.79, 24.86)	(36.59, 55.64)
Stratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.47	
95% CI	(0.34, 0.64)	
Unstratified Analysis		
p-value (log-rank)	<.0001	
Hazard Ratio	0.48	
95% CI	(0.35, 0.65)	

*Censored.
Summaries of time to event (median, percentiles) are based on Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Stratification factors: Prior Therapies, Refractory Type.

Figure 7. Kaplan Meier Plot of IRC-assessed PFS in Patients with FL (ITT population - Study GAO4753g; Data cut-off: 1 May 2015)



Comparison of efficacy in patients with iNHL vs. FL

Table 13. Comparison of Efficacy in Patients with Indolent NHL (ITT) and Subgroup of Patients with FL (Study GAO4753g; Data cut-off: 1 September 2014)

	iNHL (ITT)		FL sub-group	
Parameter	benda n=202	G-benda n=194	benda n=166	G-benda n=155
PFS (IRC)				
Patients with event	104 (51.5%)	71 (36.6%)	90 (54.2%)	54 (34.8%)
median (months)	14.9	NE	13.8	NE
HR [95% CI]; stratified*	0.55 [0.40, 0.74]		0.48 [0.34, 0.68]	
PFS (INV)				
Patients with event	115 (56.9%)	77 (39.7%)	102 (61.4%)	62 (40.0%)
median (months)	14.0	29.2	13.7	29.2
HR [95% CI]; stratified*	0.52 [0.39, 0.70]		0.48 [0.35, 0.67]	
Response (IRC-assessed)**				
Best response				
Overall (CR/PR)	76.6%	78.6%	77.0%	79.7%
CR	17.3%	16.7%	19.3%	15.7%
EOI treatment Response	63.0%	69.1%	62.6%	70.5%
DoR (IRC)	n=154	n=154	n=127	n=122
Patients with event	85 (55.2%)	48 (31.2%)	74 (58.3%)	36 (29.5%)
median (months)	13.2	NE	11.9	NE
HR [95% CI]; stratified*	0.42 [0.29, 0.61]		0.36 [0.24, 0.54]	
DFS (IRC) (patients with CR)	n=35	n=42	n=31	n=32
Patients with event	16 (45.7%)	2 (4.8%)	15 (48.4%)	2 (6.3%)
median (months)	13.2	NE	13.0	NE
HR [95% CI]; stratified*	0.09 [0.02, 0.40]		0.10 [0.02, 0.44]	
EFS (IRC)				
Patients with event	121 (59.9%)	83 (42.8%)	105 (63.3%)	64 (41.3%)
median (months)	13.7	26.8	11.8	28.3
HR [95% CI], stratified*	0.57 [0.43, 0.76]		0.52 [0.38, 0.71]	
Overall survival				
Patients with event	41 (20.3%)	34 (17.5%)	36 (21.7%)	25 (16.1%)
median (months)	NE	NE	NE	NE
HR [95% CI]	0.82 [0.52, 1.30]		0.71 [0.43, 1.19]	

iNHL = indolent non-Hodgkin Lymphoma; NE = not estimated.

* stratification factors for FL population were refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2).

** during treatment and within 12 months after start of treatment.

Table 14. Overview of efficacy in follicular lymphoma patients (Study GAO4753g; initial and updated analyses)

Cutoff date	1 September 2014		1 May 2015	
Parameter	benda n = 166	G-benda n = 155	benda n = 171	G-benda n = 164
PFS (IRC)				
Patients with event	90 (54.2%)	54 (34.8%)	108 (63.2%)	67 (40.9%)
Median (95% CI) (mo)	13.8 (11.4, 16.2)	NE (22.5, NE)	13.8 (11.5, 15.8)	29.2 (20.5, NE)
HR [95% CI]; stratified p-value*	0.48 [0.34, 0.68]; p < 0.0001		0.47 [0.34, 0.64]; p < 0.0001	
PFS (INV)				
Patients with event	102 (61.4%)	62 (40.0%)	118 (69.0%)	76 (46.3%)
Median (95% CI) (mo)	13.7 (11.0,15.5)	29.2 (17.5, NE)	13.6 (10.9, 14.8)	25.8 (17.5, NE)
HR [95% CI]; stratified p-value*	0.48 [0.35, 0.67]; p < 0.0001		0.47 [0.35, 0.64]; p < 0.0001	
Best Response (IRC)**				
	n = 161§	n = 153§	n = 171§	n = 164§
Overall (CR/PR)	124 (77.0%)	122 (79.7%)	135 (78.9%)	125 (76.2%)
% difference (95%CI)† ; p-value‡	2.72 (−6.74, 12.18); p = 0.6142		−2.73 (−11.99, 6.54); p = 0.5098	
CR	31 (19.3%)	24 (15.7%)	33 (19.3%)	25 (15.2%)
% difference (95% CI)†; p-value‡	−3.57 (−12.31, 5.17); p = 0.5440		−4.05 (−12.46, 4.35); p = 0.5041	
EOI Response (IRC)	n = 155¶	n = 149¶	n = 170¶	n = 164¶
Overall (CR/PR)	97 (62.6%)	105 (70.5%)	111 (65.3%)	111 (67.7%)
% difference (95%CI)†; p-value‡	7.89 (−3.05, 18.83); p = 0.1713		2.39 (−8.07, 12.85); p = 0.6972	
DoR (IRC)	n = 127††	n = 122††	n = 137††	n = 126††
Patients with event	74 (58.3%)	36 (29.5%)	88 (64.2%)	47 (37.3%)
Median (95% CI) (mo)	11.9 (8.8, 13.6)	NE (25.4, NE)	11.6 (8.8, 13.6)	NE (22.8, NE)
HR [95% CI]; stratified	0.36 [0.24, 0.54]		0.39 [0.27, 0.55]	
DFS (IRC)	n = 31††	n = 32††	n = 33††	n = 35††
Patients with event	15 (48.4%)	2 (6.3%)	16 (48.5%)	3 (8.6%)
Median (95% CI) (mo)	13.0 (6.9, NE)	NE (NE, NE)	13.0 (8.2, NE)	NE (NE, NE)
HR [95% CI]; stratified	0.10 [0.02, 0.44]		0.14 [0.04, 0.48]	

EFS (IRC)				
Patients with event	105 (63.3%)	64 (41.3%)	123 (71.9%)	81 (49.4%)
Median (95% CI) (mo)	11.8 (10.8, 14.9)	28.3 (13.6, NE)	11.7 (10.8, 14.1)	25.3 (13.4, 35.0)
HR [95% CI]; stratified p-value*	0.52 [0.38, 0.71]; p < 0.0001		0.52 [0.39, 0.69]; p < 0.0001	
Overall Survival				
Patients with event	36 (21.7%)	25 (16.1%)	48 (28.1%)	30 (18.3%)
Median (95% CI) (mo)	NE (39.8, NE)	NE (NE, NE)	NE (42.2, NE)	NE (NE, NE)
HR [95% CI]; stratified p-value*	0.71 [0.43, 1.19]; p=0.1976		0.62 [0.39, 0.98]; p=0.0379	

CR = complete response; EFS = event-free survival; EOI = end of induction; INV = investigator assessed; IRC = Independent Review Committee-assessed; NE = not estimated; PR = partial response.

Stratification factors for the FL population for the stratified analyses shown were refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2).

** during treatment and within 12 months after start of treatment.

n based on no. of patients who ††achieved objective (overall) response (CR or PR) (for DoR) or achieved CR (for DFS) during the study; § had at least one post-baseline assessment, or who had withdrawn from study prior to the first response assessment; ¶reached end-of-induction treatment response assessment or withdrew prematurely.

*log rank test; †Hauck-Anderson; ‡stratified Cochran-Mantel-Haenszel test.

Patient reported quality of Life

Patient-reported health-related quality of life (HRQoL) and health status, as captured by the FACT-Lym and EQ-5D health index questionnaires, respectively, showed no overall difference between the benda and G-benda arms over time for the entire iNHL population during the treatment and follow-up periods. Time to deterioration of FACT-Lym TOI score, defined as ≥ 6-point worsening from baseline, was delayed in the G-benda arm (median: 8.0 months) compared with the benda arm (median: 4.6 months (HR = 0.74; 95% CI: 0.56, 0.98).

In addition, median time to worsening of patient-reported health-related quality of life (HRQoL) (> 6 points on the Functional Assessment of Cancer Therapy-Lymphoma Trial Outcome Index (FACT-Lym TOI) was numerically longer in the G-benda arm than in the benda arm (8.0 vs. 4.6 months) in the iNHL (ITT) population. In addition, higher proportions of patients in the G-benda arm had an improvement in their FACT-Lym questionnaire scores during treatment and throughout follow-up.

Efficacy in the non-FL population

The results of Independent Review committee (IRC)- assessed progression-free survival (PFS) in the non-FL population showed a limited treatment effect of G-benda compared to benda (hazard ratio [HR] = 0.94; 95% confidence interval [CI] 0.46-1.90).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial GAO4753g

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: GA04753g			
Study identifier	GA04753g		
Design	Open-label multicenter, randomized Phase III study to investigate the efficacy and safety of obinutuzumab in combination with bendamustine compared with bendamustine alone in patients with rituximab-refractory iNHL		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		<time> N/A ongoing
Hypothesis	Non-inferiority		
Treatments groups	Bendamustine (Benda)		bendamustine was administered as monotherapy at a dose of 120 mg/m2/day IV on Days 1 and 2 of Cycles 1-6 of each 28-day cycle, for up to six cycles. 202 patients in the benda arm.
	Obinutuzumab + Bendamustine (G-Benda)		Obinutuzumab was administered by IV infusion as an absolute (flat) dose of 1000 mg for up to six cycles, on Day 1, 8 and 15 of Cycle 1; and on Day 1 only of Cycles 2-6; and every 2 months thereafter until progression or for up to 2 years (whichever was earlier). Bendamustine was administered at a dose of 90 mg/m2/day IV on Days 1 and 2 of Cycles 1-6 of each 28-day cycle, for up to six cycles. 194 in the G-benda arm
Endpoints and definitions	**Primary:** PFS	IRC_PFS	The primary efficacy endpoint, IRC-assessed PFS (IRC-PFS), was defined as the time from randomization to the first occurrence of progression or relapse as assessed by an IRC according to the modified response criteria for NHL (Cheson et al, 2007), or death from any cause on study.
	Secondary:	PFS as assessed by investigator	
		BOR	Best overall response (BOR) and best response of CR during treatment and up to 12 months after the start of treatment, as assessed by the IRC and by the investigator
		CR/PR	CR and overall response (CR or PR) rate at the end-of-induction (EOI)/early study treatment termination visit, as assessed by the IRC and by the investigator
		Overall survival	defined as the time between the date of randomization and the date of death from any cause. Patients who were not reported as having died at the time of the analysis were censored at the date when they were last known to be alive, as documented by the investigator

