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RESEARCH**

APPLICATION NUMBER:

125486Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Secondary Review

BLA	125486
Submission Type	Original BLA
Submission Date	April 22, 2013
Brand Name	Gazyva
Generic Name	obinutuzumab
Indication	treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil

1 EXECUTIVE SUMMARY

Gazyva (Obinutuzumab) is a recombinant humanized monoclonal IgG1 antibody that targets the CD20 transmembrane antigen on the surface of non-malignant and malignant preB and mature B lymphocytes.

The pharmacokinetics of obinutuzumab are complex due to the elimination of obinutuzumab by two clearance mechanisms; one time-dependent and the other linear (time-independent). At the start of treatment, the time-dependent clearance is predominant but reduces over time. At steady-state (approximately 4 months), the linear clearance dominates. The covariate analysis found that the rate at which the time-dependent clearance diminishes and the linear clearance predominates is affected by tumor size.

The sponsor's proposed dosing regimen as reviewed by Drs. Grillo and Florian, achieves its purpose of reducing infusion related adverse events with the first dose while the dose intensification over cycle 1 results in obinutuzumab exposures closer to steady state by cycle 2. While the information currently in hand is not sufficient to determine if 1000 mg is the optimal obinutuzumab dose for various patient subgroups (low vs. high body weight, males vs. females, patients with low vs. high tumor burden) the safety and efficacy results support that 1000 mg administered over 6 cycles (1000 mg weekly for 3 weeks in cycle 1) improved progression free survival (PFS) in the overall population and across all exposure quartiles.

An exposure-response relationship was identified between obinutuzumab and PFS; however, no exposure-response relationships were identified between obinutuzumab and adverse event rate. A trend of increasing PFS was observed between the control arm (chlorambucil) compared to all four obinutuzumab exposure quartiles from the obinutuzumab with chlorambucil treatment arm. In this analysis, higher obinutuzumab exposures appear to be associated with better PFS, with increasing PFS from the first (lower exposures) to the fourth (higher exposures) quartile. The data for overall survival was not mature to make a conclusion regarding the exposure-response relationship for overall survival. However, due to these trends observed between PFS and obinutuzumab exposure, the sponsor should take consideration to reduce the exposure variability between subjects in order to maximize response to obinutuzumab.

Body weight was identified as a covariate that influenced exposure. Both clearance (linear and nonlinear) and central volume of distribution of obinutuzumab increased with body weight at a

power coefficient less than that expected by allometric scaling. Simulations using the population-PK model show that the steady-state AUC (C_{trough}) was approximately 30% (32%) higher and 18% (19%) lower in patients with body weight <60 kg and >90 kg compared to patients weighing 60–90 kg, respectively. Given the exposure-response relationship observed between PFS and obinutuzumab, the body-weight dependent exposure of obinutuzumab, and the use of fixed dosing in the pivotal trial, the use of weight-based dosing of obinutuzumab may provide more consistent obinutuzumab exposures in patients, and in turn, a better anti-tumor response.

There are no dose modifications or other instructions proposed for drug-drug interactions or special populations (e.g., renal impairment, hepatic impairment, age, race, gender, weight) at this time.

2 POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

There are no post-marketing commitments or requirements suggested at this time.

3 COMMENTS TO THE APPLICANT

In addition to the two comments delineated in Dr. Grillo's review:

- Submit the results of your long-term (b) (4) frozen matrix stability testing for the ELISA developed by Roche and (b) (4) and used to detect obinutuzumab concentrations in your clinical trials submitted in support of this application when they are available.
- Submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454,

an additional comment should be sent to the sponsor to further evaluate the effect of body weight on exposure and response (see Section 4 below).

4 RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

I concur with Drs. Grillo, Schrieber, and Florian that from a clinical pharmacology perspective there is sufficient information provided in this BLA to support approval of Gazyva for the treatment of patients with untreated CLL in combination with chlorambucil. I have one additional comment that needs to be conveyed to the sponsor:

- We recommend exploring, as part of your future trials, weight-based dosing for obinutuzumab for the treatment of CLL as well as other indications that you are pursuing. While a fixed-dose of obinutuzumab was utilized in BO21004, an assessment of progression free survival based on obinutuzumab exposure quartiles indicated that higher obinutuzumab exposures were associated with longer progression free survival. These relationships remained even after accounting for confounding factors in the analysis such as baseline lymphocyte count, tumor burden, and ECOG score. In addition, the population PK analysis demonstrated that body weight was a covariate for obinutuzumab exposure, in addition to other factors such as overall tumor burden and type of disease. Altogether, these observations suggest that weight-based dosing of obinutuzumab may provide more consistent obinutuzumab exposures in patients, and in

turn, a better anti-tumor response, particularly in subjects with heavier body weights.

5 SIGNATURE

Julie M. Bullock, Pharm.D.
Team Leader
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/s/

JULIE M BULLOCK
10/07/2013

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10/07/2013

1 EXECUTIVE SUMMARY

Gazyva (Obinutuzumab) is a recombinant humanized monoclonal IgG1 antibody that targets the CD20 transmembrane antigen on the surface of non-malignant and malignant preB and mature B lymphocytes. The applicant is seeking approval for obinutuzumab in combination with chlorambucil for previously untreated patients with CLL.

Data to support the efficacy of obinutuzumab is based on a single pivotal phase 3 trial of obinutuzumab plus chlorambucil (GC1b) versus chlorambucil alone (C1b). A IRC-assessed progression free survival (PFS) median of 23.0 months was seen in the GC1b arm compared with 11.1 months in the C1b arm (stratified HR of 0.16; 95% CI [0.11; 0.24]; p-value <0.0001 (log-rank test)). The most common ADR's (≥10%) were infusion reactions, neutropenia, thrombocytopenia, nausea, anemia, diarrhea and pyrexia.

The applicant's proposed dosing regimen is based on a 28 day cycle and includes three components: i) splitting of the initial dose over two days to reduce infusion related reaction risk; ii) administration of 3000 mg in cycle 1 to overcome target-mediated drug disposition; and iii) selection of a 1000 mg dose for cycles 2-6. This dose and dosing strategy is acceptable given the PFS response observed across exposure quartiles.

The PK of obinutuzumab were described using population PK analysis (pop-PK) by a two-compartment pharmacokinetic model with two clearance mechanisms, one time-dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. No covariates (including mild to moderate renal impairment) warranting a dose adjustment were identified in the population model.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in this BLA to support a recommendation of approval of Gazyva. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?			Comment
	Yes	No	NA	
Overall	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pending labeling agreements with applicant
Evidence of Effectiveness†	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1 positive registration trial; dose-response supportive
Proposed dose for general population	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	100 mg C1D1, 900 mg C1D2, then 1000 mg C1D8, C1D15, C2-6D1 is acceptable
Proposed dose selection for others	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No dose modifications recommended from a CP perspective
Pivotal BE	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	IV administration
Labeling	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pending satisfactory agreement with applicant

†This decision is from a clinical pharmacology perspective only. The overall safety and effectiveness determination is made by the Clinical reviewer.

1.2 Post Marketing Requirements

None

1.3 Post Marketing Commitments

None

1.4 Comments to the Applicant

- 1.4.1 Submit the results of your long-term (b) (4) frozen matrix stability testing for the ELISA developed by Roche (b) (4) and used to detect obinutuzumab concentrations in your clinical trials submitted in support of this application when they are available.
- 1.4.2 Submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454.

1.5 Summary of Important Clinical Pharmacology Findings

Gazyva (Obinutuzumab) is a recombinant monoclonal humanized and glycoengineered CD20 antibody of the IgG1 isotype. Obinutuzumab targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant preB and mature B lymphocytes.

The efficacy and safety of obinutuzumab in combination with chlorambucil (Clb) in previously untreated chronic lymphocytic leukemia (CLL) patients are based on a single pivotal phase 3 trial. The most common ADR's ($\geq 10\%$) were infusion reactions, neutropenia, thrombocytopenia, nausea, anemia, diarrhea and pyrexia. Other serious risks included tumor lysis syndrome, infection, worsening cardiac conditions (tachyarrhythmia, ACS, CHF), progressive multifocal leukoencephalopathy (PML).

The applicant's proposed dosing regimen is based on a 28 day cycle and includes three components:

- i) splitting of the initial dose over two days (100/900 mg on days 1 and 2 instead of 1000 mg on day 1) to reduce infusion related reaction risk;
- ii) administration of 3000 mg (1000 mg every week for three weeks) in cycle 1 to overcome target-mediated drug disposition; and
- iii) selection of a 1000 mg dose for cycles 2-6.

The PFS results from the phase 3 trial support that the proposed dosing regimen improved PFS across all exposure quartiles. Also, the dose intensification over cycle 1 results in obinutuzumab exposures closer to steady state by cycle 2. Further, the available evidence supports that splitting of the dose achieves its purpose of reducing infusion-related adverse events with the first dose.

An exposure-response relationship was identified for obinutuzumab and PFS, duration of response, and event-free survival in subjects with previously untreated lymphocytic leukemia. No relationship was identified between overall survival and obinutuzumab exposure; however, the sample size was small. There is also evidence of increased likelihood of certain adverse events with obinutuzumab treatment, including the percentage of subjects with grade 3 or higher cardiac events, tumor lysis syndrome, neutropenia, and thrombocytopenia. The available data did not support an exposure-response relationship between obinutuzumab exposure and adverse event rate.

Five clinical studies were submitted to characterize the PK/PD of obinutuzumab, however only the three trials that enrolled CLL patients were used to describe the PK/PD of obinutuzumab.

The PK of obinutuzumab were described using population PK analysis by a two-compartment pharmacokinetic model with two clearance mechanisms, one time-dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. The model reports that at the start of treatment, the initial mean_{geo} (CV_{geo}) obinutuzumab clearance (time-dependent clearance + time independent

clearance; CL_{init}) and half-life ($t_{1/2_{init}}$) were estimated at 0.44 (78) L/day and 6.2 (69) days, respectively. Obinutuzumab's time-dependent clearance was found to decline with a half-life of approximately 17 days. At steady-state (approximately 4 months), the linear time-independent clearance dominates. The model reports that at presumed steady state the terminal mean_{geo} (CV_{geo}) obinutuzumab clearance (CL_{term}), volume of distribution (Vd_{term}) and half-life ($t_{1/2_{term}}$) were estimated at 0.09 (46) L/day, 3.8 (23) L, and 28.4(43) days, respectively. Steady state exposure estimates were consistent with the NCA derived estimates. Body weight, gender, disease type (i.e., CLL, Non-Hodgkin's lymphoma (NHL), or mantle cell lymphoma (MCL)), and tumor size were identified as positive covariates in the population model, but their impact on obinutuzumab exposure did not warrant a dose modification. Mild or moderate renal impairment did not affect obinutuzumab exposure. There is insufficient data available to determine the effect of severe renal impairment or any degree of hepatic impairment on obinutuzumab exposure.

A visual assessment of the mean dose normalized obinutuzumab C_{max} and AUC_{7d} in CLL patients from trial BO20999 shows a trend toward dose proportionality at doses studied in CLL patients (400 - 2000 mg). The calculated accumulation ratio following multiple dosing of obinutuzumab ranged from 2.7 to 3.8 and 2.3 to 2.7 based on the AUC_{7d} and C_{max} , respectively.

In the phase 1 and 2 trials, circulating CD19+ B-cells were depleted (defined as CD19+ B-cell counts $< 0.07 \times 10^9/L$) within the first three weeks of Gazyva therapy in the majority evaluable patients with CLL. In the phase 3 trial, 40 (91%) out of 44 evaluable CLL patients treated with Gazyva in combination with chlorambucil were B cell depleted at the end of treatment period. These patients remained depleted during the ensuing 6 months of follow up. Recovery of B cells was first observed within 9-18 months of follow up with a reported recovery in a total of 18 (46%) patients within 12-18 months.

