



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for ofatumumab

Proprietary Product Name: Arzerra

Sponsor: Novartis Pharmaceuticals Australia Pty  
Ltd

**January 2018**

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
AUC	Area under the curve
AUC(0-inf)	Area under the curve from time zero extrapolated to infinity
AUC(0-t)	Area under the curve from time zero throughout the dosing
BFR	Bulky fludarabine-refractory
BR	Bendamustine and rituximab
BSA	Body surface area
CI	Confidence interval
CL	Clearance
CLcr	Creatinine clearance
CLL	Chronic lymphocytic leukemia
Cmax	Maximum observed concentration
CMI	Consumer Medicines Information
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
Ctrough	Minimum concentration observed prior to next dose
CV%	Co-efficient of variation
CYP	Cytochrome
DLBCL	Diffuse large B-cell lymphoma
DR	Double-refractory; refractory to both fludarabine and
ECL	Electrochemiluminescence

Abbreviation	Meaning
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay FL Follicular lymphoma
EMAP	Emerging Markets and Asia Pacific
F/U	Follow-up
FCR	Fludarabine, cyclophosphamide, rituximab
FISH	Fluorescent in-situ hybridization
FL	Follicular lymphoma
FR	Fludarabine and rituximab
G-CSF	Granulocyte colony-stimulating growth factor
GSK	GlaxoSmithKline
HAHA	Human anti-human antibody
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IGHV	Immunoglobulin heavy chain variable region
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous
IVIG	Intravenous gamma immunoglobulin
IWCLL	International Workshop for Chronic Lymphocytic Leukemia MRD Minimal residual disease
mAb	Monoclonal antibody
MS	Multiple sclerosis
NCI-WG	National Cancer Institute-sponsored
NONMEM	Nonlinear mixed-effects modeling approach

Abbreviation	Meaning
Obs	Observation
OFA	Ofatumumab
OS	Overall survival
PD	Pharmacodynamic
PD	Progressive disease
PFS	Progression-free survival
PI	Product Information
PI3 kinase	Phosphatidylinositol-3-kinase Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Per protocol
PR	Partial response
PRO	Patient-reported outcome
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RAP	Reporting and analysis plan
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisolone
SCE	Summary of Clinical Efficacy
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SCT	Stem cell transplantation
SD	Stable disease
SOC	System organ class
TKI	Tyrosine kinase inhibitors
ULN	Upper limit of normal
V <sub>ss</sub>	Volume of distribution at steady rate

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Withdrawn
<i>Active ingredient:</i>	Ofatumumab
<i>Product name:</i>	Arzerra
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Pty Ltd Australia 54 Waterloo Road Macquarie Park NSW 2113
<i>Dose form:</i>	Injection concentrate vials
<i>Strengths:</i>	100 mg/5 mL and 1000 mg/5mL
<i>Route of administration:</i>	Intravenous (IV) infusion
<i>Dosage:</i>	The proposed schedule for maintenance is 300 mg on day 1 followed 1 week later by 1,000 mg on day 8 (cycle 1), followed by 1,000 mg on day 1 of subsequent cycles every 8 weeks for up to a maximum of 2 years. In approved indications, the schedule allows a maximum of 12 x 28 day cycles in upfront chronic lymphocytic leukaemia (CLL,) and in refractory CLL, 8 x weekly then 4 x monthly infusions.

## Product background

This AusPAR describes the application by Novartis Pharmaceuticals Pty Ltd Australia to register extension of indications of ofatumumab (tradename: Arzerra). Ofatumumab is a human monoclonal antibody (IgG1 $\kappa$ ) produced in a recombinant murine cell line (NSO).

Maintenance treatment (that is, treatment to prolong or maintain remission in a patient who has responded to induction therapy for active disease) is used in the related setting of follicular lymphoma (FL). Rituximab is approved for use in those cases, and obinutuzumab has had an extension of indication recently approved that encompasses maintenance.

In chronic lymphocytic leukaemia (CLL), there are no approved anti-CD20 maintenance treatments. Ibrutinib and idelalisib are approved for ongoing use. Otherwise, it is standard after successful induction to “watch and wait”, giving patients a treatment-free interval. This interval is not just until relapse, but until the extent of progressive disease is sufficient to require the next line of treatment. Since CLL can be indolent, this may be a considerable period of time.

The current application seeks to extend ofatumumab's indication to allow maintenance use in CLL patients at high risk of relapse, who are in complete or partial response after  $\geq 2$

lines of induction therapy. High risk of relapse is defined by the recently introduced International Prognostic Index for CLL (CLL-IPI).<sup>1</sup>

The currently approved indications of ofatumumab are:

- § *Previously untreated CLL: Arzerra (ofatumumab) is indicated in combination with chlorambucil or bendamustine for the treatment of patients with CLL who have not received prior therapy and are inappropriate for fludarabine-based therapy; and*
- § *Refractory CLL: Arzerra (ofatumumab) as a single agent is indicated for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.*

The proposed additional indication is under a new title:

- § *Maintenance Therapy in CLL: Arzerra (ofatumumab) is indicated as maintenance treatment for adult patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy.*

This is a modification of the initial proposal in the current submission, which was to register the following indication:

- § *Maintenance therapy in CLL: Arzerra (ofatumumab) is indicated as maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.*

At time of TGA submission, similar applications for ofatumumab use as maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy were under evaluation in the US, EU, Canada and Switzerland (Table 1). During the course of TGA evaluation, the US FDA approved ofatumumab as maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.

The sponsor sought the broader maintenance indication at the outset of this submission, but narrowed its proposal to “patients at high risk of relapse”. EMA rejected an application for both the broader and narrower (high risk of relapse) indications.<sup>2</sup>

## **Regulatory status**

The international regulatory status of Arzerra at the time of this submission to TGA is listed in Table 1.

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<sup>1</sup> International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 17: 779-790 (2016).

<sup>2</sup> See European Public Assessment Report (EPAR) for Arzerra (published 23 June 2016).



**Table 1: International regulatory status of Arzerra at time of this submission to TGA.**

Country / region	Submission date	Status	Indications (approved or requested)
Canada	28 Jul 2015	Rejected. Notice of non-compliance: 14 Jul 2016. Novartis withdrew application: 12 Oct 2016	Arzerra is indicated as maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.
EU centralised procedure* (includes UK, Netherlands and Sweden)	7 Jul 2015	Rejected. CHMP opinion: 23 June 2016	<ul style="list-style-type: none"> <li>Arzerra is indicated as maintenance treatment for adult patients with CLL who are in complete or partial response after at least two lines of induction therapy</li> </ul> Revised during procedure to: <ul style="list-style-type: none"> <li>Arzerra is indicated as maintenance treatment for adult patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy.</li> </ul>
Switzerland	29 Oct 2015	Under evaluation	<ul style="list-style-type: none"> <li>Ofatumumab is indicated as maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.</li> </ul> Revised during procedure to: <ul style="list-style-type: none"> <li>Ofatumumab is indicated as maintenance treatment for patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy.</li> </ul>
USA	22 Jul 2015	Approved	Arzerra (ofatumumab) is indicated for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL

\* Denmark (Rapporteur), Norway (Co-Rapporteur)

## II. Registration timeline

Description	Date
Submission dossier accepted and 1st round evaluation commenced	24 Dec 2015
1st round evaluation completed	31 May 2016
Sponsor provides responses on questions raised in 1st round evaluation	27 July 2016
2nd round evaluation completed	8 Sep 2016
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	14 Dec 2016
Sponsor's pre-Advisory Committee meeting response	16 Jan 2017
Advisory Committee meeting	2-3 Feb 2017
Withdrawal by sponsor	16 Feb 2017

### III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

### IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

### V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

#### Introduction

##### Clinical rationale

The sponsor's letter of application outlines the clinical rationale for the application to extend the indications of Arzerra (ofatumumab). The sponsor notes that there is no approved maintenance therapy for CLL. The sponsor comments that "a strategy to improve survival outcomes is to improve response durability through maintenance therapy, which is a treatment given to prolong or maintain remission in a patient who has responded to induction therapy for active disease". The sponsor comments that maintenance treatment may provide greater clinical benefit for patients after treatment for relapsed CLL than observation alone.

*Comment: The sponsor's clinical rationale is acceptable. However, it is unclear why the then sponsor (GSK) decided to investigate ofatumumab maintenance treatment in patients with CLL in response following at least 2 lines of therapy rather than at least 1 line of therapy. This matter has been raised in the Questions section.*

##### Contents of the clinical dossier

The submission contained the following clinical information:

- Clinical pharmacology data, including pharmacokinetic (PK) and pharmacodynamic (PD) data, were provided in 3 clinical efficacy and safety studies [OMB112517; OMB111827/GEN416;<sup>3</sup> and OMB112758].<sup>4</sup>
- 1 pivotal efficacy/safety study [OMB112517] supporting the proposed indication.<sup>5</sup>
- 1 other efficacy/safety study [OMB114242] not directly relevant to the proposed extension of indication.
- 1 Post-Marketing Experience Report; 1 Review of immunogenicity; data source summary table (1 page) for the updated population pharmacokinetic report; data source tables (126 pages) requested by the EU (CHMP) summarising safety data in side by side comparisons for all ofatumumab monotherapy versus combination studies (including previously evaluated studies).

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<sup>3</sup> This was a single arm clinical efficacy and safety study in re-treated subjects whose disease progressed after response or stable disease in Study Hx-CD20-406.

<sup>4</sup> This was a small, single-arm study in Japanese and South Korean patients with previously treated CLL.

<sup>5</sup> This study has since been peer reviewed and published, and also included PK and PD data updating the related information in the PI.

- 8 in vitro studies reporting analytical methods for ofatumumab plasma concentrations for the human clinical studies.
- Literature references.

*Comment: The submission included one pivotal Phase III study supporting the proposed extension of indication (OMB112517). This study also included PK and PD data updating the related information in the currently approved PI. The data in this study has been fully evaluated. No relevant supportive clinical efficacy and safety studies were submitted relating to the proposed extension of indication. The submission also included PK and PD data from Study OMB111827/GEN416 (a single arm clinical efficacy and safety study in re-treated subjects whose disease progressed after response or stable disease in study Hx-CD20-406) and Study OMB112758 (a small, single-arm study in Japanese and South Korean patients with previously treated CLL). Only the clinical pharmacology data have been reviewed from Studies OMB111827/GEN416 and OMB112758.*

The submission included 1 “other study” located (Study OMB114242). The primary purpose of this study was to evaluate progression free survival (PFS) with OFA monotherapy when compared to physicians’ choice of treatment (PC) in subjects with CLL with bulky lymphadenopathy who were refractory to fludarabine. The study was conducted to meet a specific obligation related to the Conditional Marketing Authorisation in the EU of Arzerra for the treatment of CLL refractory to fludarabine and alemtuzumab. The currently approved European SmPC includes a brief reference to the efficacy data from this study, which supplements the efficacy data from a subset of patients with CLL with bulky lymphadenopathy who were refractory to fludarabine from study HX-CD20-406 and referred to in the SmPC. The Australian PI includes no reference to the efficacy data from study HX-CD20-406 in the subset of patients with CLL with bulky lymphadenopathy refractory to fludarabine, although the PI does include other efficacy data from this study. The Australian PI summarises the safety data from study Hx-CD20-406, and includes safety data from the subset of patients with CLL with bulky lymphadenopathy refractory to fludarabine.

The annotated Australian PI included with the current submission proposes no additions to the PI based on either the efficacy or safety data from Study OMB114242. Study OMB114242 was not referred to in the sponsor’s covering letter provided for the submission, nor was the data summarised in the Clinical Overview, Summary of Clinical Efficacy or Summary of Clinical Safety. However, the safety data from the OFA and OFA salvage arms of the study were included in a tabulated summary included in the submission of the safety findings relating to OFA from all OFA monotherapy and combination studies. It is considered that Study OMB114242 is not related to the current submission to extend the indications of ofatumumab to include maintenance therapy. Nevertheless, for completeness, Study OMB114242 has been evaluated and the results included and discussed in the Efficacy and Safety sections of the clinical evaluation report.<sup>6</sup>

### **Paediatric data**

The sponsor stated that the submission did not include paediatric data as CLL affects mostly elderly patients. The sponsor commented that the median age of patients with CLL at presentation is 71 years, with 11% of patients being under the age of 55 years at diagnosis. In Australia, almost 80% of all new CLL cases are diagnosed in patients over 60 years of age. CLL is rare in patients under 40 years of age. This is particularly the case in

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<sup>6</sup> This study was included as supportive evidence for the Safety Results Across Ofatumumab Monotherapy Studies in CLL, which were conducted at higher dosages.

paediatric practice, where acute lymphoblastic leukaemia (ALL) is the most common type of leukaemia in children 0 to 14 years of age. In the EU, the applicability of the Paediatric Investigation Plan Class Waiver for ofatumumab for all treatment indications for CLL was confirmed in July 2008. In the US, the use of ofatumumab in CLL has an orphan drug designation and is therefore exempt from paediatric assessment.

*Comment: The absence of paediatric data in the submission is acceptable.*

## Pharmacokinetics

### Studies providing pharmacokinetic data

The submission included PK data from three clinical studies, outlined below:

- Study OMB112517, the pivotal Phase III, randomised, controlled trial of ofatumumab (OFA) maintenance treatment versus no further treatment (that is, observation) in subjects with relapsed CLL who are in complete or partial response after at least 2 prior lines of induction therapy. OFA was administered as a two dose first cycle (300 mg at Week 1 and 1000 mg at Week 2), followed by 1000 mg on Day 1 of subsequent eight-week cycles for up to a total of 13 cycles. The study included a total of 474 patients, including 238 randomised to the OFA arm and 236 randomised to the Obs arm. OFA plasma concentrations were collected from 224 subjects, and the PK dataset included 2,192 observations.
- Study OMB111827/GEN416 is a single arm study that re-treated subjects with fludarabine refractory CLL whose disease had progressed after response or stable disease in Study OMB111773/Hx-CD20-406. Subjects who responded in the re-treatment phase were continued on maintenance therapy. OFA was administered during the re-treatment phase as weekly infusions for 8 weeks (initial dose of 300 mg, then 2000 mg for 7 infusions), followed by maintenance treatment consisting of 2000 mg infusions every four weeks for up to 24 months. This study was previously submitted based on the interim results, and the end-of-study results were included in the submission.
- Study OMB112758 is a Phase I/II, single arm study in Japanese and South Korean subjects with previously treated CLL. OFA was administered as an IV infusion of 300 mg followed by infusions of 2000 mg weekly for seven consecutive weeks, then five weeks later by infusions of 2000 mg every four weeks for four infusions.

### Evaluator's conclusions on pharmacokinetics

The submitted PK data supplement the known data for OFA. The new PK data for the proposed OFA maintenance regimen from the pivotal study OMB112517 established that the pharmacokinetics of this regimen were consistent with the pharmacokinetics (PK) of the regimens for the approved indications. No unexpected findings relating to the PK of the proposed OFA maintenance regimen were identified. The limited PK data in Japanese and Korean patients from Study OMB112578 were consistent with the PK data in Western patients.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Studies OMB112517, OMB111827/GEN416 and OMB112758 contained pharmacodynamic data on the effects of ofatumumab administration on CD5+CD19+ cell counts.

### Evaluator's conclusions on pharmacodynamics

The data on B cell counts in the pivotal Study OMB112517 were consistent with the data from the previously evaluated studies. Following ofatumumab administration there was a rapid and sustained reduction in CD5+CD19+ counts.

### Dosage selection for the pivotal studies

The single pivotal Phase III study in the submission is OMB112517. The recommended dose for maintenance treatment of patients with CLL who are in complete or partial response after at least two lines of induction therapy is 300 mg on day 1 followed 1 week later by 1000 mg on day 8 (cycle 1), followed by 1000 mg on day 1 of subsequent cycles every 8 weeks after the first visit for up to a maximum of 2 years.

The sponsor stated that the proposed OFA dose and schedule for the pivotal study were selected based on preclinical data with OFA, clinical PPK modelling and simulation data, prior clinical experience with rituximab, and prior clinical experience with OFA.

The sponsor reported that preclinical data suggested that OFA plasma concentrations > 10 µg/mL were sufficient to suppress peripheral B cell recovery in cynomolgus monkeys as well as suppress tumour cell growth in Daudi tumour bearing SCID mice. OFA concentrations above 50 µg/mL were sufficient for complete B cell depletion. Recovery of CD20+ cells in peripheral blood and lymph nodes occurred when plasma OFA concentrations dropped below 5-10 µg/mL. Thus, a potential clinical target in developing OFA dosing regimens was prolonged maintenance of plasma concentrations > 10 µg/mL.

Pharmacokinetic data from the Phase I study in 33 subjects with relapsed or refractory CLL (study Hx-CD20-402) were analysed by the sponsor using a 2 compartment, nonlinear mixed-effects model (NONMEM). Assuming that the pharmacokinetics OFA with maintenance administration in subjects with CLL who have responded to their most recent therapy is similar to that observed with repeated weekly OFA administration, the resulting model was used to simulate concentration-time data for 500 subjects receiving OFA at 300 mg at Week 1 and 1000 mg at Week 2, followed by 1000 mg every 8 weeks for 2 years. Based on these simulations, the probability of maintaining plasma OFA target concentrations > 10 µg/mL was approximately 75% after the third 1000 mg dose at Week 17, increasing over time to approximately 90% during continued maintenance dosing and for 8 weeks after the last dose. Therefore, a dosing schedule with the first infusion of 300 mg at Week 1 and subsequent infusions of 1000 mg at Week 2 and thereafter at 8 week intervals starting with Week 9, is expected to achieve prolonged maintenance of target plasma concentrations >10 µg/mL in a high proportion of patients with CLL.