		DFS	Disease-free survival (DFS), defined for patients with a best overall response of CR, as the time from the first occurrence of a documented CR, as assessed by the IRC, until relapse defined on the basis of the IRC assessments or death from any cause on study.
		DoR	Duration of response (DoR), defined as the time from a best overall response of CR or PR to the first occurrence of progression/relapse (based on the IRC assessment) or death from any cause on study.
		EFS	Event-free survival (EFS), defined as the time between the date of randomization and the date of disease progression/relapse based on IRC assessments, death from any cause on study, or start of a new anti-lymphoma therapy (NALT
		Medical resource utilisation	Medical resource utilization, which included the number of hospitalizations related to AEs (as captured in the electronic Case Report Form [eCRF] SAE section), types of subsequent drug therapies, and medical and surgical procedures (i.e., blood transfusions, bone marrow transplantation, or stem-cell transplantation). Analysis of data on medical resource utilization will be summarized in a separate report.
		PRO	Change in health-related patient-reported outcomes (PROs) from baseline, by visit, as assessed by the Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT-Lym) instrument
		Health index scale	EuroQol-5 Dimension (EQ-5D) Health Index Scale summary scores at baseline, during treatment, and following treatment discontinuation or completion (both progression-free and after disease progression

Database lock	01 September 2014			
Results and Analysis				
Analysis description	**Primary Analysis** – Updated: cut off 1 May 2015			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Benda	G-benda	
	Number of subject	n= 209	n= 204	
	Primary PFS Events	125(59,8%)	87 (42,6%)	
	Median (95% CI) (Months)	14.1(11.7, 16.6)	29.2 (20.5, NE)	
	Hazard ratio HR [95% CI]; stratified p-value	HR: 0.53 (0.40, 0. 70); p< 0.0001		
	Secondary PFS by investigator Events	133(63.6%)	95(46.6%)	
	Median (95%CI)	14.0 (11.5, 16.0)	25.8 (20.2; 42.7)	

	HR [95% CI]; stratified p-value	*0.52 (0.40, 0.68) p < 0.0001*	
	Best response Overall	n= 209 162 (77.5%)	n=204 1514(75.5%)
	% difference (95%CI); p value	-2.02(-10.46, 6.42); p=0.5240	
	CR (assessed by IRC)	36 (17.2%)	33 (16.2%)
	Difference (95%CI); p-value	-1.05 (-8.50; 6.41) p= 0.9298	
	End of induction phase	n=208	n=204
	Overall (CR/PR assessed by IRC)	134(64.4%)	136 (66.7%)
	Percentage difference (95%CI)† ; p-value	2.24 (-7.20, 11.69); p=0.8347	
Notes	Stratification factors for the stratified analyses shown were iNHL subtype (follicular vs other); refractory type (rituximab monotherapy vs rituximab + chemotherapy) and prior therapies (≤ 2 vs > 2).		
Analysis description			

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive studies

The applicant has submitted information regarding 3 additional studies, one phase IB study (Bo21000) and two phase I/II studies (BO20999 and BO21003).

Study BO21000

Study BO21000 (GAUDI) is an open-label Phase Ib study of obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), or fludarabine and cyclophosphamide (FC) as treatment for patients with CD20+ B-cell relapsed or refractory follicular lymphoma (FL) and the combination of obinutuzumab with CHOP or bendamustine in patients with previously untreated FL.

- **In Relapsed/refractory FL patients**

Supporting Studies: Combination Therapy with Induction and Maintenance Phase					
BO21000 (GAUDI) Phase Ib Induction treatment phase is completed and CSR is available. Safety follow-up and maintenance are ongoing. (G-CHOP, G-FC, G-benda)	Open-label, multicenter, randomized	Documented $CD20^+$ relapsed/ refractory B-cell FL or documented $CD20^+$B-cell FL with no prior systemic therapy	Secondary**: ORR, CR/CRu rates, PFS, EFS	Relapsed/refractory FL	
				Patients Enrolled and Included in this Report: 56 patients with relapsed/refractory FL (28 G-CHOP; 28 G-FC) The primary CSR is available	Low-dose obinutuzumab: 400 mg or High-dose obinutuzumab: 1600/800 mg: q3w for 6–8 cycles (G-CHOP arm) or q4w for 4–6 cycles (G-FC arm) Patients with documented response after induction treatment can enter 2-year maintenance therapy (obinutuzumab q3 months until progression or for a maximum of 2 years)

- **In Previously untreated FL patients**

Study, Phase	Study Design	Population	Efficacy Endpoints	Patients	Dose, Route, Regimen
Supporting Studies: Combination Therapy with Induction and Maintenance Phase (continued)					
BO21000 (GAUDI) Phase Ib Induction treatment phase is completed and CSR is available. Safety follow-up and maintenance are ongoing. (G-CHOP, G-FC, G-benda)	Open-label, multicenter, randomized	Documented $CD20^+$relapsed/ refractory B-cell FL or documented $CD20^+$B-cell FL with no prior systemic therapy	Previously untreated FL		
			Secondary**: ORR, CR/CRu rates, PFS, EFS Exploratory: DOR	**Patients Enrolled and Included in this Report**: 81 patients with first-line FL (40 G-benda; 41 G-CHOP) The primary CSR is available	Obinutuzumab: 1000 mg G-CHOP arm, Day 1 for 6-8 cycles+extra dose on Cycle 1, Day 8 G- bendamustine: Day 1 for 4–6 cycles+extra dose on Cycle 1, Day 8 Patients with documented response after induction treatment can enter 2-year maintenance therapy (obinutuzumab q3 months until progression or for a maximum of 2 years)

The population in the BO21000 study is different from the target population in the proposed indication for the registration. Indeed, part 1 of the study investigated obinutuzumab in combination with chemotherapies different from G-benda and part 2 of the study included previously untreated FL patients; not in line with the applied indication. In addition, Study BO21000 also used different doses of obinutuzumab in combination with chemotherapy (400mg, 800mg and 1600mg) whereas 1000 mg was used in GAO4753g. Study BO21000 used a different maintenance regimen of obinutuzumab (1000 mg every 3 months for 2 years compared with 1000 mg every 2 months for 2 years in Study GAO4753g).

In the supporting study BO21000, patients were only eligible for the maintenance phase (part 2) if they had achieved a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during induction therapy. In the pivotal Study GAO4753g, patients without disease progression at the end of induction (i.e., patients with a CR, PR or stable disease [SD]) were eligible for maintenance obinutuzumab.

Study BO21003

Study BO21003 (GAUSS) is an open-label dose-escalating Phase I/randomized Phase II study of obinutuzumab as monotherapy in patients with relapsed or refractory CD20+ malignant disease.

For the Phase I dose-escalation part of the study, all patients with CD20+ malignant disease (NHL or CLL) were eligible if no therapy of higher priority was available and treatment with an anti-CD20+ antibody was deemed appropriate.

Supporting Studies: Monotherapy with Induction and Maintenance Phase					
BO21003 (GAUSS) Phase I/II Closed (G vs. R)	Open-label, multicenter, dose escalating	Phase I			
		Patients with CD20+ malignant disease	Secondary**: ORR (end of induction), CR rate, PR rate and BOR	**Patients Enrolled**: 17 patients with NHL and 5 patients with CLL **Included in this Report**: 17 NHL patients (13 patients with iNHL). Phase I primary and update CSRs are available, including a final CSR for Phase I/II	Obinutuzumab once weekly for 4 weeks. 5 dose-escalation cohorts (100 mg–2000 mg) with Cohort 6 (1000 mg) to test safety and tolerability of recommended Phase II dose

- **in Phase II**

The Phase II part of the study was restricted to patients with relapsed CD20+ iNHL and was designed to explore the safety and tolerability of obinutuzumab versus rituximab given as monotherapy, including maintenance treatment in patients with CD20+ iNHL.

Supporting Studies: Monotherapy with Induction and Maintenance Phase (continued)					
BO21003 (GAUSS) Phase I/II Closed (G vs. R)	Open-label, multicenter, dose escalating	Phase II			
		Patients with relapsed CD20+iNHL	Primary: ORR Secondary: CR rate, PR rate, BOR, PFS, EFS and DOR	**Patients Enrolled and Included in Report**: 86 patients rituximab[b] 87 patients obinutuzumab (74 with FL) A Phase II primary CSR is available, including a final CSR for Phase I/II	Obinutuzumab: 1000 mg, once weekly for 4 weeks followed by maintenance (obinutuzumab q3m until progression or for a maximum of 2 years) for non-progressing patients.

The population in the BO21003 study is different from the target population in the proposed indication for the registration (patients NHL or CCL versus FL). However, in part 2 of the study BO21003, the study population was iNHL patients and the primary endpoint was based on patients with FL only. However, the compared study treatments were different from the GAO4753g study (obinutuzumab vs. rituximab given as monotherapy in the BO21003 study); study doses ranging from 100 mg – 2000 mg were given whereas the GAO4753g study used 1000 mg for all doses; The dosing schedule was weekly dosing during induction compared with the GAO4753g study (28-day cycles during induction). In the supporting study BO21003, patients were only eligible for the maintenance phase if they had achieved a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during induction therapy; Phase I patients with SD were also eligible for maintenance if they were considered to have derived clinical benefit from induction. In the pivotal Study GAO4753g, patients without disease progression at the end of induction (i.e., patients with a CR, PR or stable disease [SD]) were eligible for maintenance obinutuzumab.

Study 20999

Study BO20999 (GAUGUIN) is an open-label dose-escalating Phase I/randomized Phase II study of obinutuzumab as monotherapy in patients with relapsed or refractory CD20-positive (CD20+) malignancies.

Phase I of the study is described in the table below:

Supporting Studies: Monotherapy Induction (No Maintenance Phase)					
BO20999 (GAUGUIN) Phase I/II Closed (G monotherapy)	Open-label, multi-center, non-randomized, adaptive dose-escalating study	Phase I			
		Patients with CD20+malignant disease for whom no therapy of higher priority is available	Secondary**:ORR, CR rate and PR rate	**Patients Enrolled**: NHL: n=21; CLL: n=13 **Included in this Report**: iNHL: n=16 Primary and update CSRs are available, including a final CSR for Phase I/II covering the retreatment period	Dose-escalation: Six cohorts of 50 mg–2000 mg of obinutuzumab with Cohort 7 to investigate the safety of the recommended Phase II doses in NHL and CLL; Day 1 and 8 for Cycle 1, Day 1 for Cycles 2–8; Cycle duration=21 days

The Phase II part of the study was designed to explore the efficacy and safety of the recommended doses identified in Phase I part of the study, in patients with CD20+ relapsed/refractory iNHL, aNHL and CLL, in order to obtain further safety information at these doses and early efficacy data in the three patient populations.

In this part of the study, patients with NHL were randomized to receive either high dose (1600 mg [Cycle 1, Day 1 and Day 8]/800 mg [all other doses]) or low dose (400 mg) obinutuzumab.