Serum samples from CLL patients in the phase 3 trial were tested during and after treatment for antibodies to Gazyva. Approximately 13% (9/70) of Gazyva treated patients tested positive for anti-Gazyva antibodies at one or more time points during the 12 month follow-up period. The presence of Gazyva in patient serum at the time of anti-therapeutic antibody (ATA) sampling can interfere with the ability of this assay to detect anti-Gazyva antibodies. As a result, data may not accurately reflect the true incidence of anti-Gazyva antibody development. Neutralizing activity of anti-Gazyva antibodies has not been assessed.

Signatures

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2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Obinutuzumab is a humanized monoclonal antibody based on a human IgG1 (κ) framework. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of

[REDACTED] (b) (4)

[REDACTED] . The calculated molecular mass of intact obinutuzumab is [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] Obinutuzumab was derived by humanization and subsequent glycoengineering. [REDACTED] (b) (4)

[REDACTED] . [REDACTED] (b) (4)

Gazyva is a sterile, clear, colorless to slightly brown, preservative free liquid concentrate for intravenous administration. Gazyva is supplied at a concentration of 25 mg/mL in 1000 mg single use vials. The product is formulated in 20 mM L-histidine/ L-histidine hydrochloride, 240 mM trehalose, 0.02 % poloxamer 188. The pH is 6.0.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Gazyva targets the extracellular loop of the CD20 transmembrane antigen expressed on the surface of non-malignant and malignant pre B- and mature B-lymphocytes, but is believed not to target haemopoietic stem cells, pro B cells, normal plasma cells or other normal tissue. The Fab portion of obinutuzumab binds to the CD20 molecule and the Fc domain mediates immune effector functions resulting in B-cell lysis in vitro. Defer to the pharm/tox reviewer regarding the acceptability of these in vitro based claims.

The proposed indication for Gazyva is for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose and schedule for Gazyva when used for the proposed indication is listed in Table 1 and is acceptable. Gazyva must be diluted in a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag prior to administration as an intravenous infusion. Other diluents such as dextrose (5%) solution should not be used. The infusion should ideally be used immediately, but the applicant suggests storage no longer than 24 hrs at 2°C to 8°C (36°F to

46°F) (b) (4) We defer to the CMC reviewer regarding the validity of this vague storage guideline.

Withholding of antihypertensive treatments 12 hours prior to Gazyva dosing and standard premedication (i.e., acetaminophen [1000 mg], an antihistamine such as diphenhydramine [50 mg], and an Intravenous glucocorticoid [20mg dexamethasone or 80mg methylprednisolone]) will be administered to all patients receiving obinutuzumab to mitigate infusion related hypersensitivity reactions. In addition the first dose is split further minimize this risk (see Section 2.2.4.2). Infusion should be interrupted or slowed if patients experience infusion reactions.

Table 1: Proposed Gazyva Dose Regimen

Day of treatment cycle	Dose of Gazyva	Rate of infusion†
Cycle 1	Day 1	100 mg
	Day 2	900 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycles 2 - 6	Day 1	1000 mg
Cycle duration = 28 days		

†In the absence of infusion reactions/ hypersensitivity during previous infusions.
Source: Applicant's proposed labeling document

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant submitted five open label clinical trials in support of dosing and other clinical pharmacology related claims in this application (Table 2). Four of these were phase 1/2 trials related to clinical pharmacology and one was a phase 3 efficacy and safety trial in the target population that also included sparse PK sampling. Only three of these trials included CLL patients (Table 2 bolded) and were used to assess the clinical pharmacology of obinutuzumab due to the disease effect noted in the population pharmacokinetic analysis (see Section 2.3.2.10).

Table 2: Clinical trials in support of dosing and other clinical pharmacology related claims in this application.

Study	Design	Target Population	Treatment	Number of Patients
PIVOTAL STUDY				
BO21004/CLL11 Phase III	Open-label multicenter, 3-arm randomized	Previously untreated CLL with comorbidities and/or renal impairment	(R + Clb [†]) G + Clb (Clb)	240 + 6 from run-in phase 22 cross over patients
SUPPORTING STUDIES				
BO21000 Phase Ib	Open-label, multi-center, safety, efficacy, PK	Part I: Relapsed/ refractory fNHL Part II: Previously untreated fNHL	G + FC G + CHOP G + CHOP G + benda	137 NHL (56 rel/ref and 81 1 st line)
BO20999 Phase I/II	open-label, multi-center, adaptive dose-escalating (Phase 1)	Relapsed/refractory NHL or CLL	G	33 CLL (13 Ph. I and 20 Ph. II) 101 NHL (21 Ph. I and 80 Ph. II)
BO21003 Phase I/II	Open-label, multi-center, dose-escalating (phase 1)	Phase I: CD20+ disease lymphoma or CLL) Phase II: relapsed iNHL	G	5 CLL (Ph. I) 104 NHL (17 Ph. I and 87 Ph. II)
JO21900 Phase I	Open-label, multicenter Nonrandomized dose escalation	CD20+ relapsed/refractory NHL	G	12 Japanese NHL

aNHL = aggressive non-Hodgkin's lymphoma; benda, = bendamustine; CHOP = cyclophosphamide, doxorubicin (hydroxy-daunorubicin), vincristine, and prednisone; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; FC = fludarabine and cyclophosphamide; fNHL = follicular non-Hodgkin's lymphoma; G = obinutuzumab; iNHL = indolent non-Hodgkin's lymphoma; R = rituximab.

† Data from the RClb arm will not be used to support this application.

Source: Applicant's Clinical Pharmacology Summary and Listing of Clinical Studies

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint for the pivotal trial BO21004/CLL11 was PFS as assessed by the investigator. PFS based on IRC assessments was also analyzed to support the primary analysis. The key secondary efficacy endpoints were end of treatment response, molecular response (minimum residual disease [MRD] negative rate), OS and event-free survival (EFS). All patients were assessed for response to treatment according to standard NCI/International Workshop on CLL (IWCLL) guidelines. PFS was deemed an acceptable endpoint for other biologic agents to treat CLL such as Rituxan® (rituximab). Further, the Agency stated that PFS is an acceptable primary endpoint for this study in a 7/2/2009 communication. Safety endpoints included: adverse events and serious adverse events, infusion-related reactions, laboratory values and abnormalities, vital signs, premature withdrawals, previous diseases, concomitant medications. These safety endpoints are routinely assessed in clinical trials and are acceptable.

CD19+ B-cell counts were the primary PD variable measured in clinical trials. CD19 is a B cell-specific co-receptor expressed at early stages of B cell development. CD19 is believed to function as the dominant signaling component of a multimolecular complex on the surface of mature B cells. CD19+ B-cell measurements were summarized in clinical trials as CD19+ B-cell counts, percentage of baseline counts, nadir, time to nadir, duration of depletion, and time to recovery. In all studies, B-cell depletion is defined as $< 0.07 \times 10^9/L$. Prolonged B-cell depletion is defined as non-recovery of B-cells more than 12 months after the treatment is completed. B-cell recovery is defined as CD19+ B-cell counts $\geq 0.07 \times 10^9/L$, where patients' CD19+ B-cell counts were previously depleted. The reviewer, in consultation with the clinical team, finds B cell depletion a clinically relevant PD marker for both efficacy and safety that has also been used previously as a PD marker for other drugs with a similar indication. CD19+ B-cell related PD findings should be communicated in labeling since patients with sustained B-cell depletion are at risk of infection and prescribers should be aware of how long B-cell depletion will last for their patients. It should also be noted that, although the depletion of B-cells in the peripheral blood is a measurable pharmacodynamic effect, it is not directly correlated with the depletion of B-cells in solid organs or in malignant deposits. Since the definition of B cell depletion is not standardized the applicant's definition should be provided as context when this information is discussed in labeling.

2.2.3 Are the active moieties in the serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

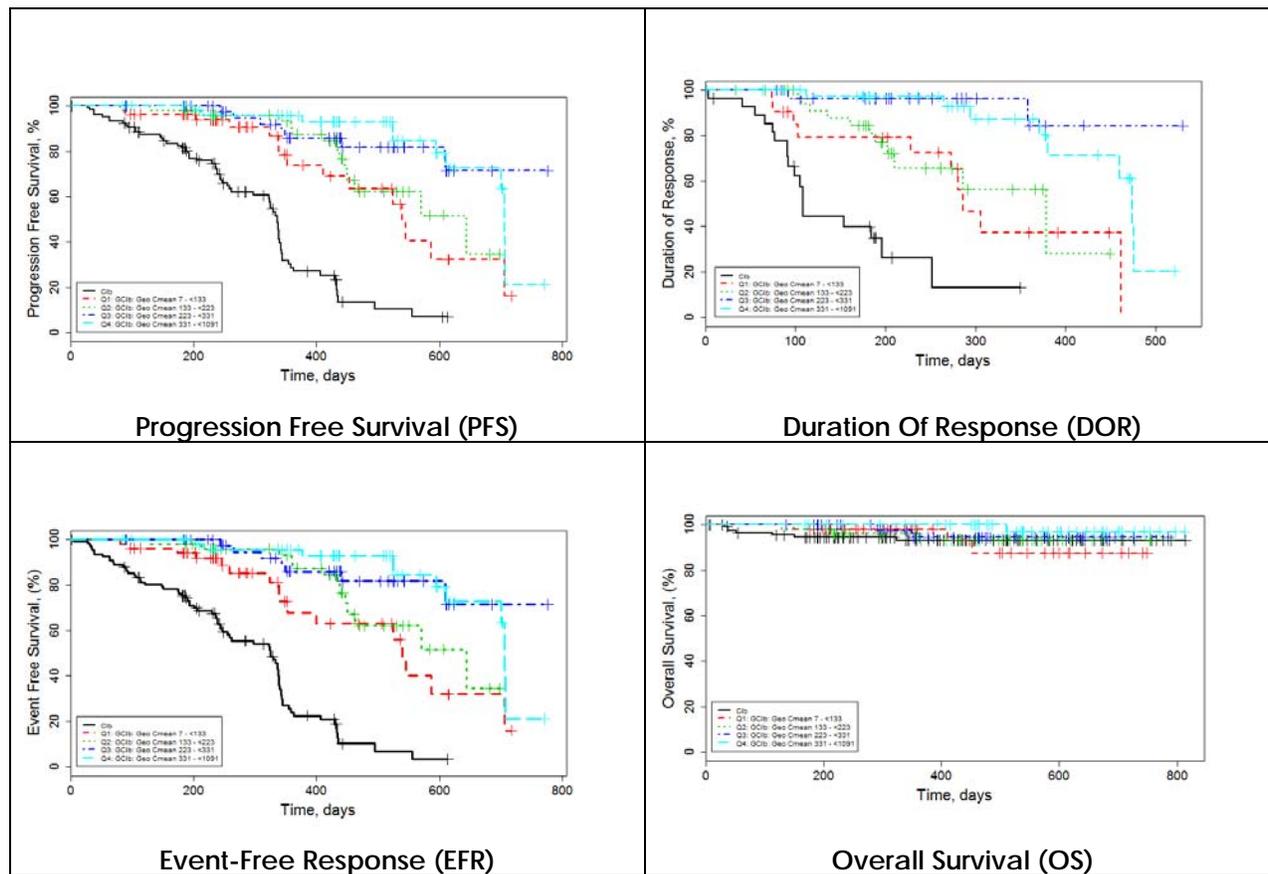
Yes. The applicant's method is acceptable; however it is not ideal given the issues identified with cross validation of the two assay laboratories (See Section 2.6.1)

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

An exposure-response relationship was identified for obinutuzumab and PFS, duration of response, and event-free survival in subjects with previously untreated lymphocytic leukemia (Figure 2). No relationship was identified between overall survival and obinutuzumab exposure, however the overall number of events in either treatment at the time of data submission (9

events out of 118 subjects in the chlorambucil arm and 13 events out of 238 subjects in the obinutuzumab and chlorambucil arm) was low.