The sponsor stated that prior clinical experience with rituximab suggests that prolonged administration schedules enhance response duration in patients with non-Hodgkin lymphoma (NHL).<sup>7</sup> Two Phase II studies in patients with CLL have examined maintenance

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<sup>7</sup> Collins-Burow B, Santos ES. Rituximab and its role as maintenance therapy in non-Hodgkin lymphoma. *Expert Rev of Anticancer Ther.* 7: 257-273 (2007); van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. *Curr Oncol Rep.* 9: 378-383 (2007).

therapy with rituximab, 1 study examined 4 weekly infusions of 375 mg/m<sup>2</sup> every 6 months for up to 2 years in patients with objective response or stable disease after initial rituximab treatment,<sup>8</sup> and 1 study examined 4 monthly infusions of 375 mg/m<sup>2</sup> followed by 12 monthly infusions of 150 mg/m<sup>2</sup> in patients with CR or PR positive for minimal residual disease (MRD) after fludarabine/rituximab treatment.<sup>9</sup> The sponsor stated that these studies suggest that prolonged administration schedules enhance response duration in patients with CLL. The existing clinical experience with maintenance rituximab suggests that administration of an anti-CD20 monoclonal antibody should be tolerable for up to 2 years.

Prior clinical experience in a Phase I/II trial of OFA in subjects with relapsed or refractory CLL (Study Hx-CD20-402) suggested that a total dose of 6500 mg (weekly doses of 500, 2000, 2000, and 2000 mg) was effective and well tolerated.<sup>10</sup> In the pivotal trial in subjects with refractory CLL (Study Hx-CD20-406), OFA was given as an initial infusion of 300 mg, followed by seven 2000 mg infusions at weekly intervals, followed 5 weeks later by 2000 mg infusions every 4 weeks for 4 doses.<sup>11</sup> This initial high dose intense regimen followed by monthly high dose infusions was tolerated, suggesting that 1000 mg OFA every 2 months for 2 years should be tolerated. As AEs in previous trials had been primarily infusion related events on the day of the first infusion, the prolonged treatment schedule in Study OMB112517 was not expected to affect the overall safety profile.

*Comment: The sponsor's rationale for the selected dose and dosing schedule is considered to be acceptable.*

## Efficacy

### Studies providing efficacy data

#### *Pivotal efficacy study (OMB112517 [PROLONG])*

- Title: A phase III, open-label, randomized multicentre trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia who have responded to induction therapy.

The title **PROLONG** is derived from the following letters (capitalised, bolded, underlined) included in the study title – “**Phase III Trial in Relapsed CLL Of a Monoclonal Antibody Ofatumumab maintenance therapy to delay progression versus observation**”.

The study was undertaken by GSK (the then sponsor of Arzerra) in collaboration with the Dutch-Belgian Cooperative Trial Group for Haematology-Oncology (HOVON) and the Nordic CLL Study Group. The study was initiated at 201 centres with 130 principal investigators in 24 countries. The 24 countries were located in North America, South America, Europe and Asia. There were 5 Australian centres. The study was initiated on 6 May 2010 and the data cut-off date for the submitted Clinical Study Report (CSR) was 19 June 2014.

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<sup>8</sup> Hainsworth JD, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minnie Pearl Cancer Research Network. *JCO* 21: 1746-1751 (2003).

<sup>9</sup> Del Poeta G, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. *Cancer* 112: 119-128 (2008).

<sup>10</sup> Coiffier B, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 111:1094-1100 (2008).

<sup>11</sup> Wierda WG, et al. Characteristics Associated With Important Clinical End Points in Patients With Chronic Lymphocytic Leukemia at Initial Treatment. *J Clin Oncol.* 27: 1637-1643 (2009).

*Comment: The pivotal study has been recently published in Lancet Oncology,<sup>12</sup> and is accompanied by an editorial.<sup>13</sup>*

- The primary efficacy objective of the study was to evaluate PFS in patients treated with OFA maintenance treatment compared to no further treatment after remission induction in patients with relapsed chronic CLL.
- The secondary efficacy objectives of the study were: (a) to evaluate the improvement in response, time to next CLL treatment and overall survival (OS); and (b) to evaluate PFS after next-line therapy and time to progression after next-line therapy.
- Other secondary objectives of the study were: (a) to evaluate safety and tolerability; (b) to evaluate health related quality of life (Patient Reported Outcomes [PROs]); (c) to evaluate prognostic marker correlation with clinical response (biomarkers); and (d) to evaluate PK parameters.

### **Study OMB114242 – Bulky fludarabine refractory (BFR) CLL**

- Title: An Open Label, Multicentre Study Investigating the Safety and Efficacy of Ofatumumab Therapy versus Physicians' Choice in Patients with Bulky Fludarabine-Refractory Chronic Lymphocytic Leukaemia (CLL).

The primary purpose of Study OMB114242 was to evaluate the effect on PFS of treatment with OFA monotherapy compared to physicians' choice of treatment (PC) in patients with CLL with bulky lymphadenopathy with at least 1 lymph node > 5 cm who were refractory to fludarabine. The study was conducted to meet a specific obligation for the Conditional Marketing Authorisation of OFA for the treatment of CLL refractory to fludarabine and alemtuzumab in the EU. Conditional marketing authorisation is granted by the EU to a “medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required.”<sup>14</sup>

EMA conditionally approved OFA for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab on the basis of one, open label, single arm Study Hx-CD20-406.<sup>15</sup> TGA has also approved OFA as a single agent for the treatment of CLL refractory to fludarabine and alemtuzumab presumably on the basis of study Hx-CD20-406. The Australian PI and the European SmPC indicate that in study Hx-CD20-406, OFA was given to patients who were refractory to fludarabine and alemtuzumab (n = 95), and the ORR in this group was 49% (95.3% CI: 39, 60). The European SmPC, **but not the Australian PI**, states that OFA was also given to a group of patients (n = 112) from Hx-CD20-406 with bulky lymphadenopathy (defined as at least one lymph node > 5 cm) who were also refractory to fludarabine, and that the ORR in this group was 43% (95.3% CI: 33, 53). The median PFS in the BFR group treated with OFA in Hx-CD20-406 was 5.5 months.

In addition, the current European SmPC includes the following statement based on the results of Study OMB114242:

*...an open label, two arm, randomised study (OMB114242) was conducted in patients with bulky fludarabine refractory CLL who had failed at least 2 prior therapies (n=122) comparing Arzerra monotherapy (n = 79) to physicians' choice (PC) of therapy (n=43). There was no statistically significant difference in the primary*

<sup>12</sup> Van Oers MHJ, et al. Ofatumumab maintenance versus observation in relapsed lymphocytic leukaemia (PROLONG): an open-label multicentre, randomized phase 3 study. *Lancet Oncol.* 16: 1370-1379 (2015).

<sup>13</sup> Wiestner A. Editorial: PROLONGing remission in patients with CLL. *Lancet Oncol.* 16: 1282-1284 (2015).

<sup>14</sup> European Medicines Agency, Committee for medicinal products for human use (CHMP), “Summary of opinion (initial authorisation): Arzerra (ofatumumab)”, EMA/CHMP/21426/2010, 20 January 2010.

<sup>15</sup> Blum KA, et al. Computed tomography scans do not improve the predictive power of 1996 National Cancer Institute Sponsored Working Group Chronic Lymphocytic Leukemia Response Criteria. *J Clin Oncol.* 25: 5624-5629 (2007).



*endpoint of IRC assessed PFS (5.4 versus 3.6 months, HR = 0.79, p = 0.27). The PFS in the monotherapy Arzerra arm was comparable to the results seen with Arzerra monotherapy in study Hx-CD20-406.*

The inclusion of this statement in the European SmPC suggests that Study OMB114242 has been evaluated by EMA.

*Comment: The Australian sponsor made no reference to study OMB114242 in the covering letter to the TGA relating to the current submission. It is assumed that this is because the currently approved Australian PI includes no reference to the ORR and PFS results in patients with bulky fludarabine refractory CLL from Study Hx-CD20-406. The annotated Australian PI provided with the current submission does not include any proposed additions to the PI relating to the efficacy outcomes in patients with bulky fludarabine refractory CLL from either Study Hx-CD20-406 or OMB114242. It is noted that in the currently approved Australian PI, which summarises the incidence of adverse reactions from Study Hx-CD20-406, includes data from the subset of patients with bulky fludarabine refractory CLL.*

- The primary objective of study OMB114242 was to compare the effect of OFA treatment to physicians' choice treatment on PFS in patients with bulky, fludarabine-refractory (BFR) CLL who had received at least 2 prior therapies for the disease. Disease progression was determined by an Independent Review Committee (IRC) using the 2008 International Workshop on CLL Update of the National Cancer Institute-sponsored Working Group CLL 1996 Guidelines for Response (IWCLL updated [2008] NCI-WG 1996 guidelines).<sup>16</sup> The IRC included one independent haematologist/oncologist and one independent radiologist, and assessments by the IRC were conducted in accordance with an Independent Review Charter.
- The secondary objectives of the study were: (a) to evaluate ORR, defined as the percentage of subjects achieving either a confirmed CR or a PR; (b) to evaluate OS, defined as the time from randomisation to death due to any cause; (c) to evaluate the safety and tolerability in subjects with CLL receiving OFA compared to PC during the treatment period; and (c) to evaluate health-related quality of life (HRQoL) in subjects with CLL receiving OFA compared to PC, as assessed by changes in patient reported outcome (PRO) measures relative to baseline. The study also included pharmacogenetic research objectives,

## **Evaluator's conclusions on efficacy**

### ***Efficacy for the proposed extension of indication: Study OMB112517***

The submission to extend the indications of OFA to include maintenance treatment of patients with CLL is based on data from one pivotal Phase III study (OMB112517). This multinational, multicentre, randomised, open label study compared OFA maintenance treatment to Obs (standard of care at the time of study design) in patients with CLL who were in remission (CR or PR) following at least 2 previous induction treatments. OFA was administered IV on day 1 (300 mg), day 8 (1000 mg) and then every 8 weeks (1000 mg) for up to 2 years. The primary efficacy endpoint was investigator assessed PFS, and the two inferential secondary efficacy endpoints were OS and time from randomisation to the next-line therapy. The ITT population (n = 474) was the primary population for analysis of the efficacy endpoints (OFA, n = 238; Obs, n = 236]).

The primary efficacy endpoint was PFS as assessed by the investigator in the ITT population, calculated from the date of randomisation to the date of death from any cause

<sup>16</sup> Hallek MH, et al. Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 Guidelines. *Blood* 11: 5446-5456 (2008).



or disease progression. The assessments to determine patient response or progression were performed in both study arms at approximately every 8 weeks for up to 2 years according to the pre-specified guidelines.<sup>17</sup> The assessments included physical examination of lymph nodes and organs undertaken by the investigator, and excluded assessment based on CT scan measurements.

The median follow-up in the total population was 19.1 months, and was similar in both study arms (OFA, 19.4 months; Obs, 18.7 months). The median PFS was 14.2 months longer in the OFA maintenance arm than in the Obs arm (29.4 versus 15.2 months, respectively,  $p < 0.0001$  stratified log-rank test), with a HR of 0.50 (95% CI: 0.38, 0.66). The statistically significant median difference of 14.2 months between the two study arms is considered to be clinically meaningful (that is, median PFS is approximately 2 fold longer in the OFA arm compared to the Obs arm).

The main PFS event reported in both treatment arms was disease progression rather than death (that is, 78 [33%] patients with PFS events in the OFA arm, including 4 [2%] deaths and 74 [31%] disease progression events; 120 [51%] patients with PFS events in the Obs arm, including 4 [2%] deaths and 116 [49%] disease progression events).

The median PFS in the OFA and Obs arms were notably shorter than the assumptions used to calculate the sample size. It was assumed that median PFS for the Obs arm would be 28 months, based on induction treatment with fludarabine, cyclophosphamide, rituximab [FCR] observed in the REACH study,<sup>18</sup> and that median PFS for the OFA arm would be 39.2 months (that is, 40% improvement over the Obs arm). The sponsor comments that, unlike study OMB112517, patients with relapsed CLL in the REACH study received only one prior therapy consisting mostly of alkylators, and were rituximab naïve. It was also assumed that all subjects in Study OMB112517 would receive re-induction therapy with FCR, the “gold” standard of care at the time, and consequently would have an estimated median PFS of 28 months. However, while most patients (80%) in study OMB112517 received prior treatment with chemoimmunotherapy, the sponsor stated that treatment standards had changed, resulting in 53% of patients in the pivotal study receiving FCR, which has an estimated median PFS of 28 months,<sup>19</sup> and 24% of patients receiving bendamustine and rituximab (BR), which has a shorter estimated median PFS of 14.7 months.<sup>20</sup> Therefore, the duration of PFS estimated with maintenance treatment in Study OMB112517 would have been affected by the different induction therapies used to achieve response.

Three pre-specified PFS sensitivity analyses were conducted and all were consistent with the primary PFS analysis, demonstrating the robustness of the primary analysis. The p-values for Sensitivity Analyses 1 and 2 were  $< 0.0001$ , while the p-value for Sensitivity Analysis 3 was 0.0021, which did not meet the pre-specified interim analysis statistical criteria for PFS ( $p < 0.001$ ). Sensitivity Analysis 3 was based on PD assessment undertaken by an independent oncologist (IRC) using measurements from CT scan measurements of lymph nodes and organs to determine response rather than results from palpation of lymph nodes and organs by investigators. Nevertheless, the results for Sensitivity Analysis 3 are considered to be clinically meaningful, with the median duration of PFS being 10.2

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<sup>17</sup> Hallek MH, et al. Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 Guidelines. *Blood* 11: 5446-5456 (2008).

<sup>18</sup> Robak T, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2010 28: 1756-65 (2010).

<sup>19</sup> Robak T, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2010 28: 1756-65 (2010).

<sup>20</sup> Fischer K, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol.* 29: 3559-3566 (2011).

months longer in the OFA maintenance arm than in the Obs arm (23.7 months versus 13.5 months, respectively; HR = 0.66 [95% CI: 0.50, 0.87], p = 0.0021).

Of particular note, Sensitivity Analysis 2, which was based on the independent oncologist's (IRC) assessment of PD using the lymph nodes and organ data from investigator palpation and excluding CT scan measurements was consistent with the primary PFS analysis (that is, site investigator's assessment of response and progression using palpation of lymph nodes and organs and excluding CT measurements). In Sensitivity Analysis 2, the median PFS in the OFA maintenance arm was 15.6 months longer than in the Obs arm (30.4 months versus 14.8 months, respectively; HR = 0.55 [95% CI: 0.42, 0.72], p<0.0001. The results of Sensitivity Analysis 2 mitigate the concern relating to possible observer bias associated with the subjective nature of individual investigator assessments of disease response and progression.

In general, the subgroup analyses of investigator assessed PFS based on baseline demographic factors, prognostic factors and stratification factors supported the results of the primary analysis of PFS. The subgroup analyses of PFS based on baseline demographic factors consistently numerically favoured the OFA maintenance arm compared to the Obs arm (that is, gender, age, race, Binet stage). The subgroup analyses of PFS based on prognostic factors generally numerically favoured the OFA maintenance arm compared to the Obs arm (for example, cytogenetic abnormalities, IGHV mutational status). However, the results for PFS analyses based on high risk del 17p and del 11q cytogenetic variations are considered to be unreliable due to the small number of patients in these subgroups. Of note, the proportion of patients with cytogenetic abnormalities was low, and IGHV mutational status was not detectable in about 25% of patients. The subgroup analyses of PFS based on stratification factors consistently numerically favoured the OFA maintenance arm compared to the Obs arm (for example, response status at study entry, number of previous therapies, type of prior therapy).

Time from randomisation to next-line therapy in the ITT population was an inferential secondary efficacy endpoint. The median time from randomisation to next line therapy was statistically significantly longer in the OFA maintenance arm than in the Obs arm (38.0 months versus 31.1 months, respectively), with a HR of 0.66 (95% CI: 0.47, 0.92); p = 0.0108. At the time of the data cut-off, disease progression had occurred in 190 patients and 142 of these patients had received subsequent CLL therapy (OFA, 83% [62/74]; Obs, 69% [80/116]).

OS was an inferential secondary efficacy endpoint. At the time of the data cut-off, deaths had occurred in 32 (13.4%) patients in the OFA maintenance arm and 34 (14.4%) patients in the Obs arm. The median OS had not been reached in either of the two study arms at the time of the data cut-off. The currently available data show that OFA maintenance treatment does not result in either an OS benefit or detriment compared to Obs. It might be difficult to interpret the final analysis of the OS data, given that patients in both treatment arms who have progressed can receive next line therapy with other anti-cancer agents. It is unknown whether there is a correlation between PFS and OS with regards to maintenance treatment of CLL with ofatumumab.