Study, Phase	Study Design	Population	Efficacy Endpoints	Patients	Dose, Route, Regimen
BO20999 (GAUGUIN) Phase I/II Closed (G monotherapy)	Open-label, multi-center, non-randomized, adaptive dose-escalating study	Phase II			

		Patients with relapsed/refractory CD20+malignant disease for whom no therapy of higher priority is available	Primary: ORR
			Secondary: CR rate, PR rate, PFS, EFS, DOR
				Patients Enrolled:
				iNHL: n=40;
				aNHL: n=40;
				CLL: n=20
				Included in this Report:
				iNHL: n=40
				Phase II primary and update CSRs are available, including a final CSR for Phase I/II covering the retreatment period
					NHL: 1600 mg/800 mg or 400 mg; Day 1 and 8 for Cycle 1, Day 1 for Cycles 2–8
					(CLL: 1000 mg; Day 1, 8 and 15 for Cycle 1, Day 1 for Cycles 2–8); Cycle duration=21 days

a Four randomized patients did not receive any study medication (bendamustine); three patients withdrew consent and one patient was withdrawn due to physician's decision.
b Rituximab data not included. For Study BO21003, only data for patients with FL in the obinutuzumab arm are included.
** The primary endpoint of this part of the study was safety.
aNHL = aggressive non-Hodgkin lymphoma; benda = bendamustine; CLL = chronic lymphocytic lymphoma; CR = complete response; CRu = unconfirmed complete response; CSR = clinical study report; FL = follicular lymphoma; G = obinutuzumab; G-benda = obinutuzumab + bendamustine; G-CHOP = obinutuzumab + CHOP; G-FC = obinutuzumab + fludarabine, cyclophosphamide; NHL = non-Hodgkin lymphoma; ORR = overall response rate; PR = partial response; R = rituximab.

The population in the BO20999 study is different from the target population in the proposed indication for the registration (patients CCL/NHL). The study BO20999 investigated different doses of obinutuzumab as monotherapy (50 mg-2000 mg), whereas Study GAO4753g only investigated obinutuzumab 1000 mg. The dosing schedule was also different in the BO20999 study (21-day cycles during induction) compared with the GAO4753g study (28-day cycles during induction).

All the supportive studies included adult (male or female) patients with CD20+ disease based on local testing followed by central confirmation.

Patients in the supporting studies were assessed for disease response by the investigator using regular clinical and laboratory examinations, and CT scans, according to standard response criteria (Cheson et al. 1999 and 2007). In the Phase II part of Study BO21003, responses at the end of induction were also assessed by an IRC, and the primary endpoint was based on patients with FL only.

Table 9: Primary and Secondary Efficacy Endpoints in the supporting studies

	Study BO20999		Study BO21003		Study BO21000 (Rituximab refractory and first-line)
	Phase I	Phase II	Phase I	Phase II	
Primary Efficacy Endpoint	n/a[1]	ORR	n/a[1]	ORR	n/a[2]
Secondary Efficacy Endpoints	ORR, CR rate, PR rate	CR rate, PR rate, PFS, EFS, DoR	ORR, CR rate, PR rate, BOR	CR/CRu rate, PR rate, BOR, PFS, EFS DoR	ORR, CR/CRu rate, PFS, EFS, DoR

[1] The primary endpoint for Phase I was safety and tolerability.
[2] The primary endpoint was to investigate safety.
BOR = best overall response; CR = complete response; CRu = unconfirmed complete response; DFS = disease-free survival; DoR = duration of response; EFS = event-free survival; EOI = end of induction; INV = investigator; IRF = independent radiology facility; NALT = next anti-leukemia treatment; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome.

Results

Table 10: Summary of End-of-Treatment/End-of-Induction Response in Patients with iNHL Treated with Obinutuzumab in the Supporting Studies (Phase I/II Results)

Study	No. of Patients with Response		
	ORR	CR/CRu	PR
Relapsed or refractory disease			
Monotherapy			
Study BO20999			
Phase I – obinutuzumab dose escalation (n=16)	7 (44)	4 (25)	3 (19)
Phase II – obinutuzumab 400/400 mg (n=18)	3 (17)	0 (0)	3 (17)
obinutuzumab 1600/800 mg (n=22)	12 (55)	2 (9)	10 (46)
Study BO21003			
Phase I - obinutuzumab dose escalation (n=13)	4 (31)	0	4 (31)
Phase II - obinutuzumab 1000 mg (n=74**)	33 (45)	9 (12)	24 (32)
Combination Therapy			
Study BO21000			
Obinutuzumab[a] – FC (n=28)	26 (93)	14 (50)	12 (43)
Obinutuzumab[a] – CHOP (n=28)	27 (96)	11 (39)	16 (57)
First-line treatment			
Study BO21000			
Obinutuzumab 1000 mg + CHOP (n=40)	38 (95)	14 (35)	24 (60)
Obinutuzumab 1000 mg + bendamustine (n=41)	38 (93)	15 (36.6)	23 (56.1)

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CR/CRu = complete response/unconfirmed complete response; FC = fludarabine + cyclophosphamide; ORR = overall response rate; PR = partial response.
[a] Patients were randomized to 400/400 mg or 1600/800 mg obinutuzumab; both cohorts were pooled for the analysis.
** Patients with FL in the obinutuzumab arm only. The analysis of efficacy includes only patients with FL (a total of 149 patients; 75 in the rituximab arm and 74 in the obinutuzumab arm).

2.4.3. Discussion on clinical efficacy

The indication is based on the results of pivotal study GAO4753g investigating the efficacy and safety of obinutuzumab plus bendamustine (G-benda) compared with bendamustine (benda) in patients with rituximab-refractory, iNHL those patients who had no response to or who progressed within 6 months of treatment with rituximab or a rituximab-containing regimen.

Design and conduct of clinical studies

GAO4753g was an open-label, randomized phase III study submitted to support the application for an extension of the indication of adding obinutuzumab to bendamustine in patients with iNHL after failure of rituximab-based therapy. The study evaluated the efficacy and safety of up to 2.5 years of obinutuzumab initially in combination with 6 cycles of bendamustine, compared with bendamustine alone (6 cycles). The rationale of continued obinutuzumab in the maintenance phase was based on results with rituximab maintenance up to 2 years after induction therapy, which had shown to improve the outcomes of patients with follicular lymphoma in both first line and relapsed/refractory setting (van Oers et al. 2010, Salles et al. 2011, Vidal et al. 2011). Based on clinical and non-clinical data, Obinutuzumab was expected to have superior efficacy with similar safety to rituximab.

Patients were randomized in a 1:1 ratio to receive bendamustine 90 mg/m2 day 1 and 2 in cycles 1-6 and obinutuzumab 1000 mg day 1, 8 and 15 in cycle 1, day 1 in cycles 2-6 and as maintenance q2 monthly for up to 2 years or bendamustine as single agent 120 mg/m2 day 1 and 2 in cycles 1-6. Dynamic allocation was used for randomisation which could affect the interpretation of the robustness of presented efficacy data. However, the use of this method has been adequately justified by the applicant.

The primary efficacy endpoint of the study was PFS, which is considered acceptable in this phase III trial. Secondary endpoints were: OS, tumour response (response rate and duration of response, disease free survival (DFS)) and HRQoL based on assessment of various subscales according to functional assessment of cancer therapy for patients with lymphoma. Median PFS expected in the protocol were 9.3 months and 13.3 months respectively in the control and Gazyvaro group. The study was open-label, allowing potential subjective bias to be introduced. However, all the evaluations of endpoints were performed by a blinded independent review committee. The assessment by the investigators was considered supportive.

Different subgroups were analysed: histology including grade, gender, age, prognostic index and clinical stage, response to prior therapy, genotype. Except from the follicular lymphomas, the majority of subgroups were too small to draw any significant conclusion.

A total of 413 patients were included. In general the demographics and baseline data were well balanced between the two treatment arms both in the iNHL population and the FL subpopulation. Overall the majority of patients were male, Caucasian and less than 70 years of age, median age was 63.0 years (range 21 to 87 years). The disease and disease prognostic factors characteristics were also quite comparable in the two treatment arms, with the exception of a higher proportion of patients in the G-benda arm than in the benda arm with extranodal involvement (55.4% vs. 49.5%), indicating more advanced disease. Almost all patients were refractory to rituximab as required by the entry criteria of the protocol, 81. 3% in the benda arm and 77.5% in the G-benda arm were considered “double refractory”, i.e. also refractory to an alkylating agent.

The applicant has submitted information regarding 3 additional studies, one phase IB study (Bo21000) and two phase I/II studies (BO20999 and BO21003).There were major limitations for all 3 studies, they were small, and obinutuzumab was given as monotherapy or together with CHOP, FC. In one small study obinutuzumab was given together with bendamustine; however this was in patients on first-line therapy for follicular lymphoma. Thus, no clinical support from these applications was noted.

Efficacy data and additional analyses

The included patients appear to represent the target population.

The pivotal study GA04753g met its primary endpoint after 67% of events required for the final analysis had been observed: treatment with G-benda resulted in a statistically significant reduction by 47% in the risk of IRC-assessed PFS compared with benda alone (HR=0.53 (95% CI: 0.40, 0.70; log-rank p-value = 0.0001). The Kaplan-Meier estimated median PFS (IRC) was 14.1 months (95% CI: 11.7, 16.6) in the benda arm, compared to 29.2months (95% CI: 20.5, NE) (HR 0.52 (0.40, 0.70), p< 0.0001) an increase of 15 months, and these results were - consistent with the primary analysis. The median OS could not be estimated in either treatment arms in the primary or updated analysis.

The best overall response rates (CR/PR) and CR rates, as assessed by the IRC were not statistically different between treatment arms. Investigator-assessed results were in agreement. An exploratory analysis of MRD in blood at the end of induction in the FL patients was performed. In the G-benda arm 82.4% were MRD negative vs. 42.9% in the benda arm (p<0.0001, Chi-squared). These results however should be interpreted with caution due to a small population evaluated.

The duration of response (DoR) and DFS were longer in the G-benda arm (median not reached) compared with the benda arm (median 11.9 months for DoR and 13.0 months for DFS). Hazard ratios were 0.36 (95% CI: 0.24, 0.54) for DoR and 0.10 (95% CI: 0.02, 0.44) for DFS. EFS was longer in the G-benda arm compared with the benda arm (median: 28.3 months vs. 11.8 months) (HR: 0.52; 95% CI:0.38, 0.71, p-value < 0.0001, stratified log-rank test). Overall, the results of the IRC-assessed PFS subgroup analyses in FL patients were consistent with the results in the overall ITT (iNHL) population. A trend towards a smaller benefit was observed for patients with >2 prior therapies (n= 66; HR= 0.82, 95% CI: 0.39,1.72) with the upper 95% CI limit crossing 1.

In the subgroup of patients with FL, which comprised 81.1% of the iNHL study population, the results were similar. The HR for IRC-assessed PFS was 0.48 (95% CI: 0.34, 0.68, p-value =0.0001, stratified log-rank test). PFS as assessed by the Investigator confirmed the IRC-assessed PFS results (HR =0.48; 95% CI: 0.35, 0.67, p-value < 0.0001, stratified log-rank test). The median investigator assessed PFS in the G-benda arm (29.2 months [95% CI: 17.5; NE]) was over twice as long as that in the benda arm (13.7 months [95% CI: 11.0; 15.5]).