† Geometric mean observed obinutuzumab C_{trough} from cycle 2 through the last cycle of treatment were used as the exposure variable

Source: Reviewer Generated

Figure 2: Kaplan-Meier curve for PFS, DOR, EFS, and OS by quartile of obinutuzumab exposure[†]. For comparison, the Kaplan-Meier curve for the chlorambucil control arm is shown on each plot (black line)

A trend of increasing PFS was observed between the control arm (chlorambucil) and all four quartiles of the obinutuzumab with chlorambucil treatment arm. In addition, higher exposures appear to be associated with better PFS, with increasing PFS from the first (Q1) to the fourth (Q4) quartile. The relationship was most distinctive for exposures in the third (Q3) and fourth (Q4) quartile compared to the first (Q1) and second (Q2) quartile. For additional information regarding this analysis, including potentially confounding factors, please see Appendix Section 4.2.

Patient risk factors and demographics showed an imbalance across most obinutuzumab exposure quartiles (see Appendix Section 4.2, Figure 2). There were more males, subjects with higher baseline tumor burden, subjects with higher baseline lymphocyte count in the lower exposure groups, and a longer time from diagnosis to randomization in the lowest exposure quartile (Q1) compared to the highest exposure quartile (Q4). These results are not unexpected as the population pharmacokinetic analysis identified body weight as a significant covariate for clearance and volume, and males in the Phase 3 study had a median body weight of 76 kg compared to 65 kg in women. Likewise, the purpose of the applicant's proposed cycle 1 dosing was to overcome target-mediated drug disposition by saturating available receptors. Subjects

with higher circulating lymphocyte counts or tumor burden (as assessed by the 2-D sum of all lesions identified) may have more extensive disease, and by association, a greater number of target receptors to occupy before saturation.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

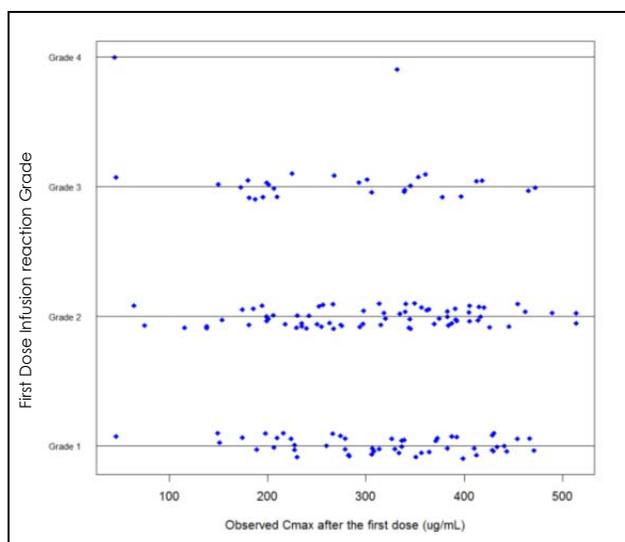
There is evidence of increased likelihood of certain adverse events with obinutuzumab treatment, including the percentage of subjects with grade 3 or higher cardiac events, tumor lysis syndrome, neutropenia, and thrombocytopenia (Table 3). Neutropenia and thrombocytopenia, in particular, were elevated in the obinutuzumab treatment arm compared to the control arm. However, the available data did not support an exposure-response relationship between obinutuzumab exposure and adverse event rate. Paradoxically, the event rate was highest in the lowest obinutuzumab exposure quartile. As the initial exposure-response safety assessment was based on geometric mean C_{trough} from cycle 2 through the last cycle of treatment, two alternative exposure metrics were calculated which may better reflect obinutuzumab exposure at the time the adverse event occurred: i) average exposure over the treatment duration plus 28 days after the last dose; and ii) the observed concentration value in closed proximity to the adverse event. In both situations, the inverse trend remained between obinutuzumab exposure and adverse event rate, though the event rates in the obinutuzumab treatment arm remained consistently higher than the control arm. Additional data from ongoing obinutuzumab studies will be necessary to better understand exposure- response safety relationships between these adverse events and obinutuzumab exposures, but the current data does not suggest the need for obinutuzumab dose adjustments in CLL patients beyond the measures implemented in the Phase 3 trial.

Table 3: Comparison of Adverse Event Rates between Obinutuzumab Exposure Quartiles and the Control Arm from BO21004

Risk Parameter	Chlorambucil Arm (N = 116)	Obinutuzumab and Chlorambucil Arm (N = 208)			
		Q1 (N=52)	Q2 (N=52)	Q3 (N=52)	Q4 (N=52)
Grade 3-5 Cardiac events	3.3%	5.8%	3.8%	0%	5.8%
Grade 3-5 Tumor lysis syndrome	0%	1.9%	0%	3.8%	0%
Grade 3-5 Infections	16.9%	13.5%	15.4%	9.6%	13.5%
Grade 3-5 Neutropenia	17.8%	51.9%	48.1%	40.4%	28.8%
Grade 3-5 Thrombocytopenia	5.1%	19.2%	19.2%	7.7%	5.8%

Source: Reviewer Generated

While the mechanism underlying infusion reactions seen with this class of biologic drugs is unclear, it has been speculated that activation of complement by the antibody bound to the surface of circulating B-cells, may contribute. The majority of the infusion-related reactions occurred within 3 days following the first dose. An applicant derived graphic analysis of the occurrence and grade of the infusion related reactions versus the predicted C_{max} obinutuzumab after the first dose did not show a relationship (Figure 3). This analysis was limited by concerns regarding the ability to accurately predict C_{max} given the sparse PK sampling and as subjects with grade 3-4 infusion related adverse reactions were more likely not to have any PK data available (56% of such subjects compared to 94% of subjects with grade 0-2 infusion-related adverse reactions).



Source: Applicant's Clinical Pharmacology Summary

Figure 3: Relationship between Grade of the Infusion Reaction Following the First Dose and Observed C_{max} after the First Dose

In trial BO21004/CLL11 (phase 1a) infusion reactions occurred primarily during the first cycle, only in the obinutuzumab and chlorambucil arm, and was associated with obinutuzumab infusion. In order to reduce the risk and severity of IRRs, and on the recommendation of the DSMB, the BO21004/CLL11 study protocol was amended to include interventions over several steps (Table 4). The applicant conducted a preliminary descriptive assessment that suggested a trend of fewer infusion reactions with these interventions (Table 4). While this finding is encouraging it cannot be considered definitive at this time due to the small sample sizes for each intervention and as it is uncertain if the interventions noted below were implemented in all patients enrolled following the protocol amendments.

Table 4: Infusion Related Reactions at First Infusion by Infusion reaction intervention in trial BO21004

IRR Intervention	Patients Enrolled N	obinutuzumab and chlorambucil Arm (N = 240)		
		All IRRs N (%)	Serious IRRs N (%)	Grade 3-5 IRRs N (%)
1. Premedication with anti-pyretic and anti-histamine	53	47 (88.7)	5 (9.4)	9 (17.0)
2. #1 + corticosteroid pre-medication with lymphocyte count > 25×10 ⁹ /L	74	53 (71.6)	9 (12.2)	19 (25.7)
3. #1 + corticosteroid pre-medication all patients	33	23 (69.7)	8 (24.2)	10 (30.3)
4. #1 + #3 + antihypertensive drugs must be paused	35	21 (60.0)	3 (8.6)	5 (14.3)
5. # 1 + #3 + #4 + Split first Dose over 2 days (100 mg/900 mg)	45	21 (46.7)	2 (4.4)	8 (17.8)

Source: Applicant's core report for trial BO21004

A reviewer initiated exposure-response safety analysis (see Appendix Section 4.2) evaluated whether there was a relationship between infusion-related adverse events and observed post-infusion obinutuzumab concentration (C_{max}). No significant trend was identified between the likelihood of infusion-related adverse events and obinutuzumab concentration, but there was a trend of lower obinutuzumab C_{max} in subjects listed as having a grade 3 or 4 infusion-related adverse event (Appendix Section 4.2, Table 16). This trend should be interpreted with caution as only 56% of subjects with grade 3 or 4 infusion-related adverse events had obinutuzumab PK collected post-infusion compared to 89% of subjects with grade 0-2 infusion-related adverse events. Similar trends are observed if instead population predicted C_{max} is used in the analysis. The incidence of severe (grade 3 or 4) infusion-related adverse events did not appear to be

more common in subjects with high baseline circulating lymphocytes counts ($>100 \times 10^9$ cells/L) or high initial tumor size (>2181 mm²). The reviewer finds this information acceptable.

2.2.4.3 Does this drug prolong the QT or QTc interval?

There have been no specific assessments of QT/QTc interval in clinical studies conducted with obinutuzumab to date. ECG monitoring was included in early Phase I studies with obinutuzumab and no cardiac safety signal were identified from the ECG monitoring. The Agency agreed with the applicant's proposal to study the effect of obinutuzumab on the QT/QTc interval in a substudy of trial BO25454 which is planned to begin on or about July 15, 2013. The applicant anticipates completion in August, 2015. The protocol for this substudy was submitted to the Agency in April 2013 and no substantive issues were identified in either the IRT or OCP reviews in May 2013. The reviewer finds this plan acceptable and recommends a comment be sent to the applicant to submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. The evidence supports that splitting of the dose achieves its purpose of reducing infusion-related adverse events with the first dose. Also, the dose intensification over cycle 1 results in obinutuzumab exposures closer to steady state by cycle 2. Finally, while the information from CL21004 is not sufficient to determine if 1000 mg is the optimal obinutuzumab dose, the PFS results support that 1000 mg administered over 6 cycles (1000 mg weekly for 3 weeks in cycle 1) improved PFS across all exposure quartiles. The dose may need adjustment depending on the disease under evaluation (non-Hodgkin's Lymphoma may require different dosing than CLL) or as information continues to emerge regarding other endpoints such as overall survival.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The main PK, PD and PK/PD results in CLL patients were obtained using pop-PK modeling on a dataset pooled from four clinical studies (BO20999, BO21003, BO21000 and BO21004/CLL11). The PK of obinutuzumab were described by a two-compartment PK model with two clearance mechanisms, one time-dependent and the other linear. At the start of treatment the time-dependent clearance is predominant but reduces over time. At steady state the linear clearance dominates. The time-dependent clearance component is consistent with target-mediated drug disposition.