#### *Limitations of the efficacy data*

The efficacy data in the pivotal study was based on data reviewed by the IDMC relating to PFS at the second of the two pre-specified interim analyses. The second interim analysis was triggered when at least 2/3rds of the total number of planned PFS events had occurred (that is, 187 of 280 events). The second interim analysis used a pre-specified conservative significance level of p<0.001 for the primary analysis of PFS between the two treatment arms. The pre-specified significance level for the PFS was met at the second interim analysis and the pre-specified number of 478 evaluable patients had been enrolled at the time of this analysis. Therefore, given that the pre-specified number of evaluable

patients had been enrolled and the observed magnitude of the PFS effect seen with OFA maintenance treatment, GSK (the then sponsor) in consultation with the HOVON group, decided that further enrolment into the study be discontinued. The sponsor states that the final analysis of the study will occur when 280 PFS events have occurred.

On the basis of the efficacy results at the second interim analysis, the IDMC appears not to have recommended that the study be discontinued and all patients in the Obs arm be switched to OFA maintenance. It is noted that the relevant TGA adopted EMA guideline<sup>21</sup> states, “in general, interim analyses based on PFS data other than for futility are not encouraged”. However, the results of the primary analysis of the PFS were statistically significant and clinically meaningful, as was one of the two inferential secondary efficacy endpoints (time to next line therapy). In addition, the numerous exploratory subgroup analyses of PFS consistently favoured the OFA maintenance arm relative to the Obs arm. In addition, the observed number of events (187) represents a reasonable proportion (67%) of the planned number of events (280). On balance, it is considered that a meaningful clinical assessment of the efficacy of OFA maintenance compared to Obs can be made based on the interim primary analysis of the PFS and the analyses of the inferential secondary endpoints (that is, time to next-line treatment and OS).

One of the limitations of the study is the absence of data relating to patients who were in remission, but were not selected by investigators for enrolment. It might be that the non-selected patients were healthier, were lower risk and had a better quality of life than patients selected for enrolment. If so, then there might have been reluctance on the part of investigators to enrol patients in remission who were doing well and/or reluctance of these patients to participate in the study, given that there was a 50% chance of being randomised to the OFA maintenance arm and the known risks associated with this medicine. Therefore, it is possible that the study might have been subject to selection bias, with healthier patients being excluded from the study population.

The data on high-risk patients with cytogenetic abnormalities (17p deletion; 11q deletion; 6q deletion, 12q trisomy or 13q deletion) is limited. This raises doubts about the generalisability of the results from the general population to patients with high-risk cytogenetic abnormalities.

The submission to extend the indications of OFA is supported by one pivotal Phase III study. The relevant TGA adopted EU guidelines relating to the submission of applications with of one pivotal Phase III study<sup>22</sup> state, “there is no formal requirement to include two or more pivotal studies in the Phase III program”, but “in the exceptional event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency”. It is at least arguable that the pivotal Study OMB112517 meets these criteria, based on the clinically meaningful and statistically significant difference in median PFS of 14.2 months in favour of the OFA maintenance arm compared to the OFA arm. In any event, OFA as monotherapy is currently approved as monotherapy for the treatment of patients with CLL refractory to fludarabine and alemtuzumab, from which it can be reasonably inferred that OFA has demonstrated efficacy in a particularly difficult group of patients. Overall, despite the identified limitations of the submitted efficacy data it is considered that the efficacy of OFA for the proposed usage had been adequately established in the single pivotal study.

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<sup>21</sup> European Medicines Agency, “Guideline on the evaluation of anticancer medicinal products in man”, EMA/CHMP/205/95/Rev.4, 13 December 2012.

<sup>22</sup> European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), “Points to consider on application with 1. meta-analyses; 2. one pivotal study”, CPMP/EWP/2330/99, 31 May 2001.

***Efficacy for bulky fludarabine refractory CLL: Study OMB114242***

Study OMB114242 failed to meet its primary efficacy endpoint of demonstrating statistically significant superiority of OFA (n = 78) over PC (n = 43) for PFS assessed by the IRC in patients with BFR CLL (ITT population) who have received at least 2 prior treatments. Therefore, because the primary (gatekeeper) comparison between OFA and PC was not statistically significant all other efficacy comparisons between the two treatment arms were descriptive and exploratory.

The median PFS as assessed by the IRC was numerically longer in the OFA arm than in the PC arm (5.4 versus 3.6 months), with an HR of 0.79 (95% CI: 0.50, 1.24). However, the difference in median PFS between the two treatment arms was not statistically significant (p = 0.268). Furthermore, the median difference of 1.8 months between the two treatment arms in favour of OFA is considered to be not clinically meaningful, based on the assumption used to calculate the sample size that a clinically meaningful difference in PFS between the two arms (OFA versus PC) in the primary analysis would be 3 months. The PFS as assessed by the IRC in Study OMB114242 was similar to the PFS as assessed by the PFS in study Hx-CD20-406 for bulky fludarabine refractory CLL (5.4 months versus 5.5 months, respectively).

The two pre-specified secondary efficacy endpoints were the ORR (CR+PR) assessed by the IRC and OS. As the primary efficacy endpoint was not met, the two secondary efficacy endpoints are protocol defined as being descriptive and exploratory.

The ORR assessed by the IRC was 38% (n = 30) in the OFA arm (CR, n = 0; PR, n = 30) and 16% (n = 7) in the PC arm (CR, n = 0; PR, n = 7), nominal p = 0.0190. The odds ratio was 2.94 (95% CI: 1.17, 7.42), nominal p=0.022. The results showed a numerically higher ORR assessed by the IRC in the OFA arm compared to the PC arm, but no patients in either of the two treatment arms achieved a CR. The ORR assessed by the IRC in OMB114242 in patients treated with OFA was consistent with the ORR assessed by the IRC in patients with bulky fludarabine refractory CLL treated with OFA who had received prior rituximab therapy in Hx-CD20-406 (ORR = 38% in both studies).

The median OS was 4.7 months longer in the OFA arm compared to the PC arm (19.2 versus 14.5 months), with a HR of 0.68 (95% CI: 0.41, 1.15); nominal p = 0.130. At the time of the analysis, 46% (n = 36) of patients had died in the OFA arm compared to 63% (n = 27) of patients in the PC arm. The median OS in study OMB114242 in the OFA arm was similar to the median OS in Study Hx-CD20-406 in patients with bulky fludarabine refractory CLL treated with OFA (19.2 months versus 17.4 months, respectively).

Overall, the benefits of OFA for the treatment of patients with BFR CLL were not statistically significantly superior to the benefits of PC in this patient group. In general, the efficacy endpoints in the OFA arm were numerically greater than in the PC arm, but the differences between the two arms are of doubtful clinical significance.

The PFS results from Study OMB114242 supports the following statement found in the current European SmPC:

*An open-label, two arm, randomised study (OMB114242) was conducted in patients with bulky fludarabine refractory CLL who had failed at least 2 prior therapies (n = 122) comparing Arzerra monotherapy (n = 79) to physicians' choice (PC) of therapy (n = 43). There was no statistically significant difference in the primary endpoint of IRC assessed PFS (5.4 versus 3.6 months, HR = 0.79, p = 0.27). The PFS in the monotherapy Arzerra arm was comparable to the results seen with Arzerra monotherapy in Study Hx-CD20-406.*

The sponsor is not proposing to include the above statement in the Australian PI. Based on the currently approved Australian PI, there is no compelling reason to add the above statement referring to the results of Study OMB114242 to the PI. Study Hx-CD20-406 has

been previously evaluated by the TGA, and the currently approved PI does not refer to efficacy in the subset of patients with bulky fludarabine refractory CLL treated with Arzerra in this study.

## Safety

### Studies providing safety data

#### ***OFA maintenance treatment: Study OMB112517***

##### *Studies providing evaluable data*

The safety data for OFA maintenance treatment for the proposed extension of indication were provided by the pivotal Phase III study (OMB112517). The safety data for the proposed extension of indication reviewed in this clinical evaluation report are from the pivotal study.

The protocol specified that adverse events (AEs) and serious adverse events (SAEs) were to be collected from the first dose of study treatment for patients in the OFA maintenance arm), or from the first visit (Visit 1) for patients in the Obs arm, until 60 days after the last dose for patients in the OFA maintenance arm, or 60 days after last visit (up to Visit 14) for patients in the Obs arm. In addition, all SAEs were collected from 60 days after last dose or last visit to the end of the follow-up period (up to 60 months after last visit).

Both “lack of efficacy” or “failure of expected pharmacological action” were not reported as AEs or SAEs. However, signs and symptoms and/or clinical outcomes resulting from lack of efficacy were reported if they fulfilled the definition of an AE or SAE. Events that did not meet the definition of an AE included: (a) any clinically significant abnormal laboratory finding or other abnormal safety assessment that were associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient’s condition; (b) the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition; (c) medical or surgical procedure (for example, endoscopy, appendectomy), but the condition leading to the procedure was an AE; (d) situations where an untoward medical occurrence did not occur (for example, social and/or convenience admission to a hospital); (e) anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that did not worsen; and (f) B cell depletion and hypogammaglobulinemia due to OFA treatment.

Haematologic toxicity (platelets, haemoglobin and neutrophils) was evaluated according to an adaptation of the IWCLL Grading Scale for Hematological Toxicity in CLL Studies.<sup>23</sup>

Abnormal laboratory test results (haematology, clinical chemistry or urinalysis), or other safety assessments (for example, ECGs, vital signs measurements) including those that worsened from baseline, and events that were considered to be clinically significant in the judgment of the investigator were to be recorded as an AE or SAE, in accordance with the definitions provided in the protocol.

An event that was part of the natural course of the disease under study (that is, disease progression) was not required to be reported as a SAE. However, if the progression of the underlying disease was greater than normally expected, or if the investigator considered that there was a causal relationship between treatment with investigational product or

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<sup>23</sup> Hallek MH, et al. Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 Guidelines. *Blood* 11: 5446-5456 (2008).

protocol design/procedures and disease progression, then the event was reported as a SAE.

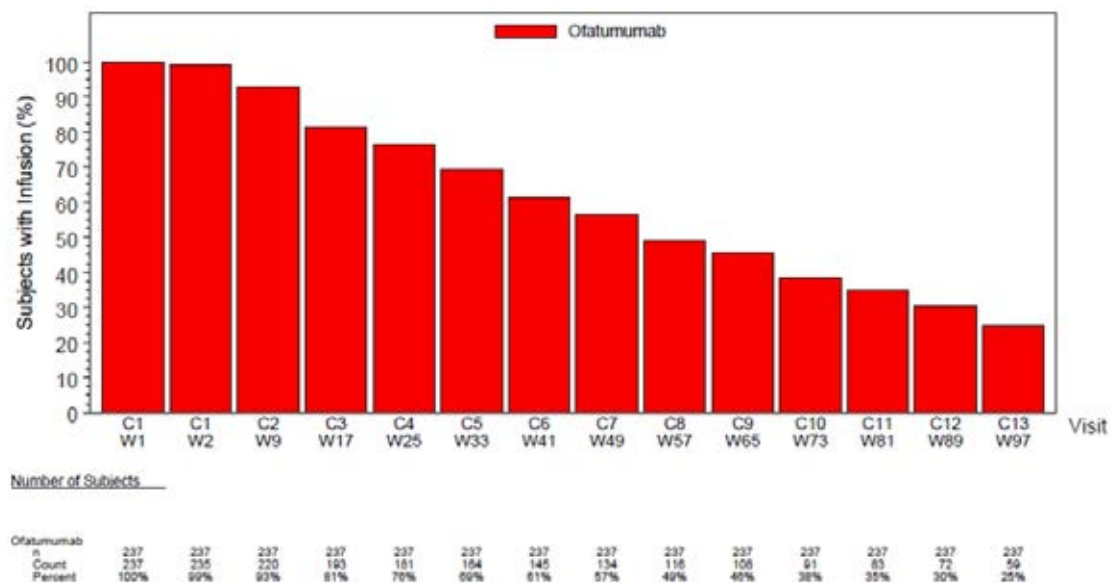
*Comment: The CSR, Clinical Overview, and Clinical Summary of Safety all focused on AEs and SAEs reported during the treatment/observation phase (i.e., from the first dose of treatment [OFA maintenance arm] or from the first visit [Obs arm] for up to 2 years), rather than on the protocol specified collection period (i.e., from the first dose [OFA maintenance arm], or from the first visit [Obs arm], until 60 days after the last dose [OFA maintenance arm], or 60 days after last visit [Obs arm]). In this CER, the approach to the review of AEs and SAEs has been to follow the approach presented in the sponsor’s documents (i.e., primary focus on AEs and SAEs collected in the treatment/observation phase). The sponsor is requested to comment on why the documents focused on AEs and SAEs reported in the treatment/observation phase rather than from the protocol defined collection period (see Question 12 of this CER). The reporting of AEs and SAEs collected during the treatment/observation phase was not specified in the study and appears to be a post hoc dataset. There was no marked difference between the proportions of patients with AEs reported in the treatment/observation and in the protocol specified period, while SAEs were reported more frequently in the treatment/observation phase than in the protocol specified period.*

**Patient exposure**

The safety population (n = 474) comprised 237 patients in each of the two study arms and included all randomised patients based on actual treatment received. One patient was randomised to the OFA maintenance arm, but did not receive any study drug and was included in the Obs arm for the safety analyses.

At the time of data cut-off, the median treatment duration for patients in the OFA maintenance arm was 382 days (range: 1, 834 days). Of all patients in the OFA maintenance arm, 49% (n = 116) received at least 8 cycles of treatment, and 25% (n=59) received all 14 infusions (that is, from Cycle 1 through to and including Cycle 13). The percent of patients in the OFA maintenance arm receiving OFA infusions during the course of treatment at each Cycle/Week is summarised below in Figure 14.

**Figure 1: OMB112517 – Percent of patients in the ofatumumab treatment arm receiving ofatumumab infusions during the course of the study; safety population.**





The median cumulative dose of OFA received by patients in the OFA maintenance arm during the course of the study was 7,300 mg (range: 300 to 13,300 mg), with the median duration of an infusion being 4.25 hours (range: 0.8 to 8.6 hours).

Over the duration of treatment, 2038 OFA infusions were administered to 237 patients and 22% (n = 51) of these patients had a total of 77 infusion interruptions or stops. The following number of interruptions or stops were experienced by the following number of patients: 1 by 38 [16%] patients; 2 by 7 (3%) patients; 3 by 2 (<1%) patients; 4 by 2 (<1%) patients; 5 by 1 (<1%) patient; and 6 by 1 (<1%) patient. The primary reason for patients interrupting or stopping OFA infusions was adverse events (86% [44 of 51 patients]).

## Post marketing data

### Overview

Post-marketing data were provided in the Summary of Clinical Safety. Ofatumumab was first approved for marketing in the USA on 26 October 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Ofatumumab has since been approved in several countries for the treatment of patients with CLL who have not received prior therapy. Based on the latest data available from Intercontinental Medical Statistics (IMS) Health, estimated cumulative post-marketing exposure to ofatumumab through 30 September 2014 was approximately 7269 patients. This is assuming each patient received a full approved treatment course (that is, 300 mg initial infusion followed by 6.78 doses of 2000 mg [13,860 mg], equivalent to 693 mL). The submitted post-marketing experience represents data from spontaneous reports and cases from post-marketing surveillance (PMS) activities, including the Named Patient Program, Temporary Access for Use, Market Research, an epidemiological study, and a Regulatory Authority's registry. The reported post-marketing safety data were consistent with the known safety profile of ofatumumab.

### Total number of events

As of 21 December 2014, there were a total of 825 spontaneous and post-marketing adverse event reports from 29 countries. The majority of reports were from spontaneous sources (670 reports), and the remaining 155 reports were received from post-marketing surveillance (PMS) activities. Within these 825 reports, there were a total of 2206 AEs (serious and non-serious). The 10 most frequently reported AEs from spontaneous and post-marketing cases are summarised below in Table 2.

**Table 2: The 10 most-frequently reported adverse events from spontaneous and post-marketing surveillance reports.**

MedDRA Preferred Term	Adverse Events n (%)
All Preferred Terms	2206 (100) <sup>b</sup>
Pyrexia <sup>a</sup>	95 (4%)
Infusion related reaction <sup>a</sup>	75 (3%)
Rash <sup>a</sup>	74 (3%)
Off-label use	59 (3%)
Urticaria <sup>a</sup>	51 (2%)
Dyspnoea <sup>a</sup>	48 (2%)
Neutropenia	47 (2%)
Chills <sup>a</sup>	43 (2%)
Disease progression	39 (2%)
Pruritus <sup>a</sup>	38 (2%)

a. AEs associated with infusion reactions and described in the ofatumumab CSI.

b. These 2006 AEs were contained in the total 825 spontaneous and PMS reports in-scope for the submitted post-marketing evaluation at the time of the data lock point.

### **Fatal events**

Of the 825 spontaneous and post-marketing reports, 118 (14%) were fatal (see Table 3 below). The System Organ Classes (SOCs) with the highest percentage of fatal AEs were “general disorders and administration site conditions” (21%) and “infections and infestations” (18%). Of note, “general disorders and administration site conditions” SOC includes preferred terms such as “death” and “disease progression”.