Regarding the geographical stratification factor, there is a heterogeneity in the PFS responses for both IRC and investigator assessment levels in the ITT population: HR=0,92 95%CI (0,43 – 2,00) in Eastern Europe population (perhaps linked to low number of analyzed patients), HR=0,35 95%CI (0,21 – 0,58) in the North America patients and HR=0,68 95%CI (0,44 – 1,05) in the Western Europe patients. These results were confirmed in FL patients.

The updated OS data show that the median OS has not been reached yet, but fewer patients with FL had died in the G-benda arm (30/164 [18.3%]) compared to the benda arm (48/171 [28.1%]).

Patient reported outcomes (FACT-Lym questionnaire and EQ-5D index scale) during the treatment and follow-up periods, showed that health-related quality of life was generally maintained. The addition of obinutuzumab to bendamustine delayed the time to worsening of quality of life as measured by the FACT-Lym TOI score (HR: 0.74; 95% CI: 0.56, 0.98). However, these results could have been biased by the open-label design of the study.

The majority of patients completed treatment as planned. The proportion of patients who received 90% of their planned obinutuzumab doses during induction was high (90.2%).

In the Maintenance Phase, almost all patients (97.2%) received >90% of planned obinutuzumab during their time on treatment. The proportion of patients who withdrew from all study medication due to an AE was higher in the benda arm (15.7% of patients) than in the G-benda arm (11.3% of patients).

Since non-FL iNHLs express CD20 and are known to respond to rituximab (Kiesewetter et al. 2015;

Bennett and Schechter 2010), it is biologically plausible that obinutuzumab will have efficacy in non-FL iNHL, as well as FL. The Study BO21004/CLL-11 established the superiority of obinutuzumab + chlorambucil (G-Clb) versus rituximab + chlorambucil (R-Clb) in patients with CLL (Report No. 1056550). Because CLL and SLL are considered different manifestations of the same disease entity (Sun and Weistner 2015), the efficacy of obinutuzumab-based therapy has effectively already been shown for one subtype of non-FL. The results of Independent Review committee (IRC)- assessed progression-free survival (PFS) in the non-FL population showed a limited treatment effect of G-benda compared to benda (hazard ratio [HR] = 0.94; 95% confidence interval [CI] 0.46-1.90). This result need to be interpreted in light of the small patient numbers with non-FL and the small number of patients who had had an event at the time of data cutoff for the primary analysis.

In the light of the above results the indication for obinutuzumab is focusing on patients with FL. A statement has been included in Section 5.1 of the SmPC "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." A randomized Phase III trial - BO21223 (GALLIUM) (in which chemotherapy-naïve patients are randomized to G-chemo followed by G maintenance vs. R-chemo followed by R maintenance) includes approximately 200 patients with advanced MZL and is currently ongoing.

Data from the supportive studies presented were not pooled because of differences in treatment regimens used and patient population enrolled and for these reasons they would mainly be considered as supportive of the efficacy for the present application. Indeed, the population treated by G-benda in the study B021000 is a first-line treated population, not in line with the applied indication.

2.4.4. Conclusions on the clinical efficacy

The efficacy results showed a clinically significant and statistically robust improvement in PFS supporting the indication of obinutuzumab in combination with bendamustine followed by maintenance for the treatment of patients with follicular lymphoma who did not respond to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. OS data were currently immature; . Final OS analysis is expected at study Completion (See RMP).

2.5. Clinical safety

Introduction

Safety data for obinutuzumab in patients with iNHL are primarily derived from the pivotal phase III study GA04753g. The applicant also reports safety data from supporting studies: BO21000: Phase 1 study with 137 FL patients, BO21003-Phase I/II study 186 patients (100 patients with iNHL [Phase I and II] were exposed to obinutuzumab, 86 patients with iNHL [Phase II] were exposed to rituximab [Rituxan, MabThera]) and BO20999 Phase I/II study with 56 patients. Safety data from the pivotal and supporting studies were not pooled, because of key differences in the study design, patient population and treatment regimens.

Patient exposure in pivotal study GAO4753g

Clinical safety data are available for a total of 409 patients. At the time of the clinical cutoff date 154 of 204 (75.5%) patients enrolled in the G-benda arm started the Maintenance Phase and 29 patients were still receiving maintenance treatment; therefore, the Follow-Up period after the completion of maintenance was relatively short and there is limited long-term Follow-Up data available.

The safety population was defined as all subjects who received any amount of obinutuzumab or bendamustine therapy. In the induction phase, the proportion of patients who received all planned infusions of bendamustine was 71.7% in the benda arm and 78.3% in the G-benda arm (median 12 doses over 170 days in both arms).

The majority of patients received >90% of the planned dose of study medication for their time on treatment. Given the differing planned doses of bendamustine between treatment arms, the median cumulative dose of bendamustine during induction was higher in the benda arm (2347 mg) than in the G-benda arm (1920 mg). The most common reason for dose modification of benda was AE.

In the G-benda arm 81.9% of patients received all scheduled cycles of their planned obinutuzumab dose. A total of 22.2% of patients had an infusion modification of obinutuzumab during the induction phase, mostly in cycle 1 (19.6% of patients) and due to AE. Almost all patients 89.7%received > 90% of the planned obinutuzumab dose intensity.

Table 3 Summary of Exposure by Treatment Phase (Cutoff: 1 May 2015)

Treatment Phase	**Induction**			**Maintenance**
Treatment arm	**benda n = 205**	**G-benda n = 204**		**G-benda n = 204**
	N = 205	N = 203	N = 204	N = 154
Treatment	bendamustine	bendamustine	obinutuzumab	obinutuzumab
Patients who received all scheduled cycles*, n (%)	147 (71.7%)	159 (78.3%)	167 (81.9%)	50 (32.5%)
Median no of doses received† (range)	12 (2-12)	12 (1-12)	8 (1-8)	7 (1-12)
Median cumulative dose, mg (range)	2366 (394-3744)	1920 (128-2700)	8000 (394-8069)	7000 (1000-12000)
Patients who received ≥ 90% dose intensity*, n (%)	157 (76.6%)	161 (79.3%)	183 (89.7%)	150 (97.4%)
Median duration of treatment (days)	170 (25-243)	170 (1-233)	169 (1-264)	394 (15-729)

* for induction, 6 cycles, each of 28-days (†bendamustine: 2 infusions in each cycle of Cycles 1-6 (Day 1 and 2), total 12 infusions); obinutuzumab: 3 infusions in Cycle 1 (Day 1/2, 8 and 15), and one infusion in each cycle of Cycles 2-6 (Day 1), total of 8 infusions).

For Maintenance Phase, up to 12 cycles (or disease progression) each of 2 months (one obinutuzumab infusion per cycle (up to total of 12 infusions).

Updated safety results (Cut off 1 may 2015))

Summary of Exposure to Study Medication in Maintenance Phase (Patients who Started Maintenance Obinutuzumab) (Safety Population) Update 1 May 2015

Protocol(s): GA04753g/G001297 (K01297J)
Analysis Population: Patients Who Entered Maintenance Phase - Phase III
Snapshot Date: 11AUG2015 Cutoff Date: 01MAY2015:23:59:59

	G-B (N=154)
Study Drug	
GA101	
Dose intensity during Maintenance	
<60 %	2 (1.3%)
60 - <80 %	1 (0.6%)
80 - <90 %	1 (0.6%)
>=90 %	150 (97.4%)
n	154
Duration of exposure in Maintenance	
n	154
Mean (SD)	397.93 (254.85)
Median	394.00
Min - Max	15.0 - 729.0
Total dose during Maintenance	
n	154
Mean (SD)	7144.08 (4255.54)
Median	7000.00
Min - Max	1000.0 - 12000.0
Total nr. of doses during Maintenance	
n	154
Mean (SD)	7.1 (4.3)
Median	7.0
Min - Max	1 - 12
Nr. of missed doses during Maintenance	
n	154
Mean (SD)	0.0 (0.2)
Median	0.0
Min - Max	0 - 1

Time unit is in number of days, dose unit is mg.
Treatment duration is the date of the last dose of study medication minus the date of the first maintenance dose plus 28 days.
Or if new antileukemia therapy was started within these 28 days exposure duration is the time interval between first maintenance dose and start of new antileukemia therapy minus 1 day.
Dose intensity is the total dose actually received divided by the total planned dose.

Program: /opt/BIOSTAT/prod/cdt7159z/t_ex2.sas
Output: /opt/BIOSTAT/prod/cdt7159z/k01297j/reports/t_ex2_297_SEM.out

Adverse events update 1 May 2015

Table 4 Overview of Adverse Events over the Entire Study Period (Safety Population)

Analysis	Primary GAO4753g CSR		Updated Data (this report)	
Cutoff date	01 Sep 2014		01 May 2015	
Treatment arm	benda n = 198	G-benda n = 194	benda n = 205	G-benda n = 204
Total number of deaths	41 (20.7)	34 (17.5)	56 (27.3)	42 (20.6)
Total number of deaths due to PD	29 (14.6)	22 (11.3)	43 (21.0)	27 (13.2)
Total number of patients with at least one:				
AE	194 (98.0)	191 (98.5)	201 (98.0)	200 (98.0)
Grade 3–5 AE	123 (62.1)	132 (68.0)	132 (64.4)	141 (69.1)
Grade 5 AE (fatal outcome)	12 (6.1)	12 (6.2)	13 (6.3)	15 (7.4)
Serious AE	65 (32.8)	74 (38.1)	73 (35.6)	84 (41.2)
AE leading to withdrawal from any study treatment	31 (15.7)	35 (18.0)	34 (16.6)	39 (19.1)
AE leading to dose modification (dose decreased or held)	82 (41.4)	96 (49.5)	86 (42.0)	99 (48.5)
AEs of particular interest				
Gr 3-5 Neutropenia	58 (29.3)	69 (35.6)	61 (29.8)	73 (35.8)
Gr 3-5 Infusion-related AEs	11 (5.6)	21 (10.8)	11 (5.4)	22 (10.8)
Gr 3-5 Infections	34 (17.2)	35 (18.0)	38 (18.5)	40 (19.6)
Gr 3-5 thrombocytopenia	32 (16.2)	21 (10.8)	32 (15.6)	22 (10.8)
Gr 3-5 acute thrombocytopenia	0	1 (0.5%)	0	1 (0.5%)
Gr 3-5 hemorrhagic AEs	5 (2.5)	9 (4.6)	5 (2.4)	9 (3.4)
Gr 3-5 cardiac events	3 (1.5)	9 (4.6)	3 (1.5)	9 (4.4)
Gr 3-5 second malignancy	7 (3.5)	6 (3.1)	8 (3.9)	8 (3.9)
Gr 3-5 tumor lysis syndrome	2 (1)	1 (0.5)	2 (1)	1 (0.5)
Gr 3-5 GI perforation	0	1 (0.5)	0	1 (0.5)
Gr 3-5 hepatitis B reactivation	1 (0.5%)	0	1 (0.5%	0

Source: Table 47 of Primary GAO4753g CSR, Report No. 1051204, July 2015;
t_ae_osafe2_emerge_297_SE; t_dd_c_surv_297_SE; t_ae_byterm_emerge_gr345_297_SE;
t_ae_death_fatal_297_SE; t_ae_byterm_emerge_ser_297_SE;
t_ae_c_aespecial_emerge_rel24_297_SE; t_ae_c_aespecial_emerge_neu_297_SE;
t_ae_c_aespecial_emerge_inf_297_SE; t_ae_c_aespecial_emerge_throm_297_SE;
t_ae_c_aespecial_emerge_haem_297_SE; t_ae_c_aespecial_emerge_tls_297_SE;
t_ae_c_aespecial_emerge_gip_297_SE; t_ae_c_aespecial_emerge_card_297_SE;
t_ae_c_aespecial_emerge_secmal_297_SE; t_ae_c_aespecial_emerge_hepbre_297_SE.