2.2.5.1 What are the single dose and multiple dose PK parameters?

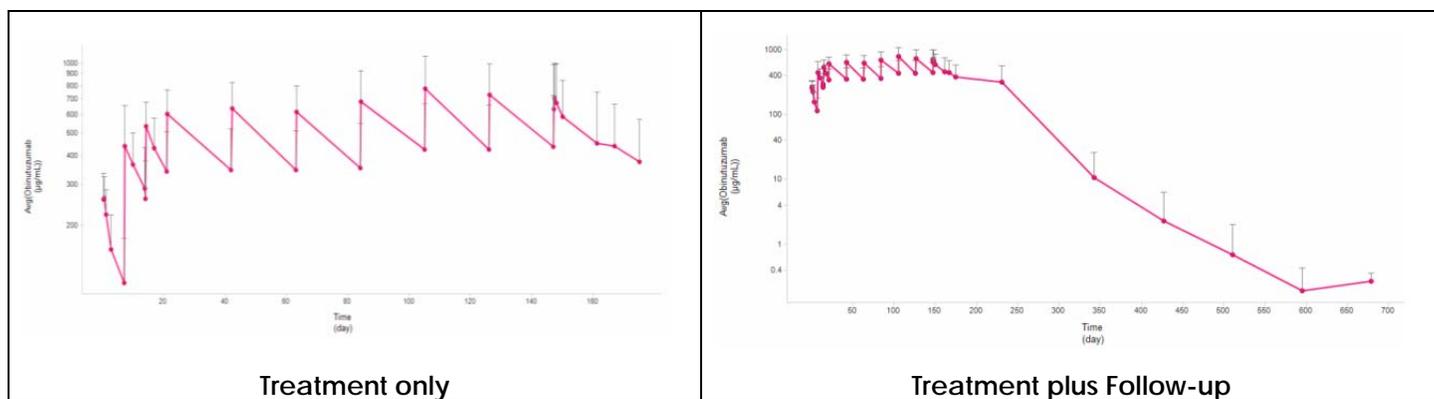
The clinical pharmacology characteristics of obinutuzumab were determined exclusively in oncology patients. Dose escalation studies in Phase 1 explored doses from 50 to 2000 mg. With the exception of the pivotal trial BO21004/CLL11, the remaining clinical pharmacology related trials were populated by patients with non-CLL CD20+ disease lymphomas or a combination of both CLL and non-CLL CD20+ disease lymphomas. Given the pop-PK analysis findings that steady-state clearance is depended on the cancer disease subtype (see Section 2.3.2.10) the reviewer will focus on pharmacokinetic information from CLL patients.

A non-compartmental analysis (NCA) was used to analyze the obinutuzumab concentration data in trials: BO20999, BO21003, BO21000 (only first-line follicular NHL [fNHL] patients) and JO21900 (Japanese). The reviewer agrees with the applicant's position that using the NCA derived estimates of primary PK parameters (e.g., CL and V_{ss}) and secondary PK parameters (e.g., t_{1/2}) are of limited value because of the apparent time-dependent clearance that is described in detail below and the relatively sparse PK sampling schedule. The reviewer finds that

the NCA derived PK parameters representing obinutuzumab exposure (C_{max} , AUC_{7d} and AUC_{last}) are more reliable and are of value in confirming the exposure estimates derived from the population PK modeling. This is because the estimation of C_{max} under the very sparse sampling schedule of the phase 3 trial, that represents the bulk of the CLL population modeled, using a pop-PK modeling approach can be unreliable.

The BO20999 trial contained the majority of the CLL patient PK sampling data used to describe the NCA derived obinutuzumab exposure parameters. This trial was an open-label, multi-center, phase 1/2 study of obinutuzumab monotherapy with a non-randomized, adaptive, dose-escalating phase 1 and a randomized (NHL arms only) phase 2. Thirty-three (13 Phase 1 and 20 Phase 2) of the 134 patients enrolled in this trial had the diagnosis of CLL and received one dosing levels outlined in Table 5 below. Pharmacokinetic sampling for obinutuzumab was sparse with 6 samples around the C1D1 dose and 8 samples around the C8D1 Dose. In addition, 2-3 samples were collected around the other dosing times.

Mean serum obinutuzumab concentration–time profiles following the administration of 1000 mg of obinutuzumab during eight cycles (10 doses total) and follow-up in CLL patients during phase 2 of the trial are shown in Figure 4. Both C_{max} and C_{trough} values increased markedly during Cycles 1 and 2 as a consequence of the three administrations of 1000 mg of obinutuzumab during Cycle 1 (Days 1, 8 and 15) and Cycle 2 (Day 1), with only small changes in C_{max} and C_{trough} values thereafter. In addition, a visual analysis of the concentration–time profiles over the entire phase 1 dosing range (50-2000 mg) in all patients combined (both CLL and non CLL cancer) suggest the presence of target-mediated disposition (TMDD) because there is little to no accumulation in obinutuzumab observed upon multiple dosing at lower doses; however such accumulation is observed at higher doses. Target-mediated disposition was also identified in the pop-PK analysis. Based on these findings the reviewer agrees with the applicant's position that TMDD plays a significant role in the PK behavior of obinutuzumab.



†Dosing was on Cycle 1 Days 1, 8 and 15, then on Day 1 of Cycles 2-8 (10 infusions in total)
 Source: Report No. 1048574, November 2012.

Figure 4: Obinutuzumab Serum Concentrations (Sparse) in CLL Patients Following Administration of 1000 mg Obinutuzumab over Eight Cycles (10 doses total)[†] in Phase 2 of trial BO20999

NCA derived exposure parameters for obinutuzumab following single and multiple dosing in this CLL population can be found in Table 5 below. The AUC_{7d} will be used for comparison across doses because the last time point of the AUC_{last} varies from patient to patient depending on PK sample availability. Do to the sparse sampling, these NCA findings are deemed acceptable, but not optimal. NCA estimates of primary PK parameters (e.g., CL and V_{ss}) and secondary PK parameters (e.g., $t_{1/2}$) following multiple dosing are provided in Appendix Section 4.1, Table 11, but are considered of limited value.

Table 5: NCA derived obinutuzumab serum PK exposure parameters in CLL patients following single and multiple dosing in phase 1 and 2 of trial BO20999

Cycle/ Day	Phase	Dose†	n	C _{MAX} ug/mL	AUC _{7D} day•ug/mL	AUC _{LAST} day•ug/mL
C1D1	1	400/800	2	104.1(8.6) 104.5[95.9-113]	276.9(19.4) 281.2[232-330.5]	275(18.7) 279[231.7-326.4]
		800/1200	3	215.7(32.1) 223[151-298]	916.4(20.5) 836[774.1-1189.1]	971.4(19.3) 1006.9[770.5-1181.4]
		1000/1000	3	209.6(80.8) 235[96.5-406]	790.8(104.9) 790.8[328.5-1904.2]	858(106) 1026[328.2-1875.5]
		1200/2000	3	306.9(19.5) 318[243-374]	1442(6.3) 1446.5[1336.7-1550.8]	1417.8(5.7) 1413.9[1325.9-1520.3]
	2	1000/1000	13	271.6(19.4) 254[203-348]	1200.6(27.5) 1017.8[1000.8-1786.7]	1363.7(26.8) 1453.7[996.2-1764.4]
C8D1	1	400/800	3	485.4(45.1) 375[371-822]	2460(51.2) 1871.6[1803.1-4411.3]	16464(113) 10876.7[8624.8-47572.8]
		800/1200	3	573.5(70.7) 763[271-912]	3042.7(114.8) 4448.6[1047.2-6046.7]	21261.5(187.1) 42573.3[4789-47140.9]
		1000/1000	3	740.9(29.8) 781[526-990]	4043.6(45.4) 4449.1[2455.2-6052.9]	29623.4(167.2) 25608.4[9622.5-105496.1]
		1200/2000	3	1732.6(31.7) 1690[1310-2510]	10783.3(39.9) 10437.9[7588.4-17204]	111125.9(83) 104911.6[60220-265553.7]
	2	1000/1000	10	672.1(44.5) 697.5[329-1170]	3456.3(59.5) 3758.3[1683.3-7667.7]	34482.8(88.5) 39867.7[11433.4-86583.9]

Bolded doses reflect the administered dose relative to the reported parameters for that row. Parameter estimates represented as meanGeo(CV_{geo}) and Median [min-max].

† In Phase 1 patients with CLL received a total of 9 infusions, on Days 1 (half of the target dose) and 8 during Cycle 1 and then every 3 weeks thereafter from Cycle 2 to Cycle 8. During Phase 2 patients with CLL were dosed on Cycle 1, Days 1, 8 and 15, then every three weeks thereafter on Day 1 of Cycles 2-8 (10 infusions in total).

Source: derived from the applicant dataset located at \\cber fs3\Me\CTD_Submissions\STN125486\0004\m5\datasets\pop-pk\bo20999\listings\pknca.xpt

Similar NCA PK findings were reported in the 5 CLL subjects in phase 1 of the BO21003 trial which was designed, in part, to investigate the PK of obinutuzumab over a wide range of doses (100–2000 mg [800-2000 in CLL]). In this trial obinutuzumab was administered once weekly for 4 weeks followed by a maintenance regimen in which obinutuzumab was administered every 3 months for 2 years. Given the limited sample size, these data are evaluated as part of the pop-PK analysis.

A pop-PK analysis of obinutuzumab time-concentration profiles following intravenous doses from Studies BO20999, BO21000, BO21003, and BO21004/CLL11 in CLL and NHL patients was also conducted by the applicant to describe the PK of obinutuzumab and identify important covariates that may affect it. Using this approach the PK of obinutuzumab were described by a two-compartment pharmacokinetic model with two clearance mechanisms, one time-dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. The model reports that at the start of treatment, the initial mean_{geo} (CV_{geo}) obinutuzumab clearance (time-dependent clearance + time independent clearance; CL_{init}) and half-life (t_{1/2}_{init}) were estimated at 0.44 (78) L/day and 6.2 (69) days, respectively (Appendix Section 4.1, Table 12). Obinutuzumab's time-dependent clearance was found to decline with a half-life of approximately 17 days. At steady-state (approximately 4 months), the linear time-independent clearance dominates. The model reports that at presumed steady state the terminal mean_{geo} (CV_{geo}) obinutuzumab clearance (CL_{term}), volume of distribution (Vd_{term}) and half-life (t_{1/2}_{term}) were estimated at 0.09 (46) L/day, 3.8 (23) L, and 28.4(43) days, respectively (Appendix Section 4.1, Table 12). The reviewer finds the population model and the derived PK parameter estimates acceptable. Steady state exposure estimates were consistent with the NCA derived estimates above. Pop-PK model derived PK exposure and parameter estimates by trial can be seen in Appendix Section 4.1, Table 12. Alone

the population-based exposure estimates are not considered definitive for the reasons discussed above regarding C_{max} and the fact that some subjects, particularly in the 21004 trial, may not have been at steady state clearance by the last treatment cycle.

2.2.5.2 How does the PK of the drug and any major active metabolites in healthy volunteers compare to that in patients?

Not applicable because the clinical pharmacology characteristics of obinutuzumab were determined exclusively in oncology patients.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable because obinutuzumab is administered via intravenous infusion.

2.2.5.4 What are the characteristics of drug distribution?

Obinutuzumab appears to be distributed mainly intravascularly. The population PK based analysis reports that at presumed steady state the mean_{geo} (CV_{geo}) obinutuzumab $V_{d_{term}}$ is estimated at 3.8 (23) L. An assessment of protein binding is not applicable to biologics.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance trial was not conducted for obinutuzumab. Mass balance studies are generally not performed for protein drugs because they are degraded into amino acids that then recycled into other proteins.

2.2.5.6 What are the characteristics of drug metabolism?

Metabolism studies were not conducted for obinutuzumab. Metabolism studies are generally not performed for protein drugs because they are degraded into amino acids that are then recycled into other proteins.