**Table 3: Distribution of fatal events per SOC (5% cut-off).**

MedDRA Preferred Term	Adverse Events n (%)
All Preferred Terms	502 (100) <sup>a</sup>
General disorders and administration site conditions	103 (21%)
Infections and infestations	92 (18%)
Respiratory, thoracic and mediastinal disorders	46 (9%)
Blood and lymphatic system disorders	43 (9%)
Investigations	33 (7%)
Gastrointestinal disorders	27 (5%)

a. These 502 AEs were contained in the total 118 spontaneous and PMS reports with a fatal-outcome, which are in-scope for the submitted post-marketing evaluation at the time of the data lock point.

### **Infusion reactions**

Of the 825 reports, 72 (9%) events contained the preferred term “infusion-reaction”. However, many reports describing infusion-reactions did not use the specific preferred term. Of note, there was 1 report of a fatal infusion-reaction in a patient who died the day after their first cycle of ofatumumab. Concurrent medical conditions included multiple sclerosis diagnosed in 1980. The patient did not have a history of cardiac disease. The patient’s CLL was diagnosed in 2007 and he had received prior treatments. Prior to the ofatumumab infusion, the baseline lymphocyte count was  $164 \times 10^9/L$  and blood pressure measured 132/63 mmHg with a heart rate of 118 beats/min. The patient described chest pain and dyspnoea 150 minutes after initiation of therapy with 300 mg ofatumumab. At that time, the speed of the infusion was 200 mL/h. The patient was hypertensive (182/85 mmHg) and had tachycardia (heart rate = 137 beats/min); treatment was stopped and the patient was transferred to the emergency department. Twenty minutes after transfer, the patient became hypotensive (80/45 mmHg) and went into cardiac arrest. Resuscitation efforts were unsuccessful.

The sponsor stated that the fatal case described above resulted in an update to the “Warnings and Precautions” section of the ofatumumab label to warn that infusion reactions have the potential to be fatal. The sponsor comments that infusion reactions, including cytokine release syndrome, are well characterised with ofatumumab. Overall, the sponsor commented that the nature and severity of reports describing infusion reactions remains consistent with the known safety profile of ofatumumab.

### **Cardiac events**

Of 825 reports, 52 events were categorised as “cardiac disorders” (SOC). Many of these events were temporally related to recent ofatumumab infusions and were consistent with an infusion-related reaction. Others occurred in patients with known cardiac risk factors or co-morbidities, such as older age, coronary artery disease, hypertension, hypercholesterolemia, cardiac arrhythmias (that is, atrial fibrillation), congestive heart failure, or prior history of cerebrovascular accident or thromboembolic events.

There was 1 report of QT prolongation up to 630 milliseconds in duration occurring 7 h into an ofatumumab infusion in a child patient with acute lymphocytic leukaemia and Epstein-Barr virus lymphoproliferative disorder. Baseline QTc values over the previous 6-9 months had been 400-440 milliseconds. The event was significantly confounded by hypokalaemia, hypothyroidism and hypothermia. The event resolved.



There was one report of suspected “torsade de pointes” (TdP) in an elderly patient, who also experienced several other cardiac events. The medical history of this patient included paroxysmal atrial fibrillation. The patient was being treated with flecainide, a drug known to be associated with prolongation of the QT interval, and acenocoumarol. The relevant regulatory agency (France) indicated that TdP was not confirmed, but was a hypothesis.

#### ***Small bowel obstruction***

Two reports of small bowel obstruction have been received from post-marketing reports.

#### ***Tumour Lysis Syndrome (TLS)***

Seven reports of TLS in association with ofatumumab administration have been received from post-marketing sources.

#### ***Infections***

Of the 825 reports, 200 events were categorised as “infections and infestations” (SOC). The sponsor maintains that, in general, ofatumumab does not increase the risk of infection, with the exception of HBV re-activation.

#### ***Progressive Multifocal Leukoencephalopathy***

Six cases of PML in association with ofatumumab have been reported from spontaneous or PMS activities. Two of the six reports confirmed the diagnosis of PML through diagnostic testing, which included MRI and John Cunningham (JC) virus DNA in the central nervous system. Four of the spontaneously reported PML cases were not assessable as they contained inadequate documentation.

#### ***Hepatitis B Virus (HBV)***

Four spontaneous reports of HBV infection and/or re-activation in association with ofatumumab have been received. No reports have been received from PMS activities.

#### ***Cytopenias***

Of the 825 reports, 162 events were categorised as “blood and lymphatic system disorders” (SOC). Reports of cytopenias, most commonly neutropenia and, to a lesser degree, leukopenia, anaemia and thrombocytopenia have all been received in the post-marketing setting.

#### ***Severe mucocutaneous reactions***

There has been one case of SJS reported in the post-marketing setting in a 70 year old man with no history of allergic drug reactions.

#### ***Regulatory areas of interest***

There have been no spontaneous reports or PMS activity reports of drug interactions or pregnancy associated with ofatumumab. There were 22 spontaneous reports of drug overdose, including 7 serious and 15 non-serious cases. There were 2 poorly documented fatal cases of drug overdose associated with ofatumumab. There were 6 cases of drug abuse, 1 of which was fatal and was also documented as a fatal overdose.

#### ***Evaluator’s conclusions on safety***

##### ***Proposed extension of indication: Study OMB112517 – pivotal data***

In the pivotal study (OMB112517), the safety profile of patients in the OFA maintenance arm was compared to patients in the Obs arm, with 237 patients being included in the safety population in each of the two study arms. At the time of data cut-off, the median treatment duration for patients in the OFA maintenance arm was 382 days (range: 1-834 days). Almost half (49% [n = 116]) of all patients in the OFA maintenance arm received at

least 8 cycles of treatment (that is, through to Week 57), and 25% (n = 59) of patients received all 14 planned infusions (that is, from Cycle 1 through to and including Cycle 13 [Week 97]). Based on the “rule of threes”, a population of 237 patients treated with OFA for a median duration of 382 days is large enough to reliably identify AEs occurring with an incidence of  $\geq 1\%$  with the drug.

AEs reported in the treatment/observation phase were reported more frequently in the OFA maintenance arm than in the Obs arm (87% [n = 206] versus 75% [n = 177], respectively). In addition, Grade  $\geq 3$  AEs were reported notably more frequently in this phase in the OFA maintenance arm than in the Obs arm (51% [n = 120] versus 36% [n = 84], respectively). AEs leading to infusion interruption and/or delay occurred frequently in the OFA maintenance arm (40% [n = 95]), and more commonly than permanent treatment discontinuation due to AEs (8% [n = 20]). Discontinuations due to AEs in the Obs arm were reported in 1 (<1%) patient, while AEs leading to treatment interruption and/or delays were not applicable to patients in this study arm. SAEs were reported during the treatment/observation phase in a similar proportion of patients in the two treatment arms (OFA, 33%, [n = 78]; Obs, 30%, [n = 70]), while fatal SAEs in this phase were reported more frequently in the Obs arm than in the OFA arm (8% [n = 19] versus 3% [n = 8], respectively).

Significant AEs examined during the study included liver events and secondary malignancies. Two patients in the OFA maintenance arm had liver enzyme elevations meeting the study stopping criteria, including 1 patient with Hy’s law criteria associated with gallstones considered to be unrelated to treatment and 1 patient with elevated liver enzymes related to hepatitis B reactivation considered to be related to treatment. Secondary malignancies were reported in the treatment/observation phase more frequently in the OFA maintenance arm than in the Obs arm (12% [n = 19] versus 7% [n = 17], with none being fatal in the OFA arm and 5 being fatal in the Obs arm. The increased incidence of secondary malignancies in the OFA maintenance arm compared to the Obs arm was accounted for by the higher incidence of skin and subcutaneous tissue malignancies. It is likely that further secondary malignancies will arise as the follow-up phase continues.

AEs of special interest during the study included cytopenias, infections, infusion reactions, mucocutaneous reactions, cardiac events, small bowel obstruction, and tumour lysis syndrome. Neutropenia occurred notably more commonly in the OFA maintenance arm than in the Obs arm, while anaemia and thrombocytopenia occurred in a similar proportion of patients in both study arms. There was a higher incidence of Grade  $\geq 3$  neutropenia and prolonged severe neutropenia (Grade 3 or 4) in the OFA maintenance arm than in the Obs arm, which is likely to have contributed to the higher incidence of infections (AEs) in the OFA maintenance arm compared to the Obs arm in the treatment/observation phase (65% [n = 164] versus 51% [n = 120]). No cases of PML were reported in the study.

Infections reported as AEs during the treatment/maintenance phase occurred in 65% (n = 154) of patients in the OFA maintenance arm and 51% (n = 120) of patients in the Obs arm, while SAEs in this phase occurred in 20% (n = 47) and 18% (n = 42) of patients, respectively.

Infusion related AEs occurred in 46% (n = 109) of patients in the OFA maintenance arm, and most of these reactions were Grade 1 or 2 in severity. In the OFA maintenance arm, there were 9 (4%) patients with Grade  $\geq 3$  infusion-related AEs, and 1 (<1%) patient with an infusion-related SAE. Mucocutaneous reactions occurred more frequently in the OFA maintenance arm than in the Obs arm (29% [n = 68] versus 15% [n = 36], respectively). Of the 68 patients in the OFA maintenance arm with AEs considered to be mucocutaneous reactions, 12 (18%) had events that were also classified as infusion reactions. This could explain why more mucocutaneous reactions were reported in the OFA maintenance arm

than in the Obs arm, as infusion-reactions were not reported in the Obs arm. Serious mucocutaneous reactions were rare in both study arms (OFA, <1%; Obs, 1%). No cases of SJS of TEN were reported in the pivotal study.

A similar proportion of cardiac AEs and SAEs occurred in the two study arms in the treatment/observation phase (AEs 6% and SAEs 3% in each arm), suggesting no increased risk of cardiovascular events associated with OFA maintenance treatment. Small bowel obstruction occurred in 1 patient in the OFA maintenance arm (fatal SAE) and 2 patients in the Obs arm (non-serious AEs). No cases of tumour lysis syndrome were reported in the study.

There were no marked differences in vital signs between the two study arms. Subgroup analyses of AEs by age, gender, body weight, and number and type of prior therapy did not suggest any meaningful differences compared to the total safety population.

Ongoing post-marketing safety surveillance through 21 December 2014 revealed no significant new safety findings associated with the use of OFA for marketed indications.

Overall, the safety profile of OFA in Study OMB112517 for the maintenance treatment of patients with CLL who were in CR or PR after at least 2 prior lines of induction therapy was consistent with the established safety profile of OFA for the approved indications. There were no unexpected AEs associated with OFA reported in the pivotal study, although long term safety data are limited. Not unexpectedly, AEs occurred more commonly with OFA maintenance treatment than with observation and consisted predominantly of neutropenia, infections, and infusion reactions. In general, AEs associated with OFA maintenance were manageable by dose interruptions and/or delays rather than by permanent treatment discontinuation.

#### ***Bulky-Fludarabine Refractory CLL: Study OMB114242***

The safety profile of OFA in patients with BFR CLL was consistent with the known safety profile of the drug in patients with refractory CLL. In particular, the safety profile of OFA in patients with BFR CLL in Study OMB114242 was consistent with the safety profile of OFA in the subset of patients with BFR CLL in Study Hx-CD20-406. No unexpected safety findings associated with OFA emerged from the data in patients with BFR CLL. There were some differences in the safety profiles of the OFA and PC treatment arms in study OMB114242, but the safety data from both arms is considered to be acceptable in patients with BFR CLL.

Numerical comparisons of the frequency of the safety parameters between the OFA arm (n = 78) and the PC arm (n = 43) should be interpreted cautiously, due to the longer duration of both time on treatment and safety follow-up in the OFA safety population compared to the PC safety population (that is, median time on treatment 161 versus 64 days, median safety follow-up 362 versus 149 days).

The study design partly accounted for these differences in exposure and follow-up between the two treatment arms. Patients in the OFA arm who had no disease progression at Week 24 underwent a second 2:1 randomisation to the OFA extended arm or the observation arm, and patients in the OFA extended arm could be exposed to 24 additional weeks of OFA treatment. In addition, for the safety analyses, patients in the PC arm who received OFA salvage therapy at disease progression were separately grouped in the "OFA salvage" arm and not included in the PC arm, which contributed to the large difference in follow-up time for safety.

In both the OFA arm (n = 78) and the PC arm (n = 43), most patients experienced at least one AE (91% versus 86%, respectively). AEs occurring in  $\geq 10\%$  of patients in either treatment arm (OFA versus PC, respectively) were, neutropenia (28% versus 30%), pneumonia (18% versus 21%), cough (14% versus 2%), chills (13% versus 2%), pyrexia

(13% versus 12%), thrombocytopenia (13% versus 12%), nausea (10% versus 12%), anaemia (10% versus 21%), and upper respiratory tract infection (8% versus 12%).

In the OFA arm, Grade  $\geq 3$  AEs were reported in more frequently than in the PC arm (64% versus 58%, respectively). AEs Grade  $\geq 3$  reported in  $\geq 5\%$  of patients in either of the two treatment arms (OFA versus PC, respectively) were, neutropenia (24% versus 28%), pneumonia (14% versus 12%), anaemia (8% versus 16%), thrombocytopenia (8% versus 9%), sepsis (1% versus 14%), leukopenia (1% versus 5%), autoimmune haemolytic anaemia (0% versus 5%), and hyperglycaemia (0% versus 5%). No AEs<sup>3</sup> Grade 3 occurred in  $\geq 5\%$  more patients in the OFA arm than in the PC arm. However, AEs<sup>3</sup> Grade 3 of anaemia, autoimmune haemolytic anaemia, sepsis and hyperglycaemia were all reported in  $\geq 5\%$  more patients in the PC arm than in the OFA arm.

AEs leading to permanent treatment discontinuation were reported in a similar proportion of patients in the two treatment arms (OFA, 13% [n = 10]; PC, 12% [n = 5]). The AEs leading to permanent treatment discontinuation in the 10 patients in the OFA arm were pneumonia in 2 patients and 1 patient each for hepatitis B, atrial fibrillation, cardiac arrest, cardiac failure, chorea, chorioretinal atrophy, hypotension, aseptic meningitis, multi-organ failure, myocardial infarction, pulmonary oedema and renal failure. The AEs leading to permanent treatment discontinuation in the 5 patients in the PC arm were 1 patient each with bronchopneumonia, myelodysplastic syndrome, neutropenic sepsis, pleural effusion, and tumour lysis syndrome.

AEs leading to dose delays or interruptions were reported more frequently in the OFA arm than in the PC arm (42% [n = 33] versus 33% [n = 14], respectively). AEs leading to dose delays or interruptions reported in at least 2 patients in either of the two treatment arms (OFA versus PC, respectively) were pneumonia (n = 4, 5% versus n = 2, 5%), chills (n = 4, 5% versus n = 1, 2%), febrile neutropenia (n = 3, 4% versus 0%), anaemia (n = 2, 4% versus 0%), dyspnoea (n = 2, 3% versus 0%), flushing (n = 2, 3% versus 0%), hypotension (n = 2, 3% versus 0%), pleural effusion (n = 2, 3% versus 0%), urticaria (n = 2, 3% versus 0%), pyrexia (n = 1, 1% versus n = 3, 7%), neutropenia (n = 1, 1% versus n = 3, 7%), and bronchitis (0% versus n = 2, 5%).

Other significant AEs assessed in the study included secondary malignancies, and liver chemistry abnormalities triggering pre-defined study stopping criteria. No clinically meaningful differences between the two treatment arms occurred as regards secondary malignancies (OFA, 3% [n = 2]; PC, 5% [n = 2]). Similarly, no clinically meaningful differences between the two treatment arms occurred as regards liver chemistry stopping criteria (OFA, 3% [n = 2]; PC, 5% [n = 2]).

AEs of special interest, identified based on data from previous OFA studies and events observed with other anti-CD20 monoclonal antibodies with enhanced complement dependent cytotoxicity, included cytopenias, infusion reactions, mucocutaneous reactions, infections, cardiac events, TLS, and small bowel obstruction.

The incidence of AEs associated with cytopenias, including neutropenia, anaemia, and thrombocytopenia, was high in patients in both treatment arms. However, higher proportions of patients in the PC arm compared to the OFA arm had AEs associated with decreased neutrophil counts (35% versus 29%, respectively) and decreased haemoglobin concentrations (21% versus 12%, respectively), while the incidence of AEs associated with decreased platelet counts was similar in both treatment arms (13% versus 12%, respectively). The higher incidence of AEs related to both decreased neutrophil counts and decreased haemoglobin concentrations in the PC arm than in the OFA arm may have been due to the cytotoxic chemotherapy treatment regimens used in the PC arm. However, based on clinical laboratory evaluations, Grade 3 and 4 myelosuppression (neutropenia, anaemia, or thrombocytopenia) was more frequent in the OFA arm than in the PC arm (58% versus 30%), which may have been due to the longer treatment duration in the OFA

arm compared to the PC arm. Fatal SAEs related to cytopenias included 1 case of treatment-related febrile neutropenia (OFA arm) and 2 cases of treatment-related neutropenic sepsis (PC arm). Other haematologic AEs of special interest included 3 patients with treatment-unrelated autoimmune haemolytic anaemia (OFA x 1 patient; PC x 2 patients).