Overall Safety by Treatment Phase (ITT Population)(Cutoff: 1 May 2015)

Phase	Entire Study Period		Induction		Maintenance	Follow-Up		
Treatment arm	benda	G-benda	benda	G-benda	G-benda	benda	G-benda	
							monotherapy	no monotherapy
	N = 205 n (%)	N = 204 n (%)	N = 205 n (%)	N = 204 n (%)	N = 154 n (%)	N = 189 n (%)	N = 122 n (%)	N = 42 n (%)
Total number of deaths	56 (27.3)	42 (20.6)	7 (3.4)	2 (1.0)	0	49 (25.9)	20 (16.4)	20 (47.6)
Total number of deaths due to PD	43 (21.0)	27 (13.2)	3 (1.5)	2 (1.0)	0	40 (21.2)	11 (9.0)	14 (33.3)
AE	201 (98.0)	200 (98.0)	200 (97.6)	199 (97.5)	118 (76.6)	101 (53.4)	51 (41.8)	5 (11.9)
Grade 3–5 AE	132 (64.4)	141 (69.1)	107 (52.2)	113 (55.4)	46 (29.9)	46 (24.3)	29 (23.8)	5 (11.9)
Grade 5 AE (fatal outcome)	13 (6.3)	15 (7.4)	5 (2.4)	3 (1.5)	1 [a] (0.6)	8 (4.2)	8 (6.6)	3 (7.1)
Serious AE	73 (35.6)	84 (41.2)	44 (21.5)	58 (28.4)	20 (13.0)	35 (18.5)	20 (16.4)	5 (11.9)
AE leading to withdrawal*	34 (16.6)	39 (19.1)	34 (16.6)	29 (14.2)	11 [b] (3.2)	NA	NA	NA
AE leading to dose modification†	86 (42.0)	99 (48.5)	86 (42.0)	86 (42.2)	27 [c] (17.5)	NA	NA	NA

* from any study treatment

†dose decreased or held.

[a] By definition, an AE that occurred 28 days after the last dose of monotherapy study treatment is attributed to the Maintenance Phase. In some instances, the number of AEs in a the Maintenance Phase might differ from the number of deaths due to AEs, the number of treatment/study withdrawals or the number of dose modification due to AE, which are not based on the AE reporting period. For this reason, the 1 patient death due to a Grade 5 AE presented here as per t_ae_death_fatal_mnt_297_SEM is not consistent with the disposition information presented in t_dd_c_survphas_297_SE .

[b] Includes 6 events that have occurred according to listing in follow-up since greater than 28 days since last dose, but have been attributed to the Maintenance Phase in this table because they occurred before the next monotherapy dose was due. Hence, although t_ae_byterm_emerge_twithd_mnt_297_SEM states 5 patients, 6 additional patients have been included in this table.

[c] Includes 4 events that have occurred according to listing in follow-up since greater than 28 days since last dose, but have been attributed to the Monotherapy Phase in this table because they occurred before the next monotherapy dose was due. Hence, although t_ae_byterm_emerge_tdosmod2_mnt_297_SEM states 23 patients, 4 additional patients have been included in this table.

Commonly affected SOCs in which the incidence of all grade individual AEs was higher (>5%) in the G-benda arm than in the benda arm, included: neutropenia, fatigue, pyrexia, asthenia, upper respiratory tract infections and coughing, IRR, arthralgia, pruritus and hypotension.

GI AEs were more common in the benda arm (82.3% vs. 74.7%) mainly due to: nausea, vomiting and diarrhea. The incidence of thrombocytopenia was also higher in the benda arm, probably due to the higher dose of bendamustine. All these adverse events are well known for the two substances and in this patient population. The AEs are manageable, and AE due to IRRs should be managed by prophylactic treatment in an appropriate clinical setting.

As for AE incidence by age group, ie. < 65, 65-75 and 75-85 and >85 years, the difference between the treatment arms in terms of AE incidence in G-benda arm did not increase with older age.

The adverse events including the serious AEs are well known for the two substances and in this patient population. The most common serious AEs were reported in the blood and lymphatic system, (5.6% of the patients in the benda arm and 10.3% in the G-benda arm) and infections (15.6% in the benda arm and 16.4% in the G-benda arm). Number of patients in the different AE groups were small. The main difference between the two treatment arms was reported in neutropenia which occurred in 3.1% in the G-benda arm compared with 0.5% in the benda arm. However no difference was reported in number of febrile neutropenia or number of “infections and infestations” between the two treatment arms, the AEs seems manageable and are therefore not of major concern.

Other adverse events of special interests (AESI)

All grade events of IRRs, neutropenia, thrombopenia, infection, tumour lysis syndrome (TLS), GI perforation, cardiac events, second malignancy and hepatitis B reactivation were identified as AESI.

IRR

IRRs were AEs related to any study medication, which occurred during infusion or within 24 h from the end of infusion. The majority of IRRs were grade 1 or 2 and most IRRs resolved after treatment, no fatal IRRs was noted in this study. The incidence of IRRs was higher in the G-benda arm (68.6%) compared

with the benda arm (63.1%), as was the incidence of Grade 3 and 4 IRRs, serious IRRs, IRRs leading to withdrawal from treatment or dose reductions/- interruptions. 36.9% of patients in the benda arm and 77.8% in the G-benda arm received prophylactic corticosteroids. In these patients, the incidence of IRR was 13.7% in the benda arm, and 32.5% in the G-benda arm. In those who did not receive premedication, the incidence of IRRs was 24.0% and 55.8 respectively.

IRRs led to interruption of bendamustine in 13/198 (6.6%) of patients in the benda arm and 11/194 (5.7%) of patients in the G-benda arm. Few patients required dose reduction (2 patients in each arm) or withdrawal (3 patients vs. 1 patient) of bendamustine due to IRR. The incidence of IRRs was higher in the first cycle and decreased in the following cycles.

In total, 110/194 (56.7%) patients had AEs related to obinutuzumab infusions. The Obinutuzumab infusion was interrupted in 45/194 (23.2%) patients, most of whom went on to receive the full dose, while only 5 (2.6%) patients did not receive the full infusion and 4 (2.1%) patients discontinued obinutuzumab. In the maintenance period IRRs were observed in 8.4% of the patients, obinutuzumab had to be discontinued in 1.4% of the patients.

Guidance for prophylaxis and premedication administration of obinutuzumab for IRRs is noted in the SmPC, patients should continue to receive repeated prophylaxis prior to each subsequent infusion at the physicians discretion. Obinutuzumab should be administered under appropriate clinical setting as mentioned in the SmPC.

Neutropenia

The incidence of neutropenia in the study overall was higher in the G-benda arm, (31.8% benda vs. 37.6% G-benda), mainly due to more grade 4 events in the G-benda arm. No grade 5 event occurred in each arm. In the induction phase the incidence of neutropenia AEs was similar in the two arms (30.8% vs. 31.4%) and also generally constant over time. In the maintenance period with obinutuzumab, the incidence of neutropenia was 11.9%. all the neutropenia AEs resolved and no fatal neutropenia events were reported.

The use of myeloid growth factors was permitted for the primary prevention of febrile neutropenia or as prophylactic support for patients who experienced Grade ≥ 3 myelosuppression with febrile neutropenia, at the investigator's discretion.

Granulocyte-colony stimulating factor (G-CSF) administration was prespecified in cases of Grade 3 or 4 neutropenia requiring dose delay or modification of bendamustine and/or obinutuzumab. There was no imbalance in the use of G-CSF between the treatment arms as concomitant medication (31.7% in benda arm, 36.6% in G-benda arm).

Prolonged Neutropenia and Late Onset Neutropenia

Prolonged neutropenia was defined as ANC < 1.0x109 cells/mm3, that had not resolved to within the normal range by the previous visit before receiving the last dose of obinutuzumab. Late onset neutropenia was defined as an initial ANC < 1.0x109/ cells/mm3 at any time after the last dose of obinutuzumab. Prolonged neutropenia occurred in 5 patients (2.6%) in the G-benda arm. One of these patients had serious instances of prolonged neutropenia. Late onset neutropenia occurred in 14 patients (7.2%) in the G-benda arm (7 of these patients had serious instances of late onset neutropenia, one patient had a fatal sepsis.

Infections

The incidence of infections throughout the whole study was higher in the G-benda arm (65.5%) compared with 55.6% in the benda-arm. Each arm had a similar proportion of grade 3-5 infections, serious infections and fatal infections (7 patients in the benda arm and 5 patients in the G-benda arm) Infections

in both arms included viral infections (most commonly herpes virus relates infections), fungal infections and bacterial infections with no imbalance between the treatment arms.

One case of **Hepatitis B reactivation** was reported as an AE in the benda arm, this event recovered after adequate treatment. No cases of progressive multifocal encephalopathy (PML) in either treatment arm was reported.

Thrombocytopenia

Thrombocytopenia in the study overall was higher in the benda arm compared with the G-benda arm (23.7% vs. 14.9%). A higher incidence of thrombocytopenia during the first cycle of therapy was reported compared with the subsequent cycles, but no difference between the two treatments arms. There was no grade 5 event of thrombocytopenia in either arms, but the event was reported serious in 4 patients (2.1%) in the G-benda arm vs. none in the benda arm. Grade 3/4 thrombocytopenia was not associated with significant bleeding events. In the benda arm 6.1% patients and 3.6% in the G-benda arm discontinued the treatment due to thrombocytopenia. Most thrombocytopenia events resolved (83% patients with events in each arm), and 21.3% and 34.5% in the benda and G-benda arm respectively received treatment for this AE. One patient in the G-benda arm had acute thrombocytopenia, defined as occurring within 24 h after the infusion. This was a grade 3 serious event, obinutuzumab was interrupted, and the symptoms resolved without treatment.

In the maintenance phase two patients (1.4%) in the G-benda arm had grade 3/4 thrombocytopenia after the first maintenance cycle, in the subsequent assessments no events were reported.

The incidence of haemorrhagic events in the study overall was similar in the two treatment arms, 10.1% in the benda arm vs. 10.8% in the G-benda arm. Hemorrhagic events were reported as serious in 3 patients (1.5%) in the benda arm and 6 patients (3.1%) in the G-benda arm. Most events resolved, 85% in each arm, and 30.0% of patients in the benda arm and 47.6% patients in the G-benda arm received treatment for this AE. No grade 5 event was reported.