2.2.5.7 What are the characteristics of drug excretion?

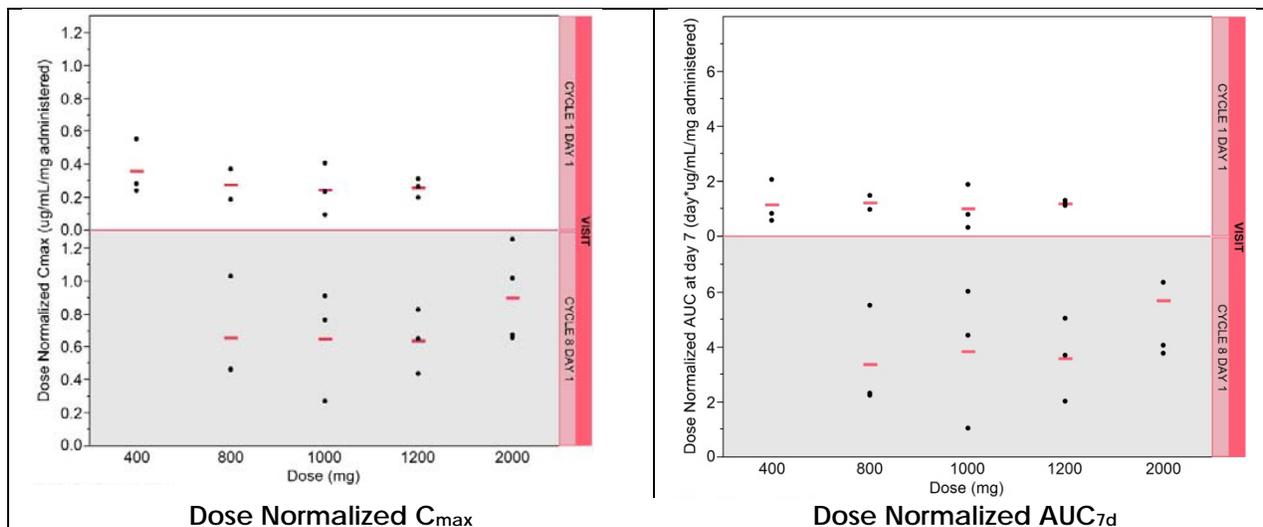
The elimination of obinutuzumab can be described by two clearance mechanisms, one time-dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. At steady-state (approximately 4 months), the linear time-independent clearance dominates. The Pop-PK covariate analysis finds that the rate at which the time dependent clearance diminishes and the linear predominates is affected by tumor size (see Section 2.3.2.10).

The pop-PK model reports that at the start of treatment, the initial mean_{geo} (CV_{geo}) obinutuzumab clearance (time-dependent clearance + time independent clearance; CL_{init}) and half-life ($t_{1/2_{init}}$) are 0.44 (78) L/day and 6.2 (69) days, respectively. These parameters change over time as the time-dependent clearance declines so that at presumed steady state the mean_{geo} (CV_{geo}) obinutuzumab clearance (CL_{term}) and half-life ($t_{1/2_{term}}$) are 0.09 (46) L/day and 28.4(43) days, respectively.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The degree of linearity in the dose-concentration relationship of obinutuzumab in patients with CLL was assessed primarily in trial BO20999. A formal analysis of linearity (e.g., comparing dose-normalized and mean values of exposure using an analysis of variance (ANOVA)) was not conducted due to the limited sample sizes in the various dosing groups (see Table 5). A visual assessment of the mean dose normalized obinutuzumab C_{max} and AUC_{7d} in CLL patients from trial BO20999 by the reviewer (Figure 5) shows a trend toward dose proportionality at doses

studied in CLL patients (400 - 2000 mg). A definitive determination was not possible due to the limited cohort sample sizes and high variability. These limitations are a possible explanation for the higher mean exposure seen in the 2000 mg cohort. This trend was not apparent at lower doses (50 – 200 mg) in non-CLL patients studied in this trial and is possibly the result of greater TMDD due to reduced receptor saturation at the lower doses. No additional evaluation of this issue is recommended at this time.



Source: Derived from the applicant dataset located at \\lclber-fs3\lme\CTD_Submissions\STN125486\0004\m5\datasets\pop-pk\bo20999\listings\pkncnca.xpt

Figure 5: Dose normalized obinutuzumab C_{max} and AUC_{7d} (mean =red hash mark) by dose cohort following single (C1D1) and multiple dosing (C8D1) in CLL patients from trial BO20999

2.2.5.9 How do the PK parameters change with time following chronic dosing?

As stated in Section 2.2.5.7, the elimination of obinutuzumab can be described both time-dependent and linear clearance with the latter predominant with chronic dosing to steady state. The accumulation of obinutuzumab following repeated doses is moderate. When obinutuzumab was administered to CLL patients at doses of 400-2000 mg on Days 1 (half of the target dose) and 8 during Cycle 1 and then every 3 weeks thereafter from Cycle 2 to Cycle 8 in Study BO20999, the reviewer calculated accumulation ratio (i.e., C8D1 compared to C1D1) of obinutuzumab based on the AUC_{7d} ranged from 2.7 to 3.8 (Table 5). The accumulation ratio based on C_{max} ranged from 2.3 to 2.7. A definitive determination was not possible due to the limited cohort sample sizes and high variability secondary to TMDD; however, these estimates are deemed acceptable. No additional evaluation of this issue is recommended at this time.

Based on the results from the pop-PK analysis of trial BO21004/CLL11, obinutuzumab concentrations approach steady-state levels after approximately 4 months of dosing. This estimate is acceptable.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Pharmacokinetics across the dose ranging trials that enrolled CLL patients (BO20999, BO21003) reported high inter-patient variability (e.g., CV range [AUC_{7d}]: 28 to 144% and CV range [C_{max}]: 21 to 74%). This high variability is likely the result of TMDD and possible covariate effects outlined in Section 2.3. In contrast, there is less variability reported in the pop-PK derived steady state PK parameters (see Appendix Section 4.1, Table 12) from the BO21004/CLL11 trial (i.e., CV range: 23 to 45%) which likely represents the minor TMDD component present during this phase of the treatment regimen.

2.2.6 What are the PD characteristics of the drug and its major metabolite?

A pooled analysis of 30 of 35 CLL patients from trials BO21003¹ and BO20999² shows that circulating CD19+ B-cells were depleted (defined as CD19+ B-cell counts < 0.07 x 10⁹/L) within the first three weeks of obinutuzumab therapy in the majority of evaluable patients with CLL and 86% were B-cell depleted at the end of treatment. Twenty of these patients had at least 6 months follow-up information (after the last study drug intake) and at that time 8 of 20 patients (40%) were considered as recovered. At one year 13 of 20 patients (65%) had recovered.

In the BO21004 trial, CD19+ B-cell counts were sampled at screening, day 1 of each treatment cycle and at follow-up at follow-up months 3, 12, 18, and every 6 months thereafter until recovery. Forty (91%) out of 44 evaluable CLL patients treated with obinutuzumab in combination with chlorambucil were B-cell depleted at the end of treatment period. These patients remained depleted during the ensuing 6 months of follow-up. Recovery of B-cells was first observed within 9-18 months of follow-up with a reported recovery in a total of 18 (46%) patients within 12-18 months. The reviewer finds these results acceptable and should be communicated in the product labeling in a manner consistent with the recommendations in Section 2.2.2.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

A covariate modeling approach emphasizing parameter estimation was implemented as part of the obinutuzumab pop-PK analysis (see Appendix Section 4.2). Potential covariate-parameter relationships were identified based on scientific interest, mechanistic plausibility, exploratory analysis and exploratory graphics. The following covariates were tested: weight, gender, age, creatinine clearance, disease subtypes (e.g., NHL, CLL), and baseline tumor size. Additionally, body surface area (BSA), body-mass index (BMI), baseline B-cell and lymphocyte count, and presence of anti-therapeutic antibodies (ATAs) were checked for their influence on PK parameters by the diagnostic plots.

The covariate analysis indicated that weight, gender, disease subtypes and baseline tumor size had an effect on obinutuzumab clearance and/or volume of distribution as described in detail below. The magnitude of these covariate effects are deemed unlikely to affect obinutuzumab exposure to a degree that potentially would impact efficacy or safety in the CLL population (See Sections 2.2.4.1 and 2.2.4.2).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose modifications are recommended because the magnitude of the identified covariate effects is deemed unlikely to affect obinutuzumab exposure to a degree that potentially would impact efficacy or safety in the CLL population.

¹ Leucocyte Immunophenotyping sampled at screening (Day -14); pre-infusion, end of infusion, 2-5 hours post-infusion on Days 1 of cycles 1-4; the safety follow-up (+28 days from last obinutuzumab dose); and at relapse.

² Leucocyte Immunophenotyping sampled at screening; pre-infusion, end of infusion, 2-5 hours post-infusion on Cycle 1 (Days 1, 8 and 15); C2D1; C3D1; C5D1; C7D1; and at the safety follow-up (28 days from last obinutuzumab dose). Additional samples were collected at follow-up months 2, 6, 9, 12, 15, 18, and every 6 months thereafter until recovery.

2.3.2.1 Elderly

The covariate analysis indicated that the PK of obinutuzumab was independent of age. The reviewer agrees with this finding.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The PK of obinutuzumab was not evaluated in pediatric patients. The applicant is seeking a disease-specific waiver based on obinutuzumab's orphan drug designation.

2.3.2.3 Body Weight

The covariate analysis indicated that the time independent clearance (CL_{TI}) and central volume of distribution (V_{d_c}) of obinutuzumab increased with body weight at a power coefficient less than that expected by allometric scaling. Based on these findings model-based simulations and simulations based on conditional estimates of the individual PK parameters indicate that the steady-state AUC_{τ} (C_{trough}) for the dosing regimen evaluated in study BO21004/CLL11 was approximately 30% (32%) higher and 18% (19%) lower in patients with body weight <60 kg and >90 kg compared to patients weighting 60–90 kg, respectively. The reviewer finds these results acceptable and agrees with the applicant's position that a dose modification is not required at this time.

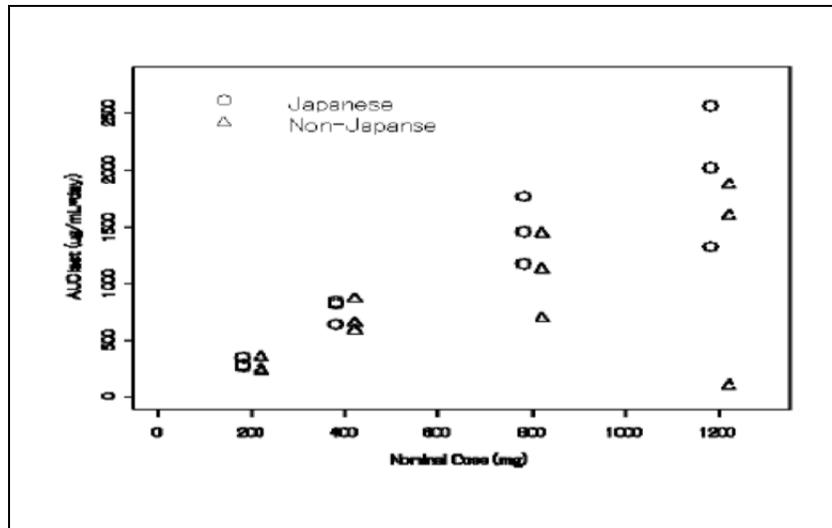
2.3.2.4 Gender

The covariate analysis indicated that CL_{term} and V_{d_c} were higher in males by 23% [$CI_{95\%}$: 14–32%] and 18% [$CI_{95\%}$: 13–22%], respectively. In addition, the time dependent clearance (CL_{TD}) was 52% higher in males. Based on these findings model-based simulations and simulations using conditional estimates of the individual PK parameters indicate that the steady-state AUC_{τ} (C_{trough}) for the dosing regimen evaluated in study BO21004/CLL11 was approximately 26% (29%) lower in males. The reviewer considers these results inconclusive because this covariate may have been potentially confounded with body weight, the impact of disease on exposure, and the sampling schedule. (b) (4)

2.3.2.5 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

The applicant attempted to explore the potential impact of Japanese ethnicity on the PK by conducting a post hoc descriptive analysis comparing AUC_{last} from trial JO21900 with trial BO20999 which employed a similar design. There were no CLL patients in trial JO21900. Following a request from the FDA the applicant stated, in a 6/3/13 response, that NCA dataset for trial JO21900 was not immediately available and could not be submitted. Therefore, these data could not be verified by the Agency.