Infusion reactions were reported notably more frequently in the OFA arm than in the PC arm (42% versus 26%, respectively), while Grade  $\geq 3$  infusion-reactions were infrequent in both treatment arms (4% versus 0%, respectively). The higher incidence of infusion-reactions in patients in the OFA arm might be accounted for, at least in part, by the fact that not all patients in the PC arm received therapy administered by infusions (that is, 21% of patients did not receive infusions). Infusion-reactions in the OFA arm occurred primarily on the day of the first infusion. There were no fatal infusion-reactions reported during the study.

Mucocutaneous reactions reported as AEs occurred notably more frequently in patients in the OFA arm than in the PC arm (26% versus 9%, respectively), while Grade  $\geq 3$  mucocutaneous AEs were infrequent in both treatment arms (3% versus 0%, respectively). Approximately 50% (9/20) of all mucocutaneous reactions reported in the OFA arm were considered to be infusion-reactions, while all (4/4) mucocutaneous reactions reported in the PC arm were considered to be infusion-reactions. No cases of SJS or TEN were reported in the study. There were no fatal mucocutaneous reactions reported in the study.

The incidence of infections was similar in patients in the two treatment arms (OFA, 59% versus PV, 56%), while Grade  $\geq 3$  infections occurred more frequently in the OFA arm than in the PC arm (29% versus 21%, respectively) as did SAE infections (32% versus 28%, respectively). Respiratory tract infections were the most commonly reported infections in patients in both treatment arms, and these were mainly upper respiratory tract infections (OFA, 23%; PC, 26%) and pneumonia (OFA, 18%; PC, 21%). Lower respiratory tract infections (grouped preferred terms including pneumonia) were reported in 28% of patients in both treatment arms. Fatal SAEs associated with infection were reported in 4 (5%) patients in the OFA arm, including 1 case of treatment-related PML and 3 cases of treatment-unrelated pneumonia. One additional patient in the OFA arm had treatment-related HBV re-activation during OFA extended treatment and died approximately 12 weeks later from multi-organ failure. No other cases of HBV re-activation occurred in the study. There were 3 (7%) patients in the PC arm with treatment related fatal SAEs of infection, including 2 cases of neutropenic sepsis and 1 case of pneumonia. There was 1 patient in the OFA arm with a fatal treatment-related SAE of PML.

Cardiac disorder AEs were reported notably more frequently in patients in the OFA arm than in the PC arm (17% versus 7%, respectively), as were SAEs (9% versus 5%, respectively). Cardiac disorder SAEs reported in  $\geq 2$  patients in the OFA arm (versus PC arm) were cardiac failure (2 patients [3%] versus 1 patient [2%]), atrial fibrillation (2 patients [3%] versus 1 patient [2%]), and cardiac arrest (2 patients [3%] versus no patients). All other cardiac disorder SAEs were reported in 1 patient each in the OFA arm (cardiovascular insufficiency, myocardial infarction, supraventricular tachycardia, and ventricular tachycardia) and no patients in the PC arm. Four (6%) patients in the OFA arm and 1 (2%) patient in the PC arm had fatal cardiac disorder SAEs. The 4 fatal SAEs in the OFA arm were sudden cardiac arrest (2 patients), cardiac failure (1 patient) and myocardial infarction (1 patient). The 1 fatal SAE in the PC arm was cardiac failure. None of these events were considered related to treatment, except for the fatal SAE of cardiac failure in the OFA arm (associated with Grade 4 pneumonia).

One non-serious AE of TLS in the OFA arm and 1 fatal treatment-related SAE of TLS in the PC arm were reported. No small bowel obstructions were reported in the study.

There were no confirmed OFA induced HAHAs detected in the study in 69 of the 78 patients with data in the OFA arm, or in 18 of the 22 patients in the OFA salvage arm. Median IgG, IgA, and IgM levels remained within the same range in the OFA and PC treatment arms throughout the treatment period. "Immune system disorders" (SOC) were reported in 1 (1%) patient in the OFA arm (1 x cytokine release syndrome) and 3 (7%) patients in the PC arm (1 x each for cytokine release syndrome, anaphylactic reaction, and hypogammaglobulinaemia). One (5%) patient in the OFA salvage arm experienced a hypersensitivity reaction.

There were a total of 63 deaths reported in the study, including 36 (46%) in the OFA arm and 27 (63%) in the PC arm. Of the 36 deaths in the OFA arm, 8 occurred during or after OFA extended treatment, and 4 occurred during observation. Of the 27 deaths in the PC arm, 13 occurred in patients who did not receive OFA salvage therapy and 14 occurred in patients after the start of OFA salvage therapy. The incidence of deaths in the PC arm was similar in patients who did not receive OFA salvage therapy (62%, 13/21) and in patients who did receive OFA salvage therapy (64%, 14/22).

Fatal SAEs were reported in 17% (13/78) of patients in the OFA arm (including 2 on extended OFA treatment and 2 on observation), and 23% (14/43) of patients in the PC arm (including 6 not on OFA salvage treatment and 4 on or after OFA salvage treatment). In addition to the 23 fatal SAEs, there was 1 death due to sepsis (OFA salvage therapy) and 1 death from myelodysplastic syndrome (PC arm) not reported as fatal SAEs.

In the OFA arm, treatment related fatal SAEs were reported in 5 (6%) patients, including: 1x cardiac failure and 1x renal failure in patients who died before the second randomisation; 1 x multi-organ failure in a patient treated with extended OFA after the second randomisation; and 1 x PML in a patient initially treated with OFA and then randomised to observation after the second randomisation.

In the PC arm, treatment-related fatal SAEs were reported in 5 (12%) patients, including: 1 x tumour lysis syndrome, 1 x multi-organ failure, 1 x neutropenic sepsis, and 1 x pneumonia in patients excluding OFA salvage therapy; and 1 x toxic hepatitis in 1 patient during OFA salvage therapy. In addition, in the PC arm (excluding OFA salvage arm) 1 patient died due to pulmonary embolism caused by cancer and had a fatal SAE of cardiac failure, and 1 patient died due to the disease under study and had a fatal SAE of neutropenic sepsis.

The differences in the numerical risks of treatment between the OFA and the PC treatment arms are difficult to interpret, due to the longer duration of time on treatment and longer safety follow-up in the OFA safety population compared to the PC safety population. Nevertheless, the safety profile of OFA in Study OMB114242 is consistent with the known safety profile of the drug. No new or unexpected safety findings associated with OFA were observed in patients with BFR CLL. Overall, the safety of OFA for the treatment of patients with BFR CLL is considered to be acceptable. The safety findings do not give rise to concerns relating to the continued approval of OFA, as a single agent, for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

## **First round benefit-risk assessment**

### **First round assessment of benefits**

In patients with CLL in remission (CR or PR) following at least two lines of induction therapy the main benefit of maintenance treatment with OFA compared to Obs was a clinically meaningful and statistically significant improvement in investigator-assessed median PFS of 14.2 months (that is, 29.4 versus 15.2 months, respectively;  $p < 0.0001$ ). The HR was 0.50 (95% CI: 0.38, 0.66), which reflects a 50% reduction in the risk of

experiencing a PFS event in the OFA maintenance arm relative to the Obs arm. At the time of the data cut-off, the median follow-up was 19.1 months (OFA, 19.4 months; Obs, 18.7 months).

The proportion of patients experiencing an investigator-assessed PFS was 33% (n = 78) in the OFA maintenance arm (4 deaths [2%]; 74 disease progression [31%]) and 51% (n = 120) in the Obs arm (4 deaths [2%]; 116 disease progression [49%]). OFA maintenance reduced the absolute risk of experiencing disease progression (excluding death) by 18% compared to Obs (that is, number needed to treat [NNT] = 6 patients). Over a median follow-up of 19.4 months in the OFA maintenance arm, for every 100 patients receiving OFA maintenance treatment the disease progressed in approximately 18 fewer patients compared to Obs. However, there was no difference between the two treatment arms in the number of deaths defined as PFS events at the time of data cut-off.

The OS data was immature at the time of the analysis. Median OS (an inferential secondary endpoint) had not been reached at the time of data cut-off in either of the two study arms. There was no clinically meaningful difference in the total number of deaths between the two treatment arms at the time of data cut-off (that is, OFA, 32 [13.4%]; Obs, 34 [14.4%]).

The median time from randomisation to the next-line of therapy (an inferential secondary efficacy endpoint) was 6.9 months longer in the OFA maintenance arm than in the Obs arm (37.98 months versus 31.11, respectively; p = 0.018); HR = 0.66 (95% CI: 0.47, 0.92). At the time of the data cut-off, 190 patients had disease progression and 142 of these patients had received subsequent CLL therapy (OFA, 83% [62/74]; Obs, 69% [80/116]). The results indicate that, in patients whose disease has progressed, fewer patients in the Obs arm than in the OFA arm received next-line therapy. This is consistent with the finding that the time from disease progression to next-line therapy was notably longer in patients in the Obs arm than in patients in the OFA arm.

The results of the subgroup analyses of investigator-assessed PFS based on baseline demographic factors consistently favoured the OFA maintenance arm compared to the Obs arm. The results indicate that the benefits of OFA maintenance treatment compared to Obs relating to improvement in PFS observed in the total population (primary analysis), were also seen regardless of age (<70 and ≥ 70), gender, and Binet staging at screening. The majority of patients were white (n = 453), with non-white patients accounting for only 20 patients. Therefore, the marked imbalance in patient numbers between whites and non-whites precludes meaningful assessment of the safety differences between the two subgroups.

The results of the subgroup analyses of investigator assessed PFS based on prognostic factors generally favoured the OFA maintenance treatment arm compared to the Obs arm. However, total patient numbers in the high risk cytogenetic groups were too small to meaningfully interpret the differences in PFS between the two study arms.

The results of the subgroup analyses of investigator-assessed PFS based on randomisation stratification factors consistently favoured the OFA maintenance treatment arm compared to the Obs arm, and were comparable to the result of the primary analysis in the total population. The randomisation stratification factors were response at study entry (CR versus PR), number of previous induction therapies (2 versus 3), and type of previous induction therapy (chemoimmunotherapy, only alkylating monotherapy versus other treatments).

### **First round assessment of risks**

The most frequently reported risks associated with OFA maintenance treatment in the pivotal study (OMB112517) were neutropenia, infusion-related reactions, and infections. The majority of AEs reported in the OFA maintenance arm were manageable by dose interruptions or stops rather than treatment discontinuation.

The majority of patients in both treatment arms had AEs during the treatment/observation phase, and a higher proportion of patients in the OFA maintenance arm had at least one AE compared to patients in the Obs arm (87% [n = 206] versus 75% [n = 177], respectively). AEs reported in  $\geq 10\%$  of patients in either of the two study arms (OFA versus Obs, respectively) during the treatment/observation phase were: neutropenia (24% versus 10%); cough (21% versus 9%); upper respiratory tract infection (19% versus 10%); infusion related reaction (16% versus 0%); pyrexia (16% versus 11%); diarrhoea (14% versus 4%); fatigue (11% versus 7%); pneumonia (11% versus 8%); and rash (10% versus 4%). Each of the AEs reported in  $\geq 10\%$  of patients in either of the two study arms occurred more frequently in the OFA maintenance arm than in the Obs arm.

Grade  $\geq 3$  AEs were reported during the treatment/observation phase more frequently in the OFA maintenance arm than in the Obs arm (51% [n=120] versus 36% [n=85], respectively). The most commonly reported Grade  $\geq 3$  AE in both study arms during the treatment/observation phase was neutropenia, and this event was reported notably more frequently in the OFA maintenance arm than in the Obs arm (22% versus 9%). Apart from neutropenia, the only other Grade  $\geq 3$  AEs reported in  $\geq 2\%$  of patients in either of the two study arms (OFA versus Obs, respectively) during the treatment observation phase were pneumonia (7% versus 5%), febrile neutropenia (3% versus 2%), pyrexia (2% versus 1%), neutrophil count decreased (2% versus  $<1\%$ ), thrombocytopenia (1% versus 3%), and anaemia (1% versus 2%).

In the period between the first dose (OFA)/first visit (Obs) through to 60 days after the last treatment (OFA)/last visit (Obs), Grade  $\geq 3$  neutropenia was reported in a significantly greater proportion of patients in the OFA maintenance arm compared to the Obs arm (22% [n = 51] versus 8% [n = 19], respectively;  $p < 0.0001$ ), and Grade  $\geq 3$  infections were reported non-statistically significantly more frequently in patients in the OFA maintenance arm compared to the Obs arm (13% [n = 31] versus 8% [n = 20], respectively,  $p = 0.1112$ ). Protocol defined severe neutropenia occurred in 5% (n = 13) of patients in the OFA maintenance arm and 2% (n = 5) of patients in the Obs arm. Protocol defined late onset neutropenia occurred in  $< 1\%$  of patients in both study arms (OFA, 2 patients; Obs, 1 patient).

Deaths were reported during the study in a similar proportion of patients in the two treatment arms (OFA, 14% [n = 32]; Obs, 14% [n = 34]). There were 2 deaths in the OFA maintenance arm (unrelated to treatment) and 5 deaths in the Obs arm (unrelated to treatment) reported up to 60 days after the last treatment (OFA)/last visit (Obs). The 2 deaths in the OFA maintenance arm were septicemia 36 days after the last dose in 1 patient and small bowel obstruction 54 days after the last dose in 1 patient. The 5 deaths in the Obs arm were cardiac arrest (1 patient), complications from a fall and MDS/AML (1 patient), disease under study not reported as a SAE (1 patient), fever and gastric pain (1 patient), and subdural haematoma in setting of supratherapeutic INR and sepsis (1 patient).

SAEs were reported during the study in a similar proportion of patients in the two arms (OFA, 33% [n = 78]; Obs, 30% [n = 70]). SAEs reported during the study in  $\geq 2\%$  of patients in either of the two arms (OFA versus Obs, respectively) were pneumonia (8% versus 6%), pyrexia (5% versus 3%), febrile neutropenia (4% versus 1%), neutropenia (2% versus 1%), and anaemia ( $<1\%$  versus 2%).

AEs leading to permanent treatment discontinuing were reported more frequently in patients in the OFA maintenance arm than in the Obs arm (8% [n = 20] versus  $< 1\%$  [n = 1], respectively). AEs leading to permanent treatment discontinuation and reported in more than 1 patient in the OFA maintenance arm were neutropenia (1% [n = 3]), hypersensitivity ( $<1\%$  [n = 2]), and pneumonia ( $<1\%$  [n = 2]). The AE leading to permanent treatment discontinuation in the Obs arm was autoimmune haemolytic



anaemia (<1% [n = 1]). AEs leading to dose interruptions and/or delays were reported in 40% (n = 95) of patients in the OFA maintenance arm. AEs leading to dose interruptions/delays reported in  $\geq 1\%$  of patients in the OFA maintenance arm were infusion-related reaction (15%), neutropenia (8%), bronchitis (2%), pyrexia (2%), herpes zoster (2%), pneumonia (2%), hypersensitivity (1%), influenza (1%), pharyngitis (1%), and upper respiratory tract infection (1%).

Secondary malignancies were reported during the study more frequently in patients in the OFA maintenance arm than in patients in the Obs arm (12% [n = 29] versus 7% [n = 17]), due primarily to an increase in benign and malignant skin related lesions. The proportion of patients with neoplasms reported as SAEs was similar in the 2 study arms (OFA, 6% [n = 15] versus Obs, 4% [n = 10]). None of the neoplasms reported in the OFA maintenance arm were fatal, but 5 neoplasms in the Obs arm were reported as fatal (single cases of bladder cancer, diffuse large B cell lymphoma, malignant melanoma, prostate cancer and small cell lung cancer).

Two patients in the OFA maintenance arm had liver enzyme abnormalities during the study meeting protocol stopping criteria, including 1 patient with ALT > 8 x ULN due to hepatitis B re-activation considered to be possibly due to OFA maintenance treatment, and 1 patient with ALT > 3 x ULN and bilirubin  $\geq 2$  x ULN (that is, Hy's law) due to gallstones. There were no meaningful differences between the two study arms relating to other chemistry laboratory abnormalities. There was no evidence of clinically meaningful differences in vital signs between the two study arms.

The pivotal study reported on AEs of special interest during the study. These events were cytopenias including autoimmune hematologic complications, infusion-reactions, infections, mucocutaneous reactions, tumour lysis syndrome, cardiovascular events, and small bowel/intestinal obstruction. PML and hepatitis B virus infection and reactivation were also included as events of clinical significance.

The most frequently reported cytopenic AEs in the observation/treatment phase were associated with decreased neutrophil count, which occurred more commonly in patients in the OFA maintenance arm than in the Obs arm (28% [n = 67] versus 12% [n = 29], respectively). SAEs associated with decreased neutrophil count occurred in a similar proportion of patients in the two study arms (OFA, 5% [n = 12] versus Obs, 3% [n = 6], respectively). There were no meaningful differences between the two study arms in all AEs associated with decreased haemoglobin levels or decreased platelet counts reported during the treatment/observation phase. AEs associated with decreased haemoglobin levels were reported in a similar proportion of patients in the two study arms during the treatment/observation phase (OFA maintenance, 4% [n = 9]; Obs, 5% [n = 12]), and were primarily identified as anaemia (OFA maintenance, 3% [n = 7]; Obs, 4% [n = 9]). AEs associated with decreased platelet count were reported in a similar proportion of patients in the two study arms during the treatment/observation phase (OFA, 8% [n = 19]; Obs, 8% [n = 18]), and were primarily thrombocytopenia (OFA maintenance, 5% [n = 13]; Obs, 6% [n = 14]). Autoimmune haemolytic AEs occurring during the treatment/observation phase were reported in 1 (<1%) patient in the OFA maintenance arm and 4 (2%) patients in the Obs arm.