Tumour Lysis Syndrome (TLS)

TLS was reported in 2 patients (1.0%) in the benda arm and 1 (0.5%) in the G-benda arm. All events occurred during the first cycle of induction, treatment for this AE was given and 2 of the patients could continue study treatment as planned. One patient in the benda arm experienced renal failure on day 17, progressive lymphoma and died on day 29. This event was considered to be related to underlying disease, rather than bendamustine.

Gastrointestinal perforation

Bowel perforation has been reported in a few patients treated with obinutuzumab. In this study 2/194 patients (1%) from the G-benda arm had a bowel perforation. In one patient the perforation was thought to be due to diverticulitis, and the maintenance treatment with obinutuzumab was delayed. The other patients experienced two abdominal abscesses. Both patients were treated conservatively with antibiotics, both recovered and patient number two continued study medication.

Cardiac events

The incidence of all grade cardiac AE during the overall study was lower in the benda arm (11) compared with the G-benda (22), (5.6% vs. 11.3%). This was due to different cardiac events: cardiac failure (0% vs. 2.1%), tachycardia (1.0% vs. 2.1%), bradycardia (0% vs. 1.5%) and atrial fibrillation (1.0% vs. 2.1%) in benda vs. G- benda arm respectively. The difference was partly driven by symptoms of IRRs. The majority of cardiac events were grade 1 or 2. There were three grade 3-5 AE events, (in 3 patients) in the benda arm: atrial fibrillation, myocardial infarction and paroxysmal arrhythmia, one was considered an IRR. In the G-benda arm 10 grade 3-5 events (in 9 patients) were observed: atrial fibrillation (2 patients), cardiac failure (2 patients), myocardial infarction (1 patient), acute coronary syndrome (1

patient), atrial flutter (1 patient) coronary artery disease (1 patient) and intracardiac thrombus (1 patient), none of these were considered IRRs. None of the cardiac events were fatal.

Second malignancies

Second malignancies occurring 6 months after the start of therapy or later was similar in the two treatment arms (5.1% in the benda arm and 7.2% in the G-benda arm).

Deaths

Until the clinical cut-off date, a total of 41/198 patients (20.7%) in the benda arm and 34/194 patients (17.5%) in the G-benda arm had died during the study. PD was the most common cause of death in each treatment arm (benda 29/198, 14.6%; G-benda 22/194, 11.3%). Others died because of AE: benda 12/198 (6.1%) and in G-benda 12/194 (6.2%). Death due to AE, was mainly caused by infections, other malignancies (leukemia, colorectal cancer and T-cell lymphoma), tumour lysis syndrome and stroke. There was no imbalance in the incidence of fatal events between the two arms.

Laboratory findings

The changes in hematology parameters observed in the G-benda arm were consistent with the mechanism of action of obinutuzumab. Grade 4 neutropenia were more frequently reported in the G-benda arm, 21.2% vs. 32.0%.

The incidence of AE was higher in patients who had creatinine clearance < 50 ml/min, however number of patients was small and the results should be interpreted with caution. In 116/121 patients, B-cell depletion was only assessed in the G-benda arm. It was defined as $CD19^{+}$B-cell counts < 0.07x109/L after at least one dose of obinutuzumab had been administered. B-cell depletion started on day 8 of Cycle 1 in the majority of patients. At the time of the clinical data cut-off, recovery was only noted in 2 patients.

IgG was affected in 14.9% of the patients and was not recovered at the time of data cut-off. In other chemistry parameters, no notably differences were evident, except that hypocalcemia was more frequent in the G-benda arm (37.6% vs. 25.9%). Urinanalysis showed no clinical important trends.

Human Anti-Human Antibodies (HAHA) was positive in two patients at baseline and both patients had an IRR the same day. One patient had a grade 1 IRR and was able to continue on study treatment, the other patient had a grade 4 IRR and obinutuzumab was discontinued.

With the updated results; No major changes in the laboratory hematology or biochemistry parameters were observed in in the updated laboratory test analysis as compared with the primary analysis. As described in the primary CSR, the frequency of Grade 3-4 leucopenia, lymphocytopenia and neutropenia was higher in the G-benda arm than in the benda arm. Notably, there was no difference in the incidence of Grade 3-5 infections between treatment arms (38 patients [18.5%] in the benda arm and 40 patients [19.6%] in the G-benda arm).

Safety in special populations

Overall, the updated analysis of safety by patient age group (< 65 and ⩾ 65 years) were consistent with the primary analysis showing a higher incidence in both treatment arms of clinically important AEs, including SAEs, Grade 5 AEs and AEs leading to withdrawal from treatment in patients ⩾ 65 years old than in younger patients. The difference in incidence between arms for SAEs in patients ⩾ 65 years old remained relatively consistent (~10% higher in the G-benda arm) at both clinical cutoff dates for the primary and updated analyses.

The updated analysis of safety by renal function was consistent with the primary analysis. Only a small number of patients (33 [~8%]) had creatinine clearance (CrCL) of < 50 mL/min at baseline, and therefore the results should be interpreted with caution. In both treatment arms, the incidence of SAEs

and deaths was higher in patients with CrCL < 50 L/min at baseline compared with patients with CrCL > 50 L/min at baseline.

Overview of Safety in patients with FL (comparison with overall iNHL patients population) Cutoff: 1 May 2015)

	iNHL		Follicular Lymphoma	
	benda n = 205	G-benda n = 204	benda n = 168	G-benda n = 164
Total number of deaths	56 (27.3)	42 (20.6)	48 (28.6%)	30 (18.3%)
Total number of events	2534	3069	2136	2452
Total number of patients with at least one:				
AE	201 (98.0)	200 (98.0)	166 (98.8)	162 (98.8)
Grade 3–5 AE	132 (64.4)	141 (69.1)	105 (62.5)	111 (67.7)
Grade 5 AE (fatal outcome)	13 (6.3)	15 (7.4)	11 (6.5)	10 (6.1)
Serious AE	73 (35.6)	84 (41.2)	58 (34.5)	64 (39.0)
AE leading to withdrawal from treatment*	34 (16.6)	39 (19.1)	30 (17.9)	29 (17.7)

* any study treatment.

Source: Table 4, t_ae_osafe2_emerge_foly_297_SE; t_dd_c_surv_foly_297_SE; t_ae_byterm_emerge_gr345_foly_297_SE.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with obinutuzumab as such interactions are not expected with this mAb. A comparison of serum pharmacokinetic parameters from studies of obinutuzumab monotherapy (Studies BO20999, BO21003) with pharmacokinetic parameters from studies of obinutuzumab in combination with chemotherapy (BO21000) suggests that concomitant chemotherapy has minimal impact on the pharmacokinetics of obinutuzumab.

Discontinuation and dose modifications due to adverse events

Reasons for dose modifications/discontinuation were neutropenia, thrombocytopenia and IRRs. The proportion of patients who experienced at least one AE that led to discontinuation of study medication was 15.7% in the benda arm vs. 18.0% in the G-benda arm. The most common AEs that led to discontinuation (benda vs. G-benda) were: thrombocytopenia (6.1% and 3.6%, neutropenia (2.5% and 4.6%), infections (3.5% and 2.1%) espec. pneumonia (1.0% in both arms) and IRRs (1.5% and 2.1%)

Dose modification, i.e. dose reductions or increase were not allowed for obinutuzumab, but dose interruption, delays, discontinuations and reduction of infusion rate were permitted. The incidence of AEs that led to any drug modification (all dose modifications and interruptions) during the entire study was higher in the G-benda arm (61.3%) vs. the benda arm (43.9%), mainly due to IRRs and comparable symptoms. Thrombocytopenia led to a higher proportion of dose modifications in the benda arm compared with the G-benda (18.7% vs. 11.9%). The most common AEs that resulted in dose modification of obinutuzumab were neutropenia (21,6 %) and thrombocytopenia (11.3%). A higher incidence of AEs leading to bendamustine dose modification (41.4%) in the benda arm than in the G-benda arm. This was mainly due to the following: thrombocytopenia (benda 18.7% vs. G-benda 9.8%), GI disorders (5.1% vs. 3.6%), mainly nausea, diarrhea and stomatitis and IRR (3.5% vs. 2.1%). A total of 22.2% of patients had an infusion modification of obinutuzumab (i.e., infusion interruptions, slowing or discontinuations) during the Induction Phase, most of which occurred during Cycle 1 (19.6% of patients), and 'AE' was the most common reason (3.1%). The most common AEs that resulted in delaying the

obinutuzumab dose (other than dose interruptions and slowing of the infusion) were neutropenia (21.6%) and thrombocytopenia (11.3%). Most of these modifications did not result in discontinuation of the infusion; the majority of patients (99.4% to 100%) of patients received >90% of the planned obinutuzumab dose from Cycle 2 onwards. The most common AE that resulted in modifying the obinutuzumab dose was neutropenia.

Adverse Events During the Maintenance Phase

Safety data for the maintenance phase are only presented for the G-benda arm.

The AEs reported during the Maintenance Phase accounted for 21.6% (623/2889) of all events reported for the G-benda arm over the entire study. The overall incidence of AEs for patients in the Maintenance Phase was 76.2%, the most common AEs was neutropenia and infections (Table 69). Grade 3-5 AEs were reported in 29.4% of the patients, the most frequent which occurred in ≥ 5% of patients was neutropenia (9.8%). Other grade 3-5 AEs occurred in 1-2 patients. SAEs were reported in 18 patients, most were isolated, with the exception of febrile neutropenia and sepsis.

Other AEs that occurred in ≥ 5% of patients were all Grade 1-2. No grade 5 AEs or deaths were noted and the incidence of IRRs and neutropenia was lower in the Maintenance Phase compared with the Induction Phase.

The AEs that led to withdrawal of patients from study medication during the maintenance period, were pneumonia (2), one had a pseudomonal lung infection, neutropenia (3), AML/MDS (2) and bladder cancer (1 patient).

The most common cause of study drug delay/interruption was neutropenia, which occurred in 14.7% of the patients.

Overall the incidence of AEPI was low during the Maintenance Phase: IRRs (12 patients), neutropenia (17), infections (67), thrombocytopenia (2) and cardiac event (7 patients). The nature, frequency and severity was consistent with previous experience with obinutuzumab monotherapy.