The applicant reports that based on this analysis there was a marked overlap between the AUC_{last} distributions in the two studies and no clear difference was observed (Figure 6). Given the anecdotal nature of this analysis combined with the known disease effect (see below) and the Agencies inability to verify the JO21900 data, the reviewer finds these results inconclusive (b) (4)

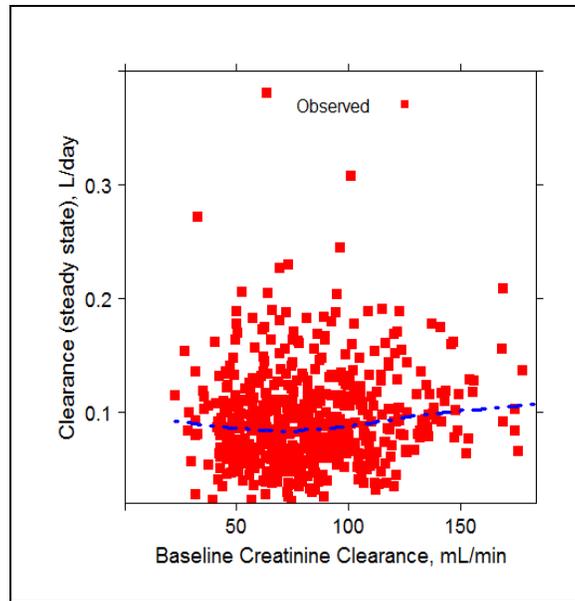


Source: Clinical Pharmacology Summary

Figure 6: Comparison of Obinutuzumab Exposure (AUC_{last}) in Japanese and Non-Japanese Patients: Study JO21900 versus Study BO20999

2.3.2.6 Renal impairment

There have been no formal clinical studies undertaken to investigate the impact of renal impairment on obinutuzumab PK. However, creatinine clearance (CL_{Cr}) was determined in all patients as this measurement formed part of the inclusion/exclusion criteria in trial BO21004/CLL11. A reduced CL_{Cr} clearance (70 mL/min or less) was one of two ways patients with co-existing medical conditions were identified in this trial. Therefore, using these data, the potential impact of CL_{Cr} on obinutuzumab PK was evaluated as part of the pop-PK covariate analysis. The analysis found that there was no apparent impact of CL_{Cr} \geq 30 mL/min on obinutuzumab PK (see Figure 7). The impact of renal function on obinutuzumab was further evaluated by the reviewer by summarizing observed obinutuzumab trough concentration and adverse event rates according to renal function category (See Appendix section 4.2, Table 4 and Table 5, respectively). No difference in obinutuzumab PK was observed across categories for normal, mild, or moderate renal function. The reviewer finds these analyses acceptable and does not recommend any dose modifications at this time. The effect of CL_{Cr} <30 mL/min on obinutuzumab exposure is could not be determined due to the limited number of such subjects with PK data available. However, renal impairment is not expected to be a major factor affecting exposure as monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes. Therefore, no additional trials are recommended at this time.



Source: Pharmacometric reviewer analysis

Figure 7: The effect of calculated baseline Creatinine clearance ($CL_{Cr} \geq 30$ mL/min) on the CL_{Term} of obinutuzumab

2.3.2.7 Hepatic impairment

There have been no formal trials undertaken to investigate the impact of hepatic impairment on obinutuzumab PK. The reviewer finds insufficient data from clinical trials to evaluate this covariate as part of the pop-PK analysis. The impact of hepatic function on obinutuzumab was further evaluated by the reviewer by summarizing observed obinutuzumab trough concentration and adverse event rates according to hepatic function category (i.e., normal, mild, moderate) (See Appendix section 4.2, Table 6 and Table 7, respectively). Due to limited data, a conclusion could not be drawn from these analyses. However, hepatic impairment is not expected to be a major factor affecting obinutuzumab exposure since monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes. Therefore, the labeling should reflect that the impact of hepatic impairment on obinutuzumab exposure is unknown. No additional trials are recommended at this time.

2.3.2.8 What pharmacogenetics information is there in the application and is it important or not

The pharmacogenomic information in this application was not deemed important by the genomics group following its review during the filing period.

2.3.2.9 What pregnancy and lactation use information is there in the application?

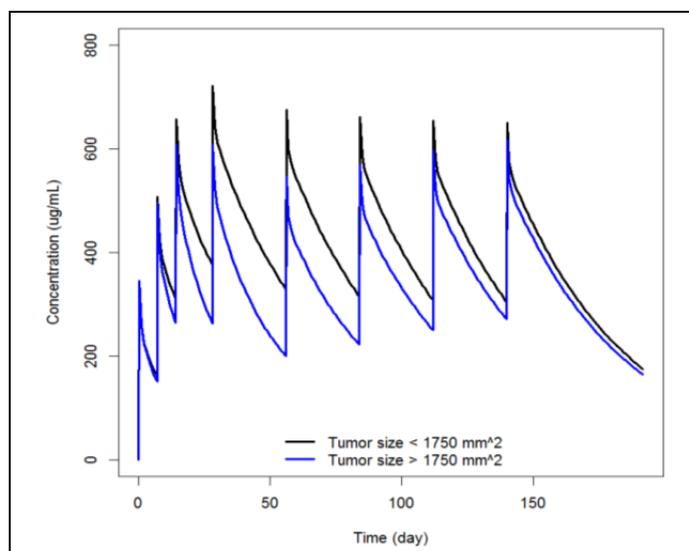
Pregnancy and lactation was not evaluated in humans. The applicant states that nonclinical studies report obinutuzumab can cross the blood-placental barrier and that that secretion of obinutuzumab in breast milk appeared to be very limited in monkeys. The reviewer defers to the pharm/tox reviewer regarding the validity of these findings. No additional human trials are recommended at this time.

2.3.2.10 Other human factors that are important to understanding the drug's efficacy and safety

The covariate analysis indicated that CL_{Term} was 19% lower in NHL patients, and 68% higher in MCL patients compared to CLL patients. In addition, the decline of CL_{TD} was 87% faster in NHL compared to CLL patients. Based on these findings model-based simulations and simulations

using conditional estimates of the individual PK parameters indicate that the steady-state AUC_{τ} (C_{trough}) following the dosing regimen of study BO21004/CLL11 was approximately 27% (39%) higher in NHL patients and 39% (54%) lower in MCL patients compared to CLL patients. This covariate finding is somewhat limited by the inability to resolve the potential contribution of the different relative tumor size associated with the respective disease types. Despite this the reviewer finds this analysis acceptable. (b) (4)

In addition, the covariate analysis indicated that the rate at which the faster time dependent clearance (CL_{TD}) diminishes and the slower linear clearance predominates was 148% faster in patients with a baseline tumor size $< 1750 \text{ mm}^2$. Based on these findings model-based simulations using conditional estimates of the individual PK parameters indicate that the steady-state AUC_{τ} (C_{trough}) will be lower in CLL patients with high baseline tumor size for the dosing regimen evaluated in study BO21004 because the faster CL_{TD} contributes to the overall obinutuzumab clearance for a longer period of time (Figure 8). The reviewer finds this analysis acceptable. A Gazvya dose modification is not recommended at this time.



Source: Clinical Pharmacology Summary

Figure 8: Model-Based Simulations of Typical Obinutuzumab Concentration-Time Course by Tumor Size (75 kg female CLL patient)

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Patients were tested for anti-product antibodies (APAs) in all clinical trials. All serum samples were screened in a bridging enzyme-linked immunosorbent assay (ELISA) assay. In studies BO20999, BO21000 and BO21003, serum samples that screened positive in the screening bridging immunoassay were further analyzed by competitive binding with obinutuzumab to confirm the positivity. Confirmed positive samples were serially diluted to establish titer values for the APA response. Neutralizing activity of anti-product antibodies was not assessed.

Immunogenicity sampling schedule in the trials was adequate. The following is the sampling time points for each trial:

- BO20999: Baseline (Cycle 1 pre-dose), Cycle 1 Day 8, every cycle thereafter (pre-dose, Day 1), and at the 28d post-treatment follow-up visit.
- BO21003: Baseline (Cycle 1 pre-dose), every cycle thereafter (pre-dose, Day 1), and at the 28d post-treatment follow-up visit.
- JO21900: Baseline (Cycle 1 pre-dose), and 4 and 13 months after the final dose.
 - If results showing unusual PK were obtained, the presence of APA was investigated retrospectively from PK samples collected at the additional time-points: Cycle 1, Day 8 (pre-dose and 144-192 hrs post-dose), Cycles 2-7, Day 1 (pre-dose), Cycle 8, Day 1 (pre-dose and 144-192 hrs post-dose), and at the 28d post-treatment follow-up visit.
- BO21000:

Induction period: Baseline (Cycle 1 pre-dose), and 3 and 6 months after the final dose.

 - If results showing unusual PK were obtained, the presence of APA was investigated retrospectively from PK samples collected at the additional time-points: Cycle 1, Day 8, every cycle thereafter (pre-dose, Day 1), and at the end of induction 28d follow-up visit.

Maintenance period: Weeks 36 and 60.

 - PK samples were collected every 12 wks and these other follow-up visit time-points could be used to measure for the presence of APA, if deemed applicable.

Post-treatment follow-up period: Every 12 wks x 8, and at the final follow-up visit.
- BO21004/CLL11: Baseline (Cycle 1 pre-dose), Cycle 4 (pre-dose, Day 1), and at the 3 and 6 mo follow-up visits.

There were two immunogenicity assays used. The first generation assay was used to analyze samples from studies BO20999, BO21000, BO21003 and JO21900. The second generation assay was used to analyze samples from Study BO21004/CLL11.

In the Phase 1/2 studies, using the first generation assay, one (1) CLL patient (Cohort 7b: 1000 mg→1000 mg) from Study BO20999 tested positive for APA to obinutuzumab at baseline, and 1 patient (Cohort 3: 800 mg→1200 mg) from Study JO21900 tested positive at the 13 month follow-up visit.

In the phase 3 trial BO21004/CLL11, using the second generation assay, the APA incidence to obinutuzumab during the follow-up period of the randomization phase was ~11% (7 of 64). Of the six patients who were enrolled in the safety run-in phase, two (~33%) tested positive for APA to obinutuzumab during the follow-up period (Table 6). Therefore, the overall APA incidence to obinutuzumab within trial BO21004/CLL11 was ~13% (9/70).

Table 6: Summary of the total number of APA evaluable and APA positive† patients for the phase 3 trial BO21004/CLL11

Center #/ Patient #	Follow-up Month		
	6	9	12
<i>Randomization Phase</i>	N=132	N=97	N=67
164649/2140			1:20
164687/2220			1:10
164819/5443			1:80
165987/3300		1:320	1:2560
166416/2341	1:20	1:2560	1:5120
166416/2342			1:20
202502/6820			1:40
<i>Safety Run-in Phase</i>	N=6	N=6	N=6
164930/1400		1:40	1:20

Table 6: Summary of the total number of APA evaluable and APA positive† patients for the phase 3 trial BO21004/CLL11

Center #/ Patient #	Follow-up Month		
	6	9	12
166415/2321			1:640

†Dilution of serum sample at which APA assay was positive.