Infusion-reactions included pre-defined infusion-related events starting after the beginning of the infusion and occurring within 24 hours following the end of an infusion and resulting in a temporary interruption or prolongation of infusion time or treatment withdrawal. Infusion related AEs were reported in 46% (n = 109) of patients in the OFA maintenance arm, and Grade  $\geq 3$  infusion-reactions were reported in 4% (n=9) of patients in the OFA maintenance arm. Infusion-related AEs associated with the first infusion were reported in 25% (n = 59) of patients, and the incidence of infusion-related AEs decreased with subsequent infusions (2% to 10%). Infusion-related AEs leading to interruption/delay of the infusion were reported in 18% (n = 42) of patients in the OFA

arm, while infusion-related AEs leading to permanent discontinuation of study treatment were reported in 2 (<1%) patients. The sponsor comments that the incidence of infusion related AEs associated with OFA maintenance treatment in the pivotal study (46%) was less than that seen in previous CLL studies (approximately 70%). The sponsor states that this could possibly be attributed to the decreased number of circulating B-cells in subjects in the pivotal study due to their remission status at enrolment.

Infections were reported as AEs during the treatment/observation phase in 65% (n=154) of patients in the OFA maintenance arm and 51% (n = 120) of patients in the Obs arm, with Grade  $\geq$  3 infections being reported in 20% (n = 47) and 16% (n = 39) of patients in the two arms, respectively. Serious infections were reported in 20% (n = 47) of patients in the OFA arm and 18% (n = 42) of patients in the Obs arm, with fatal serious infections being reported in 2% (n = 5) and 3% (n = 7) of patients in the two arms, respectively. Overall, while all infections occurred notably more frequently in the OFA maintenance arm compared to the Obs arm, the incidence of Grade  $\geq$  3 infections was similar in the two treatment arms as was the incidence of serious infections.

Mucocutaneous reactions during the treatment/observation phase were reported in 29% (n = 68) of patients in the OFA maintenance arm and 15% (n = 36) of patients in the Obs arm, with Grade  $\geq$  3 infections being reported in 3% (n = 7) and 1% (n = 7) of patients, respectively. Of the 68 patients in the OFA maintenance arm with mucocutaneous reactions, 12 (18%) patients also had events that were classified as infusion reactions. Serious mucocutaneous reactions were reported in 2 (<1%) patients in the OFA arm and 3 (1%) patients in the Obs arm, with no reactions in either of the 2 arms leading to death. There were no patients with SJS or TEN reported in the pivotal study.

The proportion of patients in the OFA maintenance and Obs arms with cardiac AEs during the treatment/observation phase was similar in the two study arms (6% [n = 14], each arm), as was the proportion of patients with cardiac SAEs (3% [n = 6], each arm). Fatal cardiac SAEs were reported in 1 (<1%) patient in the OFA arm (considered by the investigator to be unrelated to treatment) and 3 (1%) patients in the Obs arm. Small bowel obstruction was reported during the study in 1 (<1%) patient in the OFA maintenance arm and 2 (<1%) patients in the Obs arm.

In the OFA maintenance arm there was 1 (<1%) patient with  $\geq$  1 confirmed positive post-OFA HAHA result out of 205 patients with data. In the OFA maintenance arm, immunoglobulin levels in both study arms were slightly decreased at study entry and did not change significantly during maintenance treatment. In contrast, in the Obs arm serum immunoglobulin levels increased over time, possibly indicating a more pronounced recovery of B cells after induction therapy. In the OFA arm, the lower immunoglobulin levels combined with the presence of higher grades of neutropenia potentially contributed to an increased risk of infection and may have accounted for the difference in the rate of infection in the 2 treatment groups. Peripheral blood B cells started to recover 3 months after the end of OFA maintenance treatment.

### **First round assessment of benefit-risk balance**

The benefit-risk balance of ofatumumab, given the proposed usage, is favourable.

### **First round recommendation regarding authorisation**

It is recommended that the indications of ofatumumab be extended to include maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.

## Clinical questions

### Efficacy

1. In study OMB112517, why was ofatumumab maintenance treatment investigated in patients in response following 2 previous lines of therapy rather than patients in response following 1 previous line of therapy?
2. In study OMB112517, the median PFS assumptions for the sample size calculations were based on the initial results of the REACH study.<sup>24</sup> Therefore, it was assumed that the median PFS for the Obs arm would be 28 months. However, the provided reference indicates that the median PFS in the FCR induction arm in REACH was 30.6 months rather than 28 months. Please comment on the decision to use a median PFS of 28 months in the Obs arm for sample size calculation rather than 30.6 months.
3. One of the limitations of the pivotal study (OMB112517) relates to the absence of data relating to patients who were in remission but were not selected by investigators for enrolment. It might be that these patients were healthier, were lower risk and had a better quality of life than patients selected for enrolment. If so, then there might have been reluctance on the part of investigators to enrol these patients in the study and/or reluctance of these patients to participate, given that there was a 50% chance of being randomised to the OFA maintenance arm and the known risks associated with this medicine. Therefore, it is possible that the study might have been subject to selection bias by excluding healthier patients who might have been more likely to benefit from continued observation than the patients enrolled in the study. The sponsor is requested to comment on this matter.

### Safety

4. Study OMB112517: Please explain why the CSR, the Clinical Overview, and the Summary of Clinical Safety focus on the AE and SAE results from the treatment/observation phase of study OMB112517, which appears to be a non-protocol specified post-hoc data set, rather than on the AE and SAE results from the protocol specified period from the first dose until 60 days after the last dose of OFA for the OFA maintenance arm and from Visit 1 until 60 days after the last visit (up to visit 14) for the Obs arm. The explanation should include comment on the comparative strengths and weaknesses of the two AE/SAE datasets (that is, treatment/observation versus protocol specified collection periods).
5. Study OMB112517: In Section 7.2.1 (Deaths) it is stated that “no subject in the OFA maintenance arm died while in the Treatment/Obs Phase compared with 3 subjects in the Obs arm during the same Obs Phase”, and reference is given to the data in Table 33. However, the data in Table 33 identifies these deaths as occurring “on treatment” rather than in the Treatment/Obs phase. Please explain this apparent discrepancy. It appears from Table 22 that Fatal SAEs in the Treatment/Obs phase was reported in 8 patients in the OFA maintenance arm and 19 patients in the Obs arm.
6. In Study OMB114242, reporting of the AEs and SAEs in the CSR was similar to that outlined above in Safety Question 1 for Study OMB112517. Please explain why this approach was adopted in the CSR, and comment on the comparative strengths and weaknesses of the two AE/SAE datasets.
7. In Study OMB11424, the statement is made in the CSR that numerical comparisons of the AE frequencies between the OFA (n = 78) and PC (n = 43) arms presented in the CSR

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<sup>24</sup> Robak T, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2010 28: 1756-65 (2010).

should be interpreted with caution, since the duration of exposure was different in the two treatment arms due to the study design. The median duration of safety observation was 362 days in the OFA arm and 149 days in the PC arm, largely due to the potential for extended treatment in the OFA arm, and due to safety observations being discontinued in the PC arm at the time of initiation of OFA salvage therapy. Therefore, given the marked difference in exposure between the two treatment arms why were the comparative AE data not adjusted for duration of exposure?

8. In Study OMB114242, cough (irrespective of causality) was reported more frequently in the OFA arm (n = 78) than in the PC arm (n = 43) (14% versus 2%, respectively). The numerical difference between the two arms did not appear to be accounted for by a difference in respiratory tract infections between the two arms. Please comment on the difference in the incidence of cough between the two treatment arms. Is there a possible causal relationship between cough and OFA treatment?

9. Please compare the safety profiles of OFA in patients with BFR CLL from Study Hx-CD20-406 (n = 112) and from Study OMB114242 (n = 78). Please identify any clinically meaningful differences between the two safety profiles.

## VI. Pharmacovigilance findings

### Risk management plan

The sponsor submitted an EU-RMP Version 12.0 (dated 15 June 2015, DLP 21 December 2014) and Australian Specific Annex (ASA) Version 5.0 (dated 2 December 2015), which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

**Table 4: Ongoing safety concerns.**

Summary of safety concerns	
<b>Important identified risks</b>	Infusion reactions Including Cytokine Release Syndrome
	Tumour Lysis Syndrome (TLS)
	Bowel Obstruction
	Cardiovascular events
	Hepatitis B Virus (HBV) Infection and Reactivation
<b>Important potential risks</b>	Cytopenias
	Infections
	Progressive Multifocal Leukoencephalopathy (PML)
	Severe mucocutaneous reactions
	Effects on Immunisations, Including Interactions with Live Vaccines
	Immunogenicity
	Effect of Concomitant HMG-CoA Reductase Inhibitors on Ofatumumab Response
Change in safety profile following switch to acetate buffer formulation	
<b>Missing information</b>	Limited data in pregnant and lactating females
	Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary,

Summary of safety concerns	
	neurological, cerebral or psychiatric diseases.
	Limited experience in the heterogeneous non-White patient population.
	Limited experience in patients with ECOG 2 performance status.

### ***RMP reviewer's comments***

The ongoing safety concerns identified by the sponsor are identical to those previously accepted for Arzerra by TGA. No new safety concerns resulting from the increased exposure length and cumulative dose resulting from the proposed indication have been identified and submitted by the sponsor.

Since the last update of the Pharmacovigilance Plan, the Clinical Study Report for OMB112517 has been completed and the sponsor states that this is the basis of the current application to extend the indication of Arzerra to maintenance treatment of partially or completely responsive CLL. The study title was "A phase III, open label, randomized, multicenter trial of Ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukaemia (CLL) who have responded to induction therapy" and evaluated specific important identified and potential safety concerns in regards to the proposed new indication. The sponsor was requested to provide clarification of the data from this trial under Section 31 by the Prescription Medicines Authorisation Branch (PMAB) of TGA.

The incidence of neutropenic cytopenia (28%) and infection (all 60%, serious adverse events 20%) in the pivotal study (OMB112517) appear above the class related frequency reported by the sponsor. Given the prolonged exposure in the proposed indication, it is recommended that the sponsor consider changing these risks to important identified risks or submit data justifying no change.

The following other studies have been completed since the previous pharmacovigilance plan update and form part of data considered in the safety profile: OMB110921, OMB110928, OMB114242, OMB112855, OMB115991, OMB111774, WWE114429. Section III 5.2 of the submitted EU-RMP lists all completed studies and activities from the Pharmacovigilance Plan. No new safety concerns were identified from these studies.

The summary of safety concerns is considered acceptable as no new safety concerns have been identified since the last RMP update. However, the sponsor should consider whether the important potential risks of cytopenias and infections should be changed to important identified risks based on data from Clinical Trial OMB112517.

### **Pharmacovigilance plan**

The sponsor proposes to continue with all ongoing routine pharmacovigilance activities<sup>25</sup> and monitoring of safety data from ongoing clinical trials.

They undertake to "report all adverse events in clinical trials or by spontaneous reporting in line with internal procedures and compliant with the "Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines" Version 1.3, June 2014". There is a requirement to report in PSURs all identified and important potential risks, and monitor other identified safety concerns.

<sup>25</sup> Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

Ongoing studies and routine post market surveillance activities will continue to evaluate safety data and reports of adverse events regarding the important identified risks, important potential risks, and missing information including:

- use in the heterogeneous non-White patient population
- patients with relevant co-morbidities (including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases)
- pregnant and lactating females
- concomitant HMG-CoA reductase inhibitor therapy

The following important identified risk and important potential risk are to be specifically investigated by the use of targeted follow up questionnaires:

- bowel obstruction
- Progressive Multifocal Leukoencephalopathy (PML).

There are no proposed changes to the previously agreed pharmacovigilance plan, and no planned additional pharmacovigilance studies or activities in Australia in the submitted pharmacovigilance plan.

Global ongoing pharmacovigilance activities include the following, but do not include any Australian patients.

**Table 5: Global ongoing pharmacovigilance activities.**

	Description of activity (or study title if known)	Expected date of report
1	Completion and analysis of data from GEN416: Ofatumumab vs. Placebo in subjects who progressed following response or stable disease after ofatumumab in Hx-CD20-406	Final study report inclusive of follow-up for all patients available 04-Aug-13
2	Completion and analysis of data from OMB110913: Ofatumumab and Fludarabine/Cyclophosphamide vs. Fludarabine/Cyclophosphamide in Relapsed CLL, Phase III	Final study report inclusive of follow-up for all patients available Oct-15
3	Drug Use Investigation of Arzerra® Injection for Intravenous Infusion in Japan (as condition of approval)	31-Dec-18

The sponsor has committed to further post authorisation efficacy studies. This includes the completion and analysis of the data from the following trials (Hx-CD20-406, Hx-CD-20-407, OMB110911 and OMB110913) investigating the effect of chromosomal abnormalities, CD38 expression and IgVH mutations on survival in CLL. The safety and adverse event monitoring data from these trials should be included in periodic safety update reports and updates to the RMP.

#### ***RMP reviewer's comments***

The sponsor has provided details of ongoing pharmacovigilance studies internationally and their expected submission dates. They have also committed to routine pharmacovigilance practices in Australia including the reporting of all important adverse events in PSURs. No Australian specific additional pharmacovigilance activities or studies are proposed.

The extent of pharmacovigilance activities is consistent with what TGA has previously accepted for Arzerra and continues to be acceptable.

### **Risk minimisation activities**

The sponsor has concluded that routine risk minimisation activities<sup>26</sup> are sufficient in line with previously accepted risk management plans in the EU and Australia. It is stated in the submitted ASA that:

*No additional risk minimisation activities are proposed.*

The sponsor has provided the routine risk minimisation measures of the Australian PI and CMI for approval. There are no significant differences between these and what has been submitted in the EU SmPC.

### **Reconciliation of issues outlined in the RMP report**

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

#### ***Recommendation #1 in RMP evaluation report***

The sponsor should consider whether the important potential risks of cytopaenias and infections should be changed to important identified risks based on data from Clinical Trial OMB112517.

#### ***Sponsor response***

- **Cytopaenias:** Based on the data available to date, Novartis would accept to upgrade the risk of "Neutropenia" as an important identified risk in the RMP for Australia. This will be reported in the ASA and will be included in the next EU-RMP update to be submitted to EMA later this year. However, the available data for other types of cytopenia do not support upgrading them from important potential to important identified risks.

Neutropenia, as the important identified risk and other cytopenias as an important potential risk will continue to be closely monitored through routine pharmacovigilance.

- **Infections:** Novartis acknowledges the comment from TGA related to infections as current potential risk and commits to perform a reassessment of the safety profile for OFA as related to the infections. As an outcome of this assessment, updates to the risk management, if deemed warranted, will be submitted to TGA by the end of 2016.

#### ***Evaluator's comment***

- **Cytopoenias:** The sponsor provided further analysis of clinical trial from OMB112517 and post market safety data specific to each cytopaenia in the Section 31 response. The sponsor's conclusion is that neutropaenia alone is observed as an important identified risk (28% OFA versus 12% in observation arm). The incidence of the other cytopaenias (thrombocytopenia, anaemia, leukopenia) are comparable to the observation population receiving standard of care. Considering the reported incidences and the ongoing pharmacovigilance and risk minimisation measures in place, the sponsor's proposed classification of the risks of neutropenia and other cytopenias with OFA use is acceptable in the context of the RMP evaluation.
- **Infections:** The sponsor will reassess the safety data for infections with ofatumumab and if warranted, has committed to including this as an identified important risk in a revised ASA to be submitted before the end of 2016. This is acceptable in the context of

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<sup>26</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

the RMP evaluation given the ongoing pharmacovigilance and risk minimisation measures in place.

### ***Recommendation #2 in RMP evaluation report***

The sponsor has committed to further post authorisation efficacy studies. The safety and adverse event monitoring data from these trials should be included in periodic safety update reports and updates to the RMP.

### ***Sponsor response***

Novartis acknowledges the comment from TGA and commits to provide corresponding data together with the next PSUR. The RMP for Arzerra will also be updated to reflect these results at the next opportunity.

### ***Evaluator's comment***

The sponsor's response is acceptable.

## **Summary of recommendations**

### ***Minor outstanding issues***

#### *Issues in relation to the RMP*

Nil, pending the submission of a revised ASA containing the changes agreed.

### ***Comments on the safety specification of the RMP***

The clinical evaluator found that "the safety specification in the draft RMP is satisfactory" in the first round evaluation.

### ***Key changes to the updated RMP***

The sponsor has not submitted a revised RMP. EU-RMP Version 12.0 (dated 15 June 2015, DLP 21 December 2014) with ASA Version 5.0 (dated 2 December 2015) is the current RMP.