Table SAEs Reported During the Maintenance Phase (Safety Population)

t_ae_byterm_emerge_ser_mnt_297_SEM APPROVED Adverse Events - Treatment-Emergent Serious AEs - AEs During Maintenance Phase (Patients Who Entered Maintenance Phas

Protocol(s): GA04753g/GO01297 (K01297J)
Analysis Population: Patients Who Entered Maintenance Phase - Phase III
Snapshot Date: 11AUG2015 Cutoff Date: 01MAY2015:23:59:59

MedDRA System Organ Class MedDRA Preferred Term	G-B (N=154)
Total number of patients with at least one adverse event	20 (13.0%)
Overall total number of events	25
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one adverse event	2 (1.3%)
FEBRILE NEUTROPENIA	2 (1.3%)
Total number of events	2
CARDIAC DISORDERS	
Total number of patients with at least one adverse event	2 (1.3%)
ATRIAL FIBRILLATION	1 (0.6%)
ATRIAL FLUTTER	1 (0.6%)
Total number of events	2
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one adverse event	3 (1.9%)
COLITIS	1 (0.6%)
PANCREATITIS	1 (0.6%)
UPPER GASTROINTESTINAL HAEMORRHAGE	1 (0.6%)
Total number of events	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one adverse event	2 (1.3%)
PYREXIA	2 (1.3%)
Total number of events	2
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one adverse event	9 (5.8%)
SEPSIS	2 (1.3%)
BRONCHOPNEUMONIA	1 (0.6%)
LOWER RESPIRATORY TRACT INFECTION	1 (0.6%)
PNEUMOCYSTIS JIROVECII PNEUMONIA	1 (0.6%)
PNEUMONIA	1 (0.6%)
SINUSITIS	1 (0.6%)
STAPHYLOCOCCAL SEPSIS	1 (0.6%)
UPPER RESPIRATORY TRACT INFECTION	1 (0.6%)
Total number of events	9
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one adverse event	1 (0.6%)
SEROMA	1 (0.6%)
Total number of events	1

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Total number of patients with at least one adverse event	4 (2.6%)
BLADDER CANCER	1 (0.6%)
INTESTINAL ADENOCARCINOMA	1 (0.6%)
MALIGNANT MELANOMA	1 (0.6%)
POLYCYTHAEMIA VERA	1 (0.6%)
Total number of events	4
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one adverse event	1 (0.6%)
SYNCOPE	1 (0.6%)
Total number of events	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one adverse event	1 (0.6%)
PNEUMONIA ASPIRATION	1 (0.6%)
Total number of events	1

Investigator text for AEs encoded using MedDRA v18.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdt7159z/t_ae_byterm.sas
Output: /opt/BIOSTAT/prod/cdt7159z/k01297j/reports/t_ae_byterm_emerge_ser_mnt_297_SEM.out
03SEP2015 13:25 Page 2 of 2

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

The collection of safety data was the same in the two treatment arms during the Induction Phase of the study, but for patients in the G-benda arm safety data collection continued in the Maintenance Phase. Thus, differences in safety data between treatment arms should therefore be interpreted in the light of longer treatment period in the G-benda arm, and different safety reporting requirements in each arm.

Clinical safety data are available for a total of 409 patients. Due to the higher incidence of neutropenia observed in patients given bendamustine in combination with CD20-targeted agents, patients were given different doses of bendamustine in the two arms (120 mg/m^2/dose in the benda arm vs. 90 mg/m^2/dose in the G-benda arm. The treatment duration was also different, 6 months in the benda arm (6 cycles of induction therapy) and 2.5 years in the G-benda arm (6 cycles of induction G-benda followed by obinutuzumab maintenance for up to 2 years. At the time of the clinical cutoff date 154 of 204 (75.5%) patients started the Maintenance Phase and 29 patients were still receiving maintenance treatment; therefore, the Follow-Up period after the completion of maintenance was relatively short and there is limited long-term Follow-Up data available.

Overall, the pivotal study demonstrated that induction therapy with obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance has a manageable safety profile that is comparable to that of bendamustine induction therapy alone, apart from a higher incidence of SAEs, Grade 3-5 AEs, and AEs leading to dose modification/interruption. These differences were mainly due to IRRs and neutropenia, although the incidence of neutropenia was comparable in the benda and G-benda arms during the induction phase. Infections were more frequently reported in the G-benda arm, but the difference was modest and did not result in a greater incidence of withdrawals, incidence of Grade 3-5, events or fatal infections. The difference might be due to the longer duration of treatment and longer observation period in the G-benda arm, and/or differences in safety data collection between the two arms. The incidence of thrombocytopenia was higher in the benda arm compared to the G-benda arm, probably due to a higher dose of bendamustine in the benda arm. No difference was reported in the

incidence of hemorrhagic events between the two arms, most events were grade 1-2, and the grade 3-4 events were not associated with thrombocytopenia.

The safety profile of the study drugs in the overall iNHL and FL populations was similar. Overall, the safety profile of G-benda was similar to that of bendamustine alone and also consistent with previously observed, including in the pivotal study for obinutuzumab in combination with chlorambucil in patients with CLL (Goede V et al. 2015).

Number of AEs during the maintenance with obinutuzumab was lower than during induction. Most AEs were grade 1-2, and the character was well known and manageable: IRRs neutropenia and infections. The majority of IRRs were grade 1-2, no grade 5 IRRs were reported in the study. The IRRs led to withdrawal of obinutuzumab in only 4 patients (3%), and to withdrawal of bendamustine in 3 patients (2.4%) in the benda arm and 1 patient (0.8%) in the G-benda arm. These data suggests that treatment recommendations for prophylaxis and management of IRRs (incl. premedication with corticosteroids, adjustment to the infusion rate and other supportive treatment) were effective in preventing/controlling severe IRRs. The nature, frequency and severity of AEs was consistent with previous experience with obinutuzumab monotherapy.

Reasons for dose modifications/discontinuation were well known and manageable: neutropenia, thrombocytopenia and IRRs. The treatment arms were balanced with respect to the proportion of patients who experienced at least one AE that led to discontinuation of study medication, 15.7% in the benda arm vs. 18.0% in the G-benda arm. The most common AEs that led to discontinuation (benda vs. G-benda) were: thrombocytopenia (6.1% and 3.6%, neutropenia (2.5% and 4.6%), infections (3.5% and 2.1%) especially pneumonia (1.0% in both arms) and IRRs (1.5% and 2.1%)

The supportive studies provided additional evidence of the safety and tolerability of obinutuzumab maintenance treatment. In supporting studies BO21000 and BO21003, 223 patients received obinutuzumab maintenance treatment for more than 1 year, and 80 patients were treated for the full 2 year period as planned.

Other AEs of special interests were cardiac events, the incidence being higher in the G-benda arm, but with no particular pattern emerging. One third of the events were considered IRRs, and the majority were grade 1 or 2 and manageable. When viewed in isolation, the two cases of gastrointestinal (GI) perforation reported in the G-benda arm versus no cases in the benda arm of Study GAO4753g do not provide convincing evidence of a causal role for obinutuzumab in GI perforation due to other confounding factors. However, when viewed in the context of the known risk of GI perforation in NHL patients treated with rituximab, three cases of GI perforation in the supporting studies, and the two cases that occurred in the pivotal study, the data become more compelling. Accordingly, GI perforation, is considered an important identified risk for obinutuzumab.

A rather high incidence of IRRs is noted. Patients should receive prophylactic pre-treatment before the first dose of study drug the treatment should be administered under suitable clinical settings and surveillance, as mentioned in the SmPC

The safety profile of obinutuzumab in this study was as expected, as it is an anti-CD20 antibody, with infusion-related reactions (IRRs), neutropenia and infections being the most common adverse events. The safety profile of G-benda was consistent with the known safety profiles of the individual study drugs, including that seen in the pivotal CLL-11 study with obinutuzumab in combination with chlorambucil in patients with CLL (Goede V et al. 2015). The difference between the two treatment arms was mainly due to IRRs and neutropenia and manageable with the recommendations outlined in the protocol and SmPC.

The similarity in safety profile between the two treatment arms is supported by the PRO data, which also was similar in the two treatment arms, indicating no detrimental effect on quality of life with addition of

obinutuzumab to bendamustine. The time to worsening of quality of life, measured by FACT-Lym TOI score was extended with obinutuzumab treatment.

Safety data suggested, that older patients and patients with impaired renal function, were more at risk of clinically important AEs than younger patients with better renal function. However these observations applied to both treatment arms and indicate that patients in this clinical setting have a general risk to AEs rather than a risk to obinutuzumab-related events.

2.5.2. Conclusions on clinical safety

Overall, there were no unexpected safety findings or new important risks identified, , the nature, frequency and severity of ARs was consistent with previous experience with obinutuzumab monotherapy, and the regimen of G-benda induction followed by extended treatment with obinutuzumab (maintenance) was manageable and feasible. Safety updates will be provided on an ongoing basis within the PSURs; study completion is expected to occur Q4 2019 and submission of the Final Study report Q4 2020.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion related reactions Tumour lysis syndrome Thrombocytopenia Neutropenia Late onset and prolonged neutropenia Prolonged B-cell depletion Infections Hepatitis B reactivation

Summary of safety concerns	
	Progressive multifocal leukoencephalopathy Worsening of pre-existing cardiac conditions GI perforation
Important potential risks	Impaired immunization response Immunogenicity Second malignancies ~~GI perforation~~ Immune-mediated glomerulonephritis
Missing information	Use in children Use in pregnancy and lactation

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Study BO21004: Obinutuzumab + chlorambucil compared to rituximab + chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities. 3	Primary: demonstration of clinically relevant statistical superiority in PFS obinutuzumab + Clb compared to rituximab + Clb and Clb alone and RClb compared to Clb in previously untreated CLL patients with comorbidities. Includes secondary objective to evaluate and compare the safety profile of patients.	IRRs (confirmation of decrease in IRRs since protocol amendment introducing split dosing, slow infusion and reinforcing pre-existing risk minimization measures) (complete) Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2014 (Stage 2 analysis CSR; completed) Q3 2022 (Final CSR)
Study BO21005: Obinutuzumab in combination with CHOP versus rituximab and CHOP in previously untreated patients	Primary: demonstrate superiority in PFS of obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy in previously untreated	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion	Study ongoing	Q1 2017

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
with CD20-positive DLBCL 3	DLBCL patients Includes secondary objective to evaluate and compare the safety profiles of patients treated with the combination of obinutuzumab and CHOP with rituximab and CHOP	Immunogenicity Immune-mediated glomerulonephritis		
Study BO21223: Obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in previously untreated patients with advanced indolent lymphoma followed by GA101[1] or rituximab maintenance therapy in responders 3	Primary: Efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in previously untreated advanced follicular lymphoma Includes secondary objective to evaluate and compare the safety profiles between the two arms	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	~~Q4 2017~~ Q1 2018
Study MO28543: Obinutuzumab in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL 3	Primary: To evaluate the safety and tolerability of obinutuzumab alone or in combination with chemotherapy	IRRs	Study ongoing	Q4 2018
Study GAO4753g: Obinutuzumab in	To evaluate clinical benefit in terms of PFS	Thrombocytopenia	Study	~~Q4 2016~~

[1] obinutuzumab

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
combination with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL 3	of obinutuzumab in combination with bendamustine compared with bendamustine alone in patients with indolent NHL refractory to prior rituximab-containing therapy. Includes secondary objective evaluate and compare the safety profiles of patients treated with bendamustine and obinutuzumab and bendamustine alone.	Prolonged B-cell depletion	ongoing	~~(approx.)~~ (Primary CSR complete) Updated OS results: Study Completion is expected Q4 2019 submission of the Final Study report Q4 2020 Regular safety updates will be provided with the PSURs.
~~Drug Safety Report on hemorrhagic events in the context of thrombocytopenia~~ ~~3~~	~~Evaluation of the incidence, severity and temporal relationship of hemorrhagic events and assessment of relationship with thrombocytopenia~~	~~Thrombocytopenia~~	~~In preparation~~ Complete	~~Q1 2015 (complete)~~