The presence of mAb in patient serum at the time of APA sampling can interfere with the ability of this assay to detect APA. As a result, data may not accurately reflect the true incidence of APA development.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Conclusions regarding the impact of immunogenicity on obinutuzumab PK cannot be drawn at this time due to inadequate data (see Appendix Section 4.2).

In Study BO21004/CLL11, the nine (9) patients with positive ATA during the follow-up period did not have time-matched PK samples obtained at those time-points. Therefore, data for a direct comparison of obinutuzumab PK at time of positive APA samples is not available.

There was one patient (Cohort 3: 800 mg→1200 mg) in Study JO21900 with a positive ATA sample following treatment with obinutuzumab (13 month follow-up visit) who also had a time-matched PK sample. However, in Cohort 3 patients, obinutuzumab concentrations at the 13 month follow-up visit were low (mean concentration=0.00535 mcg/mL) and the impact on PK was not evaluable.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?

Samples confirmed to be APA positive were not tested for the presence of neutralizing antibodies.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?

There was one patient in Study JO21900 with a positive ATA sample following treatment with obinutuzumab (13 month follow-up visit). The best overall efficacy level achieved by this patient was stable disease.

The impact of immunogenicity on obinutuzumab efficacy was assessed in the phase 3 BO21004/CLL11 trial. As indicated in Table 6 above in section 2.3.3.1, the immunogenicity incidence rate in trial BO21004/CLL11 was ~13% (9 of 70 evaluable patients). Analyses revealed that the 7 individual APA positive patients in the randomization period had slightly lower PFS values as compared to the median PFS of 23.0 months in the obinutuzumab treated ITT population (Table 7 and section 2.2.4.1). The duration of response (DOR) values in those 6 ATA positive patients were also slightly less than the median DOR of 15.2 months in the obinutuzumab treated ITT population (Table 7 and section 2.2.4.1). Up to the data cut-off, the percentage of these 7 patients with a PFS event was 29% (2 of 7) and the percentage for losing a response was 17% (1 of 6 responders), compared to the ITT population at 22% (52 of 238 obinutuzumab ITT pop) and 19% (31 of 161 responders lost their response), respectively. Regarding drug exposure time, of the 7 ATA positive patients, 86% (6 of 7) received all 6 cycles of planned obinutuzumab treatment, which was similar to the overall obinutuzumab treatment arm where 81% (195 of 240) of patients received all 6 cycles of obinutuzumab (Table 7).

Table 7: Summary of the Trial BO21004/CLL11 efficacy results from the 7 APA positive patients who received obinutuzumab in the randomized phase.

Center #/ Patient #	PFS from IRC data, days (months*)	PFS Event (Yes/No)	DOR, days (months*)	DOR Event (Yes/No)	Drug Exposure (Number of Cycles)
164649/2140	426 (14.0)	No	261 (8.6)	No	6
164687/2220	309 (10.2)	Yes	n/a	No	2
164819/5443	595 (19.6)	No	314 (10.3)	No	6
165987/3300	543 (17.9)	No	252 (8.3)	No	6
166416/2341	587 (19.3)	Yes	306 (10.1)	Yes	6
166416/2342	525 (17.3)	No	293 (9.6)	No	6
202502/6820	539 (17.7)	No	182 (6.0)	No	6

*Days converted to months using the applicant's conversion of: 1 month=30.4 days.

DOR= duration of response; n/a= not assessable.

While there appears to be a negative trend on PFS and DOR in APA positive patients from Trial BO21004/CLL1, the impact of APA on clinical efficacy is limited due to the low number of APA positive patients (see section 2.3.3.1).

2.3.3.5 What is the impact of anti-product antibodies on clinical safety?

The impact of APA on clinical safety is limited due to the low incidence rate of APA following obinutuzumab treatment (see Section 2.3.3.1).

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

None are known at this time.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No extrinsic factor related obinutuzumab dose adjustments are recommended at this time.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

No in vitro studies were conducted. Since, monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes the reviewer finds this acceptable. Additional studies are not recommended at this time.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Unknown. See Section 2.4.2.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Unknown. See Section 2.4.2.1. Monoclonal antibodies do not generally interact directly with cytochrome P450 (CYP) isoforms or other metabolizing enzymes. While cytokine modulation may be an indirect mechanism through which a monoclonal antibody could alter CYP expression, only transient changes were reported with obinutuzumab treatment. In the CLL population of trial BO20999, there was a trend towards an increase in the levels of all the measured cytokines (IFN- γ , TNF- α , IL-6, IL-8 and IL-10) just after the first infusion of cycle 1 with values peaking at mid-

infusion and then dropping post-infusion, but still at levels considerably higher than those at baseline or pre-infusion. Therefore, cytokine mediated CYP related DDI is unlikely.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Unknown. See Section 2.4.2.1.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Unknown. See Section 2.4.2.1.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Yes. The proposed labeling specifies co-administration with chlorambucil. The interaction potential between these two agents is unknown at this time. On 10/31/2011 the applicant submitted a meeting package outlining its obinutuzumab drug interaction evaluation strategy that was found acceptable to the Agency in an 11/17/2011 response. This strategy stated that the applicant did not plan to evaluate the DDI potential between obinutuzumab and chlorambucil because the latter is "well characterized" and its ADME properties (high clearance, short half-life) make any clinically significant drug-drug interaction with chlorambucil very unlikely. In addition the applicant stated that, there have been no reported DDIs that have affected chlorambucil. Therefore, no additional investigation regarding this issue is recommended at this time.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Standard premedication to mitigate infusion related hypersensitivity reactions including oral acetaminophen/ paracetamol (650-1000 mg), an anti-histamine such as diphenhydramine (50-100 mg), and prednisolone or prednisone (100 mg given i.v. at least one hour before the antibody infusion) will be administered to all patients receiving obinutuzumab. In addition, patients may be treated to allopurinol as prophylaxis against tumor lysis syndrome and/or an antibiotic such as co-trimoxazole. There is no information regarding the potential for these agents to affect obinutuzumab PK; however, it is unlikely given monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes. No additional trials are recommended at this time.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Not at this time.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None

2.5 General Biopharmaceutics

Not applicable. This is an intravenous formulation.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the serum in the clinical pharmacology and biopharmaceutics studies?

A validated, sandwich enzyme linked immunoassay (ELISA) was used in the clinical trials to determine the concentration of obinutuzumab in human serum samples. An ELISA was developed and validated at two different sites (henceforth identified as site 1 and 2) for detection of obinutuzumab in human specimens using two different highly specific monoclonal capture and detection antibodies directed against the antigenic determinant (idiotype) of obinutuzumab. These two sites were subsequently cross validated.

Individual and pooled serum from humans (50% male and female) was used in the validation. The ELISA method used at both sites is based on the immunologic detection of obinutuzumab by

(b) (4) The ELISA consists of the following steps: (b) (4)

A summary of the findings from these validations are listed in Table 8. These validations appear consistent with the guidance "Bioanalytical Method Validation" and are acceptable.

Table 8: Summary of Analytical Methods used in Clinical Trials

Validation Report	Laboratory	Parameter	Result
Assay Validation Report 1028962	F. Hoffmann-La Roche Ltd. (Basel, Switzerland)	Assay Method	ELISA
		Matrix	Human serum
		Analyte	obinutuzumab
		Calibration Range	(b) (4)
		LLOQ	(b) (4)
		Calibration range acceptance	(b) (4)
		Intra- & Inter Assay Precision (%CV)	(b) (4)
		Intra- & Inter Assay Accuracy (%RE)	(b) (4)
		Interference	<ul style="list-style-type: none"> All lots measured below the LLOQ of the assay
		Selectivity/Specificity	<ul style="list-style-type: none"> (b) (4) of the tested spiked sera were within the acceptance range of (b) (4) of the nominal concentration.
		Cross reactivity	<ul style="list-style-type: none"> No cross reactivity by rituximab up to a serum concentration of 50µg/mL
		Dilution	<ul style="list-style-type: none"> Dilutions up to (b) (4) ULOQ show a precision (b) (4) (CV) and an accuracy (b) (4)
		Microplate homogeneity [Precision (%CV)]	(b) (4)
		Incurred Sample Re-Analysis	(b) (4) of study samples
		Assay Signal Stability After Stop	(b) (4) minutes
		Freeze-thaw stability	QC deviations of (b) (4) after 3 cycles
		Room temp stability	QC deviations of (b) (4) at 24 hours
Storage stability -20 C	QC deviations of (b) (4) after 3 months		
Storage stability -80 C	QC deviations of (b) (4) after 5 months		
Assay Validation Report 1048588	(b) (4)	Assay Method	ELISA
		Matrix	Human serum
		Analyte	obinutuzumab
		Calibration Range	(b) (4)
		LLOQ	(b) (4)
		Calibration range acceptance	(b) (4)
		Regression	(b) (4)
		Intra- & Inter Assay Precision (%CV)	(b) (4)
		Intra- & Inter Assay Accuracy (%RE)	(b) (4)
		Interference	<ul style="list-style-type: none"> At least (b) (4) of the unfortified lots measured below the LLOQ of the assay
		Selectivity/Specificity	<ul style="list-style-type: none"> At least (b) (4) of the fortified lots measured within (b) (4) of the theoretical value
		Cross reactivity	Not assessed
		Dilution	<ul style="list-style-type: none"> All results were within (b) (4) from theoretical with precision of less than (b) (4) (b) (4) was observed at concentrations exceeding (b) (4)
		Microplate homogeneity [Precision (%CV)]	Not assessed
		Incurred Sample Re-Analysis	Not assessed
		Assay Signal Stability After Stop	Not Assessed
		Freeze-thaw stability	CV% (b) (4) and the difference from theoretical did not exceed (b) (4) for high and low QC levels
Benchtop (room temp) stability	CV% (b) (4) and the difference from theoretical did not exceed (b) (4) for high and low QC levels		
Storage stability -20°C	Ongoing t (b) (4) months		
Storage stability -80°C	Ongoing t (b) (4) months		

Source: Biopharmaceutics Summary; Applicant reports 1028962, 1048588, and 1038901

A cross-validation study of the analytical assay for the quantitative determination of obinutuzumab in human serum at the two different laboratories was performed. The reference laboratory was the lab that originally validated the method at F. Hoffmann-La Roche Ltd., Basel, Switzerland, while the test laboratory was (b) (4). A total of 30 human serum samples were used for the cross validation study: 13 spiked QC samples, 2 blank QC samples, 12 pooled ex-vivo samples from a clinical study, 3 pooled pre-dose ex-vivo samples from a clinical study.

Blank serum samples (free of obinutuzumab) were successfully (at least 4 out of 5 blank samples are BLQ) identified by both laboratories as BLQ, respectively (corresponds to 80.0% success rate). For 18 of 25 cross-validation samples containing obinutuzumab at concentrations between 59.6 ng/mL and 1100 µg/mL, the %Difference was below $\pm 30\%$ (corresponds to 72.0% success rate [at least 2/3rd (66.7%) of the results of the individual samples should show a % Difference below $\pm 30\%$]). Interestingly, the success rate was 100% for the QC samples generated by spiking commercially available pooled human serum, whereas the success rate for the ex-vivo samples collected from patients with CD20+ malignant disease was only about 42%. The reason for this discrepancy is unclear, but an extended mandatory repeat analysis of study samples in routine analysis at (b) (4) is recommended (e.g. 10% instead of the usual minimum of 5%). None of the cross-validation samples was re-analyzed. This cross validation method is acceptable, however; the reviewer does not agree with the applicant's position that the results for obinutuzumab obtained with each of the ELISA methods at the two analytical sites are comparable given the discrepancy in noted in the cross validation of QC samples from the clinical trials which may contribute to the observed variability. A supplemental analysis evaluating assay laboratory as a covariate using the population PK model was unable to identify a significant impact of lab on clearance or volume. While far from ideal or conclusive, these findings are acceptable in the current submission. The impact of this discrepancy should be considered as part of the review of future submissions using the (b) (4) laboratory until the underlying cause is identified.