The sponsor has agreed in the Section 31 Response to update the Risk management plan as follows:

- Novartis would accept to upgrade the risk of "Neutropenia" as an important identified risk in the RMP for Australia. This will be reported in the ASA and will be included in the next EU RMP update to be submitted to EMA later this year.
- Analysis of safety data and adverse events monitoring from post authorisation efficacy studies (PAES) will be included in PSURs and the sponsor will update the RMP to reflect these results
- The sponsor has committed to reviewing the safety profile for the 'Infections' with respect to upgrading it from an 'important potential risk' to an 'important identified risk'. Any resultant change to the risk management plan will be submitted to TGA before the end of 2016.
- The revised safety concerns, as agreed, are below.



**Table 6: Revised safety concerns.**

Summary of safety concerns	
<b>Important identified risks</b>	Infusion reactions Including Cytokine Release Syndrome
	Tumour Lysis Syndrome (TLS)
	Bowel Obstruction
	Cardiovascular events
	Hepatitis B Virus (HBV) Infection and Reactivation
	<b>Neutropenia</b>
<b>Important potential risks</b>	<b>Cytopenias (other than neutropenia)</b>
	<b>Infections (under review by sponsor)</b>
	Progressive Multifocal Leukoencephalopathy (PML)
	Severe mucocutaneous reactions
	Effects on Immunisations, Including Interactions with Live Vaccines
	Immunogenicity
	Effect of Concomitant HMG-CoA Reductase Inhibitors on Ofatumumab Response
	Change in safety profile following switch to acetate buffer formulation
<b>Missing information</b>	Limited data in pregnant and lactating females
	Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases.
	Limited experience in the heterogeneous non-white patient population.
	Limited experience in patients with ECOG 2 performance status.

***RMP evaluator's comments***

The sponsor has satisfactorily addressed the RMP recommendations made in the Section 31 request for information. The evaluator has no objection to the above changes and recommends to the Delegate that the current RMP version and all changes agreed to above are implemented (see suggested wording for conditions of registration below).

***Suggested wording for conditions of registration******RMP***

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

*Implement EU-RMP Version 12.0 (dated 15 June 2015, DLP 21 December 2014) with ASA Version 5.0 (dated 2 December 2015), revised to the satisfaction of the TGA, and any future updates as a condition of registration.*

**VII. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

## Background

### Maintenance treatment in CLL

Maintenance treatment (that is, treatment to prolong or maintain remission in a patient who has responded to induction therapy for active disease) is used in the related setting of FL. There, rituximab is approved for that use, and obinutuzumab has had an extension of indication recently approved that encompasses maintenance:

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

In FL, standard of care is 2 years rituximab maintenance. According to the MabThera PI, the primary endpoint in the pivotal study (for maintenance) was PFS. There was a large effect size (median PFS in the MabThera maintenance arm was 42.2 months versus 14.3 months in the observation arm). Further:

*An analysis of OS confirmed the significant benefit of MabThera maintenance over observation ( $p = 0.0039$  log-rank test). MabThera maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).*

In CLL, there are no approved anti-CD20 maintenance treatments. Ibrutinib and idelalisib are approved for ongoing use. Otherwise, it is standard after successful induction to 'watch and wait', giving patients a treatment free interval. This interval is not just until relapse, but until the extent of progressive disease is sufficient to require the next line of treatment. Since CLL can be indolent, this may be a considerable period of time.

The clinical evaluator states:

*The sponsor commented that at the time the study was designed there were no approved maintenance therapies for the treatment of CLL. However, since then two kinase inhibitors (ibrutinib and idelalisib) have been approved in a number of countries (including Australia) for the treatment of CLL using prolonged maintenance treatment regimens with treatment continuing until disease progression or unacceptable toxicity occurs...*

*The Clinical Overview notes the studies relating to ibrutinib and idelalisib for the treatment of CLL and the recent regulatory approvals of these agents. The overview comments that "it is unclear how durable responses to [the kinase inhibitors] may be with finite [or capped] dosing" and that this is being "explored". It goes on to state, "therefore, prolonging remission with other agents also may be a benefit for these patients as well. Additionally, resistance to ibrutinib has already been reported, primarily due to mutation of the cysteine residue that binds ibrutinib. Given that the incidence of ibrutinib resistance may increase with longer follow-up of the patients who are dosed until progression, it remains prudent to study other agents and other mechanisms of action that can prolong PFS".*

Regarding published experience of maintenance in CLL, the clinical evaluator states:

*Two Phase II studies in patients with CLL have examined maintenance therapy with rituximab, 1 study examined 4 weekly infusions of 375 mg/m<sup>2</sup> every 6 months for up to 2 years in patients with objective response or stable disease after initial rituximab treatment,<sup>27</sup> and 1 study examined 4 monthly infusions of 375 mg/m<sup>2</sup> followed by 12 monthly infusions of 150 mg/m<sup>2</sup> in patients with CR or PR positive for minimal*

<sup>27</sup> Tam CS. Maintenance therapy in CLL: resolving the controversy. *Lancet Haematology* 3: e304-305 (2016).

*residual disease (MRD) after fludarabine/rituximab treatment.<sup>28</sup> The sponsor stated that these studies suggest that prolonged administration schedules enhance response duration in patients with CLL. The existing clinical experience with maintenance rituximab suggests that administration of an anti-CD20 monoclonal antibody should be tolerable for up to 2 years.*

The published experience in this setting is also discussed by Wiestner (2015)<sup>29</sup> in relation to publication of the PROLONG study, and by Tam (2016)<sup>30</sup> more generally.

## Clinical

A Round 1 clinical evaluation report was written. The Round 1 report **did not focus on patients at high risk of relapse**, because the sponsor introduced the narrower indication only after the initial Delegate's Overview. A separate section of this Overview considers that subgroup.

The sponsor's response to clinical questions has been considered in this Overview.

In the Round 1 report, the evaluator considered that the benefit-risk balance of ofatumumab, in the initially proposed use, is favourable:

*It is recommended that the indications of ofatumumab be extended to include maintenance treatment for patients with CLL who are in complete or partial response after at least two lines of induction therapy.*

## Pharmacology

A previous population PK model adequately described OFA concentration data obtained in Study OMB112517. Across the three studies evaluated, no unexpected findings relating to PK of the proposed OFA maintenance regimen were identified.

The evaluator describes the pharmacodynamic data:

*The data on B-cell counts in the pivotal study OMB112517 were consistent with the data from the previously evaluated studies. Following ofatumumab administration there was a rapid and sustained reduction in CD5+CD19+ counts.*

## Efficacy

### **Study OMB112517: PROLONG**

The primary efficacy objective of the study was to evaluate PFS in patients treated with ofatumumab (OFA) maintenance treatment compared to no further treatment after remission induction in relapsed chronic CLL.

The data cut-off date was 19 June 2014. The EPAR also refers to an update with a data cut-off of 28 February 2015. Enrolment in the study was stopped based on PFS results from the second pre-planned interim analysis.

Of note, an inclusion criterion was: "At least partial response according to the revised 2008 NCI-WG CLL criteria within 3 months of the response assessment after the last dose of 2nd/3rd line treatment." Also of note, patients resistant to fludarabine (so with a worse

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<sup>28</sup> van Oers MH, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncology* 16: 1370-79 (2015).

<sup>29</sup> Wiestner A. PROLONGing remissions in patients with CLL. *Lancet Oncology* 16: 1282-1284 (2015).

<sup>30</sup> Tam CS. Maintenance therapy in CLL: resolving the controversy. *Lancet Haematology* 3: e304-305 (2016).

prognosis) were excluded from the trial. In response to a question asked by the evaluator about the inclusion criterion quoted above, the sponsor explained:

*There were no approved maintenance therapies for CLL when OMB112517 was initiated and the concept itself was a novel one in this disease. In order to assess its value, the sponsor felt it necessary to allow patients the benefit of approved and available salvage therapies in the second and third line, and not compromise their efficacy by inserting a new modality of treatment for a prolonged period (maintenance therapy for 2 years). Thus, first line and first relapse patients were not enrolled in the study.*

Ofatumumab was infused IV on Day 1 (300 mg) and Day 8 (1000 mg) in the first cycle followed by 1000 mg every 8 weeks for up to 2 years. Prednisolone premedication was specified.

The primary efficacy variable was investigator-assessed PFS. The evaluator notes:

*Assessment of PFS by the investigator rather than an independent reviewer has the potential to result in bias leading to incorrect treatment comparisons. This is a particular problem for studies, such as the pivotal study, where treatment is open-label and the comparator arm is standard of care (that is, observation). However, the study included pre-specified PFS sensitivity analyses based on IRC assessment. Therefore, the use of sensitivity analyses based on independent review of disease progression mitigated bias associated with subjective assessment of this outcome based on site investigator assessments.*

There were 238 ITT patients given OFA, and 236 in the OBS arm. Median age was 64.5 yrs, very young for a 2nd-3rd line CLL population (median age at diagnosis in Australia is ~70 years for CLL, and median time since diagnosis in PROLONG was 6 years). 68% were male. 81% had PR and 19% CR as their response at study entry; 70% had 2 previous induction treatments; 27% had 3. Chemoimmunotherapy was the most recent prior therapy in 80%. Given patients had relapsed after or been refractory to at least upfront CLL treatment (to receive a second line), the frequency of 17p deletion was low at 2%.

The evaluator argued that some responders would not be enrolled into the trial, so results might not be generalisable to all responders. The sponsor's view is that "appropriate measures have been taken to limit potential selectivity or bias" (Section 31 response).

PFS results are reported from the clinical evaluation report:

*A statistically significant and clinically meaningful improvement in investigator-assessed PFS was observed in the OFA maintenance arm compared to the Obs arm: HR (OFA/Obs) = 0.50 (95% CI: 0.38, 0.66);  $p < 0.0001$ . The median time to an event (progression or death) was 29.4 months in the OFA maintenance arm and 15.2 months in the Obs arm, with the events in both study arms being predominantly disease progression rather than death.*

The primary analysis excluded CT measurements of lymph nodes, spleen and liver. The protocol definition of progressive disease follows:

*PD during or after therapy is characterised by at least one of the following:*

- Lymphadenopathy. Progression of lymphadenopathy, if one of the following is observed:
  - § Appearance of new lesion such as enlarged lymph nodes (>1.5cm), splenomegaly, hepatomegaly or other organ infiltrates
  - § An increase by 50% or more in greatest determined diameter of any previous site.

- An increase by 50% or more in the previously noted enlargement of the liver or spleen or de novo appearance of hepatomegaly or splenomegaly
- An increase by 50% or more in the numbers of blood lymphocytes with at least 5000 B lymphocytes per microliter ( $5.0 \times 10^9/L$ ).
- Transformation to a more aggressive histology (e.g. Richter's transformation).
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL

§ During therapy: Cytopenias cannot be used to define disease progression

§ After treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20g/L (2 g/dL) or to less than 100g/L (10g/dL), or by a decrease of platelet counts by more than 50% or to less than  $100 \times 10^9/L$  ( $100.000/\mu L$ ), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

*Note: Physician's discretion should be used to distinguish between potential infection versus progressive disease base on lymphocyte count. It is acceptable to defer definitive judgment of progressive disease until further evidence is available.*

Thus, important components of the assessment of progressive disease were via clinical examination by the investigator.

In sensitivity analysis 3, where CT results were incorporated, the difference in median PFS narrowed – but was still evident. Per protocol, CT scans “will be done approximately yearly while on study”. The reporting and analysis plan (RAP) notes that “events of disease progression determined by CT scan will be excluded from the primary analysis of PFS but will be included in a sensitivity analysis”. Regular CT is not necessarily standard of care, so the primary analysis reflects routine practice.

As noted by Tam:<sup>31</sup>

*Because CT scans were performed infrequently in PROLONG, it is possible that the major benefit of ofatumumab maintenance was in fact in delaying the return of peripheral blood lymphocytosis, with less material effect on the tumour in deep tissue compartments.*

Analysis of the individual components of PFS was not seen in the PROLONG CSR.

The median PFS in the observation arm was shorter than was expected.

PFS outcomes in the update referred to in the EPAR were similar.

The EPAR commented about PFS:

*...clinical relevance of this effect is doubtful because progression is often asymptomatic and can be managed with acceptable (including recently approved) treatment options that are fairly well tolerated. Thus, treatment-free periods associated with watchful waiting and avoiding severe and life-threatening toxicity are considered more clinically important rather than delaying progression.*

For OS, based on the initial cut-off date:

*As of the cut-off date, the median follow-up was 19.1 months in the total population with 32 (13.4%) deaths reported in the OFA maintenance arm and 34 (14.4%) deaths reported in the Obs arm. The median OS had not yet been reached in either of the study arms.*

<sup>31</sup> Tam CS. Maintenance therapy in CLL: resolving the controversy. *Lancet Haematology* 3: e304-305 (2016).

There was no evidence of a trend towards favourable OS outcomes in the ofatumumab arm. The EPAR discusses imbalances favouring the observation group, for example, the proportion of patients with minimal residual disease. Conversely, there was no strong evidence of a trend towards unfavourable outcomes in the ofatumumab arm.

PROLONG was not powered to detect a difference in OS across arms (particularly since at the second interim analysis, enrolment stopped because of the PFS effect). Gathering and interpreting OS in CLL trials is difficult because of the relatively long life expectancy and because of the use of many subsequent therapies.

Median time from randomisation to the next line of therapy was 6.9 months longer in the OFA arm than in the OBS arm (38.0 months versus 31.1, respectively;  $p = 0.018$ ); HR = 0.66 (95% CI: 0.47, 0.92). When death was included as an event (TTNTD), the difference across arms increased to 10.5 months.

The EPAR had the following conclusions about discordance between PFS and TTNT outcomes:

*Since the difference in median PFS (ofatumumab 29.44 months, Obs 15.24 months, gain 14.2 months) was not fully translated into a subsequently longer median "time to next anti-cancer therapy" (ofatumumab 37.98 months, Obs 31.11 months, gain 6.9 months). These data seem to indicate that there is a shorter time from progression to start of next treatment in the ofatumumab arm (8.5 mo) as compared to the Obs arm (15.9 months). This can be partly explained by different event definitions and censoring rules. The applicant is also referring to differences in clinical practice as an important factor that explains the discrepancy in the PFS and TTNT estimates. This concerns primarily the decision on when to start next therapy. Of notice is that a large proportion of the patients (ofatumumab 45%, Obs 37%) had PD but did not start next therapy. Furthermore, a much larger proportion of the patients in the ofatumumab arm (31%) as compared to the Obs arm (5%) had no documented progression but started next therapy. The question of investigator bias in this open label trial cannot be completely ruled out.*

Quality of life was not particularly different across arms.

#### **Study OMB114242: bulky fludarabine-refractory CLL**

This study does not support efficacy for the proposed new indication – the study design includes randomisation to Ofa versus Obs after 24 weeks, but only in patients initially randomised to Ofa who attained CR, PR or SD. Outcomes after second randomisation are reported in the CER.

### **Safety**

#### **Study OMB112517: PROLONG**

Exposure in this study is described. More common AEs included: neutropenia (24% OFA versus 10% OBS); cough (21% versus 9%); upper respiratory tract infection (19% versus 10%); infusion related reaction (16% versus 0%); pyrexia (16% versus 11%); diarrhoea (14% versus 4%); fatigue (11% versus 7%); pneumonia (11% versus 8%); and rash (10% versus 4%).

Of the severe AEs, neutropenia was most prominent (22% OFA versus 9% OBS). 28% of OFA patients had treatment related severe or life threatening AEs; there were no such AEs in the OBS arm. Treatment related AEs Grade  $\geq 3$  in severity reported in  $\geq 1\%$  of OFA patients were neutropenia (17%), pneumonia (3%), febrile neutropenia (2%), herpes zoster (1%), and infusion related reactions (1%). There was no major imbalance in 'severe infection' across arms. Prolonged severe neutropenia occurred in 5% of patients in the OFA maintenance arm and 2% of patients in the Obs arm.

AEs leading to permanent treatment discontinuation and reported by >1 patient in the OFA arm were neutropenia (1%), hypersensitivity (<1%), and pneumonia (<1%). The AE leading to permanent treatment discontinuation in the OBS arm was autoimmune haemolytic anaemia (<1%).

AEs leading to dose interruptions and/or delays were reported in 40% of patients in the OFA arm. Such AEs reported in  $\geq 1\%$  of patients in the OFA arm were: infusion related reactions (15%); neutropenia (8%); bronchitis (2%); pyrexia (2%); herpes zoster (2%); pneumonia (2%); hypersensitivity (1%); influenza (1%); pharyngitis (1%); and upper respiratory tract infection (1%).

Secondary malignancies were reported during the treatment/observation phase more frequently in the OFA arm than in the OBS arm (12% versus 7%), due mainly to an increase in benign and malignant skin related lesions.

### **Study OMB114242: bulky fludarabine-refractory CLL**

In the sponsor's Section 31 response dated 19 July 2015, it is noted that there is no proposal to include safety data from OMB114242 in the PI. The sponsor's view is that Study Hx-CD20-406, which is already reported in the PI, provides data about ofatumumab in refractory CLL, and that:

*...given the absence of clinically meaningful differences between the safety profile of both studies and the fact that providing data about the comparator arm from study OMB114242 may make more complex the information provided in the product information of Arzerra, Novartis does not intend to include safety data from this study in the Australian PI.*

### **Evidence in patients from PROLONG at high risk of relapse**

The Delegate evaluated material submitted in December 2016 after the initial Overview was written concerning subgroup analysis from PROLONG.