The assessor also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infusion related reactions	EU SmPC Section 4.2 Section 4.4 Section 4.8	None proposed
Tumour lysis syndrome	EU SmPC Section 4.2 Section 4.4	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.8	
Thrombocytopenia	EU SmPC Section 4.4 Section 4.8	None proposed
Neutropenia	EU SmPC Section 4.4 Section 4.5 Section 4.8	None proposed
Late onset and prolonged neutropenia	EU SmPC Section 4.4 Section 4.5	None proposed
Prolonged B-cell depletion	EU SmPC Section 4.4 Section 5.1	None proposed
Infections	EU SmPC Section 4.4 Section 4.8	None proposed
Hepatitis B reactivation	EU SmPC Section 4.4 Section 4.8	None proposed
Progressive multifocal leukoencephalopathy	EU SmPC Section 4.4 Section 4.8	None proposed
Worsening of pre-existing cardiac conditions	EU SmPC Section 4.4 Section 4.8	None proposed
GI perforation	~~None~~ EU SmPC Section 4.8	None proposed
Impaired immunization response	EU SmPC Section 4.4	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Immunogenicity	EU SmPC Section 4.4 Section 5.1	None proposed
Second malignancies	None	None proposed
Immune mediated glomerulonephritis	None	None proposed
Use in children	EU SmPC Section 4.2	None proposed
Use in pregnancy and lactation	EU SmPC Section 4.4 Section 4.6	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Furthermore, the MAH took the opportunity to make editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which accepted by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In GAO4753g the subgroup of FL comprised 81.1% of the ITT population of iNHL. A 52% reduction in the risk of PD or death based on IRC assessment was observed; the HR for IRC-assessed PFS was 0.48 (95% CI: 0.34, 0.68, stratified log-rank p-value <0.0001). The median PFS was 13.8 months (95% CI: 11.4; 16.2) in the benda arm and had not been reached in the G-benda arm. PFS as assessed by the Investigator confirmed the IRC-assessed PFS results (HR =0.48; 95% CI: 0.35, 0.67, p-value < 0.0001,

stratified log-rank test). The median investigator assessed PFS in the G-benda arm (29.2 months [95% CI: 17.5; NE]) was over twice as long as that in the benda arm (13.7 months [95% CI: 11.0; 15.5]).

Consistent efficacy results for the IRC-assessed PFS were observed in a panel of sensitivity analyses including re-randomization test, unstratified analysis, several exploratory analyses applying different censoring rules to evaluate alternative definitions of PFS (HRs for IRC-assessed PFS: 0.44-0.57), and subgroups of patients with FL based on demographics, baseline factors and potential disease prognostic markers.

The benefit of adding obinutuzumab to bendamustine in patients with FL was further supported by the secondary efficacy endpoints demonstrating the robustness of the results. Results of investigator-assessed PFS were consistent with those of the IRC (HR = 0.48; 95% CI: 0.35, 0.67, stratified log-rank p-value < 0.0001). Best overall (CR/PR) response rates were similar between treatment arms. The DoR for patients who achieved a CR/PR, and DFS for complete responders were longer in the G-benda arm compared with the benda arm. Hazard ratios were 0.36 (95% CI: 0.24, 0.54) for DoR and 0.10 (95% CI: 0.02, 0.44) for DFS. At the time of the analysis, median OS could not be estimated in either treatment arm. The updated OS data show that the median OS has not been reached yet, but fewer patients with FL had died in the G-benda arm (30/164 [18.3%]) compared to the benda arm (48/171 [28.1%]). The HR for risk of death in patients with FL was 0.62 (95%CI: 0.39, 0.98) for G-benda vs. benda. The Kaplan - Meier plot for OS in patients with FL showed a clear separation of curves in favour of the G-benda arm from 6 months and beyond.

Uncertainty in the knowledge about the beneficial effects

At the time of the analysis, median OS could not be estimated due to small numbers and a relatively short follow-up but a trend towards an improvement in OS is indicated. A final OS analysis will take place after approximately 226 deaths have occurred. The final OS results will be provided with the submission of the final study report.

Risks

Unfavourable effects

Despite the difference in treatment duration and safety reporting in the two arms, the incidence of AEs (all grades) (98.0% of patients in the benda arm vs. 98.5% of patients in the G-benda arm), deaths (20.7% vs. 17.5%), and fatal AEs (6.1% vs. 6.2%) were similar in the two treatment arms. However a higher incidence of Grade 3-5 AEs, SAEs, and AEs leading to withdrawal with G-benda was reported in the G-benda arm. The greater incidence of these events was mainly due to neutropenia and IRRs. In both treatment arms, most fatal AEs were infections or second malignancies and there was no notable imbalance in the incidence of particular fatal events between the arms.

Thrombocytopenia was more frequently reported in the benda arm (23.7%) than the G-benda arm (14.9%); consistent with the higher dose of bendamustine in the benda arm.

Overall, the nature, frequency and severity of AEs of particular or special interest in this pivotal study (IRRs, neutropenia, infection [including progressive multifocal leukoencephalopathy], TLS, thrombocytopenia [including hemorrhagic events], cardiac events, second malignancy and HBV reactivation) were consistent with previous experience. Despite the frequent incidence of IRRs, most patients in the G-benda arm received the full dose of obinutuzumab and were able to continue with obinutuzumab therapy. The first dose of obinutuzumab could be split over two days if required for IRRs but only one patient had a split dose.

The safety profile of obinutuzumab in combination with bendamustine in the subgroup of patients with FL was consistent with those for the overall iNHL (ITT) population. Overall, the safety profile of obinutuzumab in patients with iNHL in the supporting studies was consistent with the pivotal Study

GAO4753g and supports the overall safety of obinutuzumab in combination with bendamustine, as well as the safety of continued treatment with obinutuzumab monotherapy. The supporting studies provided additional evidence regarding the long-term safety of obinutuzumab. Overall, the incidence of AEs during obinutuzumab maintenance treatment was lower than during induction.

Safety data from supporting monotherapy Studies BO20999 and BO21003 demonstrated that obinutuzumab was well tolerated at the doses administered in these Phase I/II studies. There were no reports of dose-limiting toxicities in the Phase I stages of the studies and, in general, no unexpected safety issues. Similarly, in the combination Study BO21000 in first-line and relapsed/refractory setting the safety profile of obinutuzumab plus chemotherapy was consistent with the known safety profiles of the individual study drugs (CHOP, FC, or bendamustine). No new important safety signals were reported during maintenance treatment with obinutuzumab in this study.

Gastrointestinal perforation was identified as an important identified risk following an integrated analysis of the two cases of GI perforation reported in Study GAO4753g and the three reported cases of GI perforation among obinutuzumab-exposed patients in the supporting studies.

In study GAO4753g, the risk of IRRs is frequent with G-benda, in particular during the first cycle of treatment (55.2% patients have an IRR in cycle 1). This is coherent with the experience we have with GAZYVARO. Supportive therapies (e.g., supplemental oxygen, β2-agonists/epinephrine, and/or corticosteroids) were allowed for serious IRRs according to standard clinical practice. Management of IRRs is described in the SmPC section 4.2.

Uncertainty in the knowledge about the unfavourable effects

The proportion of patients who experienced second malignancies 6 months after starting treatment or later was 5.1% in the benda arm and 7.2% in the G-benda arm. There remains some uncertainty about the long-term risk of secondary cancer (See RMP).

The incidence of types of infections shows no clear pattern. The incidence of infections/infestations could be related to neutropenia and the IgG level. Although no trend is reported, there might exist especially vulnerable populations, which require special attention and where IgG substitution should be considered (See RMP). Safety updates of GA04753g study will be submitted on an ongoing basis within the PSURs.

Table 1. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by IRC in FL subgroup	Progression-free survival	Months	29,2	13.8	HR = 0.47(95%CI:0.34,0.64) P<0.0001	
PFS by IRC in ITT population		months	29,2	14.91	HR = 0.53 (95%CI:0.40,0.70) p<0.0001	
Unfavourable Effects						
IRR		(%)	68.6%	63.1%		

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Neutropenia		(%)	37.6%	31.8%		
Infections		(%)	55.6%	65.5%		
Secondary malignancies		(%)	7.2%	5.1%		
Cardiac events		(%)	11.3%	5.6%		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Patients with relapsing-remitting follicular lymphoma, resistant to chemotherapeutic agents and to rituximab which may progress to a more aggressive high-grade lymphoma have very limited treatment options and poor prognosis. Bendamustine has been shown to be effective in the treatment of patients with rituximab-refractory iNHL.

Although both rituximab and obinutuzumab targets CD20, the binding epitopes as well as their effects are different. Treatment with G-benda resulted in a statistically clinically relevant and significant reduction by 45% in the risk of IRC-assessed PFS compared with benda alone (HR=0.55 (95% CI: 0.40, 0.74; log-rank p-value = 0.0001). The Kaplan-Meier estimated median PFS was 14.9 months in the benda arm (95% CI: 12.8, 16.6), it was not reached in the G-benda arm. The results of investigator-assessed PFS were consistent with the primary analysis, median PFS was 14.0 months in the benda arm and 29.2 months in the G-benda arm (HR 0.52, 95% CI: 0.39, 0.70; log-rank test p-value<0.0001). Updated analyses of PFS are consistent with the primary analysis. The updated OS data show that the median OS has not been reached yet, but fewer patients with FL had died in the G-benda arm (30/164 [18.3%]) compared to the benda arm (48/171 [28.1%]).

The tolerability of the combined regimen appears as expected in this clinical setting.

Benefit-risk balance

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

Discussion on the Benefit-Risk Balance

The natural history of iNHL is chemo-sensitive and with a generally good prognosis at diagnoses, but relapsing-remitting with serial intermittent courses of treatment required over several years. Typically the diseases become increasingly resistant to chemotherapeutic agents and to rituximab as well as histologic transformation to high-grade NHL can occur which are more aggressive. Bendamustine has been shown to be effective in the treatment of patients with rituximab-refractory iNHL, but there is clearly an unmert medical need in this setting.

The difference in PFS between the two treatment arms in patients with FL, favouring obinutuzumab + bendamustine followed by obinutuzumab maintenance is statistically significant and clinically important and seems robust, although the OS data are still not mature. Further, a longer DoR and DFS was reported in the G-benda arm compared with the benda arm. There is a statistically significant and clinically

meaningful reduction in the risk of PD or death with the association obinutuzumab + bendamustine in the FL population. The overall survival update from the pivotal trial will be provided with the final analysis, which was defined as the time point when 226 deaths will have occurred. Study completion is expected by Q4 2019.

The safety profile is acceptable. Updated safety information will be included in the PSURs.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the MAH took the opportunity to make editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to add the treatment of patients with follicular lymphoma based on the results of the pivotal study GAO4753g. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the MAH took the opportunity to make editorial changes to sections 4.4, 4.6, 5.3 and 6.6 of the SmPC.

Summary

Please refer to the scientific discussion for Gazyvaro EMEA/H/C/002799/II/0007