#### *Subgroup analysis from PROLONG*

The data cut-off date for this ad hoc analysis from the sponsor was 28 February 2015. A group of 142 patients at high risk of relapse was identified (n = 78 ofatumumab, n = 64 observation), that is, approximately 30% of the initial population. The subgroup at high risk of relapse was identified using CLL-IPI.<sup>32</sup> In the CLL-IPI system, the five independent predictors of OS are: age; del(17p) and / or TP53 mutation;  $\beta 2$  microglobulin level; clinical stage; and IgHV mutation status. Low, intermediate, high and very high risk groups had 5-year OS (in the CLL-IPI meta-analysis)<sup>33</sup> of 93%, 79%, 64% and 23%. The studies contributing to this system did not include novel therapies.

In PROLONG, patients were categorised using the CLL-IPI system as follows.

**Table 7: Patient categorisation using the CLL-IPI system (PROLONG study).**

Risk subgroup	Ofatumumab N=240	Observation N=240	Total N=480
Low	63 (26)	80 (33)	143 (30)
Medium	99 (41)	96 (40)	195 (41)
High	72 (30)	61 (25)	133 (28)
Very high	6 (3)	3 (1)	9 (2)

<sup>32</sup> International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 17: 779-790 (2016).

<sup>33</sup> International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol.* 17: 779-790 (2016).

73% of Ofa patients and 62% of Obs patients in the high risk category had a remission after first induction therapy of <24 months (versus 57-62% in low-medium risk patients). Median age was 71 years. Few high risk patients obtained CRs in response to their last treatment.

Concerning the relevance of CLL-IPI, the CLL-IPI scoring system was devised for treatment naïve patients and their value on previously treated patients already in PR or CR is not well established.

#### *Efficacy in the high risk subgroup*

In the high risk subgroup, PFS was 23.2 months in the ofatumumab arm, 5.6 months in the observation arm. The HR was 0.47 (95% CI, 0.31-0.71). In one sensitivity analysis, 'PFS per investigator where CT scans considered', median PFS was 12.3 versus 5.5 months and the HR was 0.56 (95% CI 0.37-0.83). Indeed, when the 'PFS per IRC where CT scans considered' analysis was run, the medians were 13.9 versus 9.7 months (HR 0.67, 95% CI 0.42-1.06). Inclusion of CT scans as evidence of response has been discussed above, as has the value of independent radiological review.

OS data remain immature, with the HR 0.86 (95% CI 0.51-1.48). The sponsor considered that the ofatumumab arm was disadvantaged by imbalances in baseline prognostic factors, namely MRD positivity (82% ofatumumab, 59% observation); and unmutated IgHV (90% versus 83%, respectively).

Time to next treatment (or death) in this subgroup was median 18.8 months (Ofa) versus 11.5 months (Obs), HR 0.54 (95% CI 0.36-0.83). Median PFS2 (that is, PFS after next line of therapy) was 44 versus 33 months, HR 0.79 (95% CI 0.47-1.33).

Patient-reported outcomes in the high risk subgroup mirrored those in the broader group. The sponsor argued that Ofa maintenance produced a meaningful improvement in patient's experience of fatigue, relative to Obs.

#### *Safety in the high risk subgroup*

Grade 3+ AEs were seen at a similar frequency across arms (63% Ofa, 59% Obs) and SAEs were slightly less frequent in the Ofa arm (46% versus 53%).

There were more deaths due to infections in the ofatumumab arm (10% versus 6%), the sponsor writing that "these occurred well after treatment and are mostly confounded by post-treatment anticancer therapy". Incidences of grade 3+ infection (27% versus 38%) and of serious infection (27% versus 41%) were lower in the Ofa arm than the Obs arm.

Neutropenia was seen in 31% (Ofa) versus 22% (Obs), but incidence of febrile neutropenia was 5% per arm, neutropenic sepsis was seen in 1-2% across arms, and SAEs associated with decreased neutrophils were reported in 6% versus 9%.

Overall, there was no strong signal that ofatumumab maintenance produces significant toxicity in this high risk group, relative to observation.

### **Risk management plan**

The TGA's RMP evaluation area considered the EU-RMP and ASA included in the dossier. No issues remained unresolved (Note: the proposed indication has been modified since then).

### **Recommended condition/s of registration**

Implement EU-RMP Version 12.0 (dated 15 June 2015, DLP 21 December 2014) with ASA Version 5.0 (dated 2 December 2015), revised to the satisfaction of TGA, and any future updates as a condition of registration.



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*Note: EU-RMP version 13.1 and ASA version 6 were submitted in December 2016.*

## **Issues**

### **Ad hoc analysis of patients at high risk of relapse**

The sponsor conducted an ad hoc analysis of a particular subgroup of patients from its pivotal study PROLONG, to support a modified indication (that is, use in patients at high risk of relapse). This resulted in a much smaller sample in each arm, and also some baseline imbalances that were subsequently used by the sponsor to help explain why no survival advantage has been (or likely will be) shown for ofatumumab over observation.

In general, ad hoc analyses to rescue 'failed' studies are inappropriate; however it was the EMA that requested subgroup analysis in patients at high risk of relapse, in this case.

### **Efficacy**

The sponsor offered a single, open label study to support the proposed new indication. Only a subgroup within this study is supportive of the proposed indication.

The study population in PROLONG was seemingly young (median age 71 years in the high risk subgroup) and also there was a low frequency of subjects with 17p deletion (8% in the high risk subgroup), suggesting the population might not represent all CLL patients at high risk of relapse who attain a response after at least 2 lines of induction therapy.

The ACM is asked:

- Is PROLONG's 'high risk subgroup' representative of the target population?

The sponsor is proposing use of ofatumumab maintenance in a setting where standard of care is now 'observation'. Therefore, the choice of endpoints that establish clinical benefit in this setting is important. The sponsor chose PFS as the primary endpoint, but other endpoints such as time to next treatment, quality of life and OS might all be viewed as very relevant. Ofatumumab maintenance offered, in summary, a major increment in PFS (less in some sensitivity analyses), a modest increment in time to next treatment, a possible advance in quality of life, and no change in OS. Regarding OS, data are relatively early and the last data cut-off considered was 28 February 2015.

Relevance of these efficacy endpoints is a key issue for this application. Is PFS sufficient by itself? Is the totality of evidence for efficacy sufficient? Should no detriment (or even an advantage) in OS be shown to be likely (or even formally demonstrated) before use is approved? Some considerations are set out below.

**Table 8: Endpoint considerations.**

Endpoint	Outcome in PROLONG (median or specified)	Comment
PFS	29.4 months (OFA) versus 15.2 months (OBS)  23.2 months (OFA) versus 5.6 months (OBS) in the high risk group	Progression is a composite endpoint; progression in some patients may be asymptomatic and would not automatically trigger clinical intervention (e.g. 50% increase in blood lymphocytes). CT was not used in primary analysis. It is the typical primary endpoint for CLL and iNHL clinical trials, but maintenance is a different context. Benefit of duration of PFS for a patient should be seen in context of duration of previous remissions.
TTNTToD	36.1 months (OFA) versus 26.3 months (OBS)  18.8 months (OFA) versus 11.5 months (OBS) in the high risk group	Discord between TTNTToD and PFS in effect size. Achieving delay in time to next treatment by replacing observation with a new treatment (but next treatment might be more toxic than OFA). Decision to start next treatment is more complex than declaring progression, and imbalances in prognostic factors may influence effect size. Subjective endpoint (clinical judgement involved in deciding when to start next line, despite existence of recognised guidelines).
OS	HR for OS, 1.08 (ns)  HR for OS, 0.86 (ns) in the high risk group	Study insufficiently powered to detect OS difference. OS outcomes are immature. Confounding by subsequent therapies. Possible prognostic imbalances across arms.
QoL	No large difference, except in fatigue	Difficult to detect differences.

The ACM is asked:

- Is the PFS endpoint sufficient to assess efficacy in this setting?
- If not, is the totality of efficacy data in PROLONG's high risk subgroup (for example, including the time to next treatment endpoint, and noting the extent of OS data) sufficient to assess efficacy in this setting – and has efficacy been established?

### Safety

The extent and type of evidence for efficacy must be considered in light of a moderate increase in toxicity with ofatumumab maintenance. While severe events were mainly neutropenia, this is not insignificant. Sepsis and pneumonia were fatal AEs reported multiple times in the OFA arm in PROLONG – although similar fatal AEs were reported in the OBS arm. The extent to which neutropenia contributed to serious infection should be seen in the context that PROLONG studied a relatively young group of CLL patients.

In the high risk group, there was no strong signal of additional risk of infectious events; perhaps because control of CLL may also influence risk of infection.

The extent of infusion related reactions is also a consideration.

### Overall benefit-risk assessment, and indication

Tam writes:<sup>34</sup>

*...some patients who carry a mutated IGHV gene and who are MRD-negative after fludarabine, cyclophosphamide, and rituximab might be functionally cured of their leukaemia, and thus have no disease to treat.*

<sup>34</sup> Tam CS. Maintenance therapy in CLL: resolving the controversy. *Lancet Haematology* 3: e304-305 (2016).

It would be problematic to offer maintenance if there is ‘no disease to treat’ – although it is noted that the sponsor is proposing use in patients after at least two lines of induction therapy, implying relapse or refractoriness to first line therapy. In this setting, arguably fewer patients with ‘no disease to treat’ would be encountered. With the indication now limited to patients at high risk of relapse, it is unlikely that many patients would have no disease to treat.

It should also be noted that in analysis of efficacy by MRD status, the sponsor reports:

*Of the 28 subjects in CR randomised to the OFA maintenance arm with a baseline MRD sample, 39% (11 subjects) were MRD negative at baseline and 42% (13 subjects) were MRD negative at any visit. However, of the 28 subjects in CR randomized to the Obs arm with a baseline MRD, though 54% (15 subjects) were MRD negative at baseline, the status decreased to 38% (12 subjects) at any visit.*

The ACM is asked:

- Are there any patients likely to be captured by the proposed indication who could be considered to have “no disease to treat”?

Tam also writes:<sup>35</sup>

*For the remaining patients, the clinician must weigh up the costs and risks of 2 years of antibody maintenance, for a gain in time to next treatment of 1 year or less, and no discernible benefit in OS. In the era before the kinase inhibitors, this gain might have been worthwhile, particularly for older or infirm patients with few options for salvage therapy. Whether this benefit is still relevant today depends on the clinician’s access to novel drugs, and whether the safety of these agents hold up with longer-term follow up.*

- Overall, is there a positive benefit-risk balance in the proposed new indication?
- The ACM is invited to offer any alternative indication better supported by the data and clinical considerations.

It is also noted that ofatumumab may be used in upfront or refractory CLL. There is no clear evidence from PROLONG about use of ofatumumab maintenance in such patients.

### Summary of issues

Novartis submitted one pivotal study in support of the application: Study OMB112517 (“PROLONG”; reported by van Oers et al.).<sup>36</sup> The study compared use of ofatumumab as maintenance therapy with the current standard of care in CLL in responders, ‘observation’. PFS was the primary endpoint. Median PFS in the OFA arm was 29.4 months versus 15.2 months in the OBS arm overall, and 23.2 months versus 5.6 months (OFA versus OBS) in the high risk subgroup, according to ad hoc analysis. The difference in median time to next treatment was less dramatic but still present. The study could not show a difference in OS between arms; nor did it show any clear difference in quality of life (although patients may have had less fatigue with OFA maintenance).

Relevance of these efficacy endpoints is a key issue for this application. Is PFS sufficient by itself? Is the totality of evidence for efficacy sufficient? Should no detriment (or even an advantage) in OS be shown to be likely (or formally demonstrated) before approval?

<sup>35</sup> Tam CS. Maintenance therapy in CLL: resolving the controversy. *Lancet Haematology* 3: e304-305 (2016).

<sup>36</sup> van Oers MH, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncology* 16: 1370-79 (2015).

Another key issue is the reliance on an ad hoc analysis of the “high risk of relapse” group. The CLL-IPI approach used to select this subgroup was devised independently but not in the same context (it focused on treatment naïve patients). It has been written that “a common misuse of subgroup analysis is to rescue a trial which formally fails based on the pre-specified primary analysis”,<sup>37</sup> but here it was the EMA that asked the sponsor to conduct the ad hoc subgroup analysis.

### Questions for the ACM

1. Is PROLONG’s “high risk subgroup” representative of the target population?
2. Is the PFS endpoint sufficient to assess efficacy in this setting?
3. If not, is the totality of efficacy data in PROLONG’s high risk subgroup (for example, including the time to next treatment endpoint, and noting the extent of OS data) sufficient to assess efficacy in this setting, **and has efficacy been established?**
4. Are there any patients likely to be captured by the proposed indication that could be considered to have “no disease to treat”?
5. Overall, is there a positive benefit-risk balance in the proposed new indication?
6. The ACM is invited to offer any alternative indication better supported by the data and clinical considerations.
7. If the ACM supports approval of the indication, does the committee have any suggestions to improve the PI or CMI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### Delegate’s pre ACM preliminary assessment

The totality of efficacy data in PROLONG (including data for ‘time to next treatment’) is sufficient to characterise efficacy in patients **at high risk of relapse**, although it would be more reassuring to have further follow-up data for OS. Given that toxicity of ofatumumab in maintenance is not great, my preliminary view is that the indication is approvable, but this view is subject to change depending on the ACM’s expert advice.

### Advisory Committee considerations

The ACM, taking into account the submitted evidence of efficacy, safety and quality, and considered Arzerra injection concentrate containing 100 mg/5 mL and 1000 mg/5 mL of ofatumumab, are of the opinion that there is an overall negative benefit-risk profile for the indication:

#### *Maintenance Therapy in CLL*

*Arzerra (ofatumumab) is indicated as maintenance treatment for adult patients with CLL at high risk of relapse who are in complete or partial response after at least two lines of induction therapy.*

In making this recommendation, ACM was of the view that the risk of harm has been understated.

<sup>37</sup> European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), “Concept paper on the need for a Guideline on the use of Subgroup Analyses in Randomised Controlled Trials”, EMA/CHMP/EWP/117211/2010, 22 April 2010.

**Specific advice**

ACM advised the following in response to the Delegate's specific questions on this submission:

- *1. Is PROLONG's "high risk subgroup" representative of the target population?*

ACM advised that the subjects studied are broadly similar to those covered by the proposed indication. The definition of high risk in a relapsed setting is not set in stone, but the markers the sponsor has used are reasonable.

- *2. Is the PFS endpoint sufficient to assess efficacy in this setting?*

ACM noted that there is precedent for using PFS in an incurable malignancy, and the difference in PFS is large in the high risk groups in the pivotal study.

However, the ACM advised that the PFS definitions are not necessarily clinically meaningful, the more robust clinical benefit accrued (a modest delay in time to next treatment) is of marginal clinical significance. ACM was of the view that time to next treatment is more relevant to a patient in this setting than PFS.

- *3. If not, is the totality of efficacy data in PROLONG's high risk subgroup (for example, including the time to next treatment endpoint, and noting the extent of OS data) sufficient to assess efficacy in this setting, and has efficacy been established?*

ACM advised that given reasonably efficacious and safe options exist for treatment upon progression after a period of observation, notwithstanding the fact that maintenance therapy demonstrates only modest toxicity. In light of these factors efficacy could only be confirmed if maintenance lead to an OS benefit.

- *4. Are there any patients likely to be captured by the proposed indication that could be considered to have "no disease to treat"?*

ACM advised that the major patient group selected, relapsed CLL with high risk markers, are the least likely to be in this group of "no disease to treat" so although a very small proportion of patients with "no disease to treat" would be captured (4%) therefore this was not viewed as a major concern.

- *5. Overall, is there a positive benefit-risk balance in the proposed new indication?*

ACM advised that the actual clinical benefit for the patient (for example, time to next treatment) do not justify the risk in the proposed new indication given that reasonable alternative treatments exist.

- *6. The ACM is invited to offer any alternative indication better supported by the data and clinical considerations.*

ACM advised that an alternative indication was not immediately obvious given the lack of mature OS data and the consequent negative benefit-risk profile.

- *7. If the ACM supports approval of the indication, does the committee have any suggestions to improve the PI document or CMI?*

See above answer.

In making this recommendation, ACM advised that:

- Although an improved PFS was observed in this study, there is insufficient evidence that this translates into a clinically meaningful effect on OS or PFS2
- There is limited evidence of sufficiently positive impact on clinical symptoms or quality of life.

- Therefore a clinically relevant benefit for ofatumumab maintenance treatment in the in high-risk population defined by the CLL-IPI prognostic index is not considered demonstrated.
- The safety profile of maintenance ofatumumab is clearly well documented with the most common adverse reactions being infusion reactions, neutropenia and upper respiratory tract infections. However, these side effects are not considered acceptable where the alternative would be treatment free periods associated with watchful waiting, with initiation of subsequent therapy at the time of clinical disease progression only.

### **Outcome**

On 16 February 2017, the sponsor wrote to TGA requesting their submission be withdrawn.

## **Attachment 1. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605  
<https://www.tga.gov.au>