2.6.1.1 Which metabolites have been selected for analysis and why?

Not applicable. Protein drugs are generally degraded into amino acids that are then recycled into other proteins.

2.6.1.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Free (not bound to bound to soluble CD20 receptors or to neutralizing antibodies). Due to the use of these anti-idiotypic antibodies, the ELISA detects only the fraction of obinutuzumab with free and active binding sites and complexed obinutuzumab (e.g. bound to soluble CD20 receptors or to neutralizing antibodies) is not detected. While not optimal this is acceptable.

2.6.1.3 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1 above.

2.6.1.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Table 8 above. The assay range is acceptable given the reported exposure (Table 5) and the sample dilution validation (Table 8).

2.6.1.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Table 8 above.

2.6.1.6 What are the accuracy, precision, and selectivity at these limits?

See Table 8 above.

2.6.1.7 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Table 8 above. Given the limited long term frozen stability information the Agency issued information requests on 8/15/13 and 8/26/13 requesting additional information regarding the applicants validation plan regarding frozen stability and summary statistics indicating the mean sample storage time prior to analysis by trial and then storage temperature. In its response the

applicant provided in Table 9 and stated it plans to extend long-term frozen matrix stability testing to (b) (4). Since the available frozen storage times evaluated in the applicant's validation cover less than one standard deviation of the mean sample storage times, the potential for storage instability contributing to the observed PK variability (See Section 2.2.5.10) cannot be ruled out. The reviewer recommends that comment should be sent to the applicant to submit the (b) (4) stability to the Agency when available.

Table 9: PK Sample Storage By Temperature and Trial

Study	Assay Site	Storage Temp (°C)	Mean±SD Storage Time (days)	Median [Range] Storage Time (days)
BO21000	(b) (4)	-80±10°C	150±95	128 [17 - 810]
BO21003	(b) (4)	-80±10°C	149±92	129 [13 - 692]
BO21004	(b) (4)	-80±10°C	191±107	168 [17 - 644]
JO21900	Roche	-80°C	88±69	78 [13 - 650]
BO20999	Roche	-80°C	109±162	53 [5 - 858]
BO21003	Roche	-80°C	100±76	79 [4 - 476]

Source: Applicant response to Information request

2.6.1.8 What is the QC sample plan?

The performance of sample analysis was monitored by quality control samples in human serum spiked with three different concentrations of the analyte (0.0100, 0.100, 0.300 µg/mL for GA101). Quality control samples were analyzed along with the study samples. The QC samples bracketed the unknown samples. Results of an analytical run were accepted, if at least 2/3rd of the QC samples showed a difference of less than 20% from their respective nominal concentrations. 1/3rd of the QC samples were allowed to show a difference of more than 20% from their respective nominal concentrations, at least 50% of the QC samples at each level had to fulfill the acceptance criteria. This plan is acceptable.

2.6.2 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Five clinical trials in patients included immunogenicity analysis. Four of these trials (BO20999, BO21000, BO21003 and JO21900) used the first generation APA assay to analyze samples. The fifth trial (BO21004/CLL11) used the second APA generation assay to analyze samples. Both the first and second generation APA assays used a human serum ELISA immunogenicity assay. The assay performance of the two validated anti-therapeutic antibody assays is described in Table 10.

The first generation fully sequential bridging ELISA assay was sensitive for the detection of anti-obinutuzumab antibodies in serum samples with low obinutuzumab concentrations. The mean drug tolerance factor was 0.9 (tolerated ratio of drug-to-positive control) allowing detection of anti-obinutuzumab antibodies with a sensitivity of 0.500 µg/mL at obinutuzumab serum concentrations of up to 0.45 µg/mL Table 10.

The second generation assay was a two-step bridging ELISA, which has improved drug tolerance compared to the first generation ELISA. The mean drug tolerance factor was 95.6 (tolerated ratio of drug-to-positive control) allowing to detect anti-obinutuzumab antibodies with a sensitivity of 0.500 µg/mL at obinutuzumab serum concentrations of up to 47.8 µg/mL (Table 10).

Table 10: Performance summary of the first and second generation APA screening and confirmatory assays.

Validation Site	Assay Range (ng-equiv./mL)	Screening Cut Point Sensitivity (ng-equiv./mL)	Drug Tolerance Factor*	Accuracy, %		Precision, %	
				Intra-Assay	Inter-Assay	Intra-Assay	Inter-Assay
Roche ¹	31.3-2000	36.0	0.9	92.7 to 96.4	94.0 to 108.3	0.5 to 1.4	5.2 to 7.7
(b) (4)	29.0-2000	18.4	95.6	Not reported.		1.88 to 4.87	10.9 to 18.7

*Tolerated ratio of obinutuzumab-to-positive control (purified rabbit polyclonal antibody directed against obinutuzumab).

¹Roche assay validation report 1032264 (first generation assay used in trials BO20999, BO21000, BO21003 and JO21900).

(b) (4) assay validation report 1050193 (second generation assay used in trial BO21004/CLL11).

For the second generation APA assay, data from a panel of 50 serum samples from healthy volunteers were used to establish the assay decision thresholds, or screening cut-points. The data generated in these runs were used to calculate a normalization factor (NF) (defined as 0.093) for the screening and specificity cut point. For the screening cutpoint, the NF was used to calculate an additive floating screening cut point using the equation: CP = Mean NC + NF. Samples with raw responses greater than, or equal to, the floating cut point were reported as potentially positive and re-assayed. For the specificity cutpoint, samples subjected to 100 µg/mL of RO5072759 (obinutuzumab) during testing with responses that were inhibited by ≥85.7% were considered positive.

Refer to the CMC review for further details.

2.6.2.1 What is the performance of the binding assay(s)?

The performance of the binding assays has been reviewed in detail in the CMC review. Table 10 describes the assay performance of the two validated anti-therapeutic antibody assays. Refer to the CMC review for further details.

2.6.2.2 What is the performance of the neutralizing assay(s)?

A neutralizing assay was not used.

3 DETAILED LABELING RECOMMENDATIONS

- **Section 6.2 Immunogenicity:** Revised for consistency with other biologics and additional context regarding ATA assay interference and the lack of a neutralizing assay added.
- **Section 8.6 Renal Impairment:** Revised for section consistency. Extraneous non-actionable information removed
- **Section 8.7 Hepatic Impairment:** Revised for section consistency.
- **Section 12.2 Pharmacodynamics:** Additional context regarding B-Cell depletion and recovery from the submitted clinical trials added to provide a balanced presentation of the issue. The caveat that depletion of B cells is blood peripherally may not correlate with reduction of tumor burden was added. QT/QTc prolongation information added
- **Section 12.3 Pharmacokinetics:**
 - [REDACTED] (b) (4)
 - [REDACTED] (b) (4) omitted.
 - Pop-PK based PK parameters revised to FDA estimates.
 - Special population sections revised for section consistency and to reflect FDA findings and concerns.

4 APPENDICES

4.1 Tables, figures and graphs referred to but not included in the text

Table 11: NCA derived obinutuzumab serum primary PK parameters and secondary PK parameters in CLL patients following single and multiple dosing in phase 1 and 2 of trial BO20999

Phase	Dose	n	CL _{ss} L/day	VD _{ss} L	t _{1/2} days
1	400/800	3	0.137(59.503) 0.189[0.071-0.191]	6.6(29.6) 5.7[5.4-9.6]	18.6(32.9) 22.7[12.5-22.8]
	800/1200	3	0.144(167.8) 0.087[0.06-0.571]	7.3(148.6) 6.6[2.6-23.5]	17.8(81.6) 23.3[7.8-31]
	1000/1000	3	0.115(57.5) 0.099[0.073-0.214]	6.2(30) 5.3[4.9-8.9]	34.4(61.6) 47.1[17.4-49.4]
	1200/2000	3	0.069(44.6) 0.077[0.042-0.099]	4.8(12.3) 4.7[4.1-5.6]	26.1(53.5) 21.5[18.7-54]
2	1000/1000	10	0.119(73.5) 0.108[0.049-0.306]	8.6(185.5) 5.6[3.4-113.8]	20.6(82.4) 22[4.7-41.8]

Bolded doses reflect the administered dose relative to the reported parameters for that row. Parameter estimates represented as meanGeo(CVgeo) and Median [min-max].

† In Phase 1 patients with CLL received a total of 9 infusions, on Days 1 (half of the target dose) and 8 during Cycle 1 and then every 3 weeks thereafter from Cycle 2 to Cycle 8. During Phase 2 patients with CLL were dosed on Cycle 1, Days 1, 8 and 15, then every three weeks thereafter on Day 1 of Cycles 2-8 (10 infusions in total).

Source: derived from the applicant dataset located at \\cber-fs3\MeCTD_Submissions\STN125486\0004\m5\datasets\pop-pk\bo20999\listings\pkncaxpt

Table 12: Population PK model derived PK exposure and parameter estimates by trial^{1 2}

Trial	n	CL _{term} (L/Day)	CL _{init} (L/Day)	Vd _{term} (L)	t _{1/2} _{init} (Day)	t _{1/2} _{term} (Day)	C _{trough} ³ (µg/mL)	C _{max} ⁴ (µg/mL)	AUC _{last} ⁵ (Day•µg/mL)
20999	30	0.09(52) 0.086[0.039-0.232]	0.58(88) 0.59[0.22-2.1]	3.7(24) 3.8[2.5-6.3]	4.6(79) 4.9[1.4-13.1]	28.8(46) 29[11.5-64.2]	259.1(160) 342.9[15.2-1695.5]	671(62) 675.7[273.5-2374.4]	11620(97) 13095.9[2621.4-55903]
21003	4	0.077(59) 0.095[0.035-0.111]	0.65(50) 0.61[0.4-1.24]	3.6(17) 3.7[2.8-4.2]	3.9(49) 3.7[2.4-7]	32.4(69) 26.6[19.8-78.7]	95(1103) 318.6[1.3-612.1]	687.4(57) 844.2[316.6-989.7]	8718.3(190) 14571[1396.1-19558.3]
21004	220	0.094(45) 0.094[0.022-0.274]	0.42(75) 0.39[0.12-2.79]	3.8(23) 3.8[2.2-6.1]	6.5(65) 7.1[1.3-22]	28.3(42) 28.9[11.2-101.1]	180.6(163) 209.6[0-1177]	532.2(40) 532.6[201.5-1499.9]	8454(73) 8986.2[524.4-36395.8]
All CLL	254	0.094(47) 0.093[0.022-0.274]	0.44(78) 0.4[0.12-2.79]	3.8(23) 3.8[2.2-6.3]	6.2(69) 6.8[1.3-22]	28.4(43) 28.8[11.2-101.1]	186.6(177) 221[0-1695.5]	549.1(45) 560[201.5-2374.4]	8781.9(80) 9546.7[524.4-55903]

1 =Parameter estimates represented as meanGeo(CVgeo) and Median [min-max]

2 =The PK parameters are based on the dose each patient received at the final treatment cycle.

3 =C_{trough} was based on the trough concentration 28 days after the last dose.

4 =C_{max} was obtained immediately following the end of the last infusion.

5 =AUC was calculated from the time of the last dose through 28 days.

Source: derived from the applicant dataset located at \\cber-fs3\MeCTD_Submissions\STN125486\0004\m5\datasets\pop-pk\bo20999\listings\pkncaxpt

4.2 Pharmacometric Review

**OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRICS REVIEW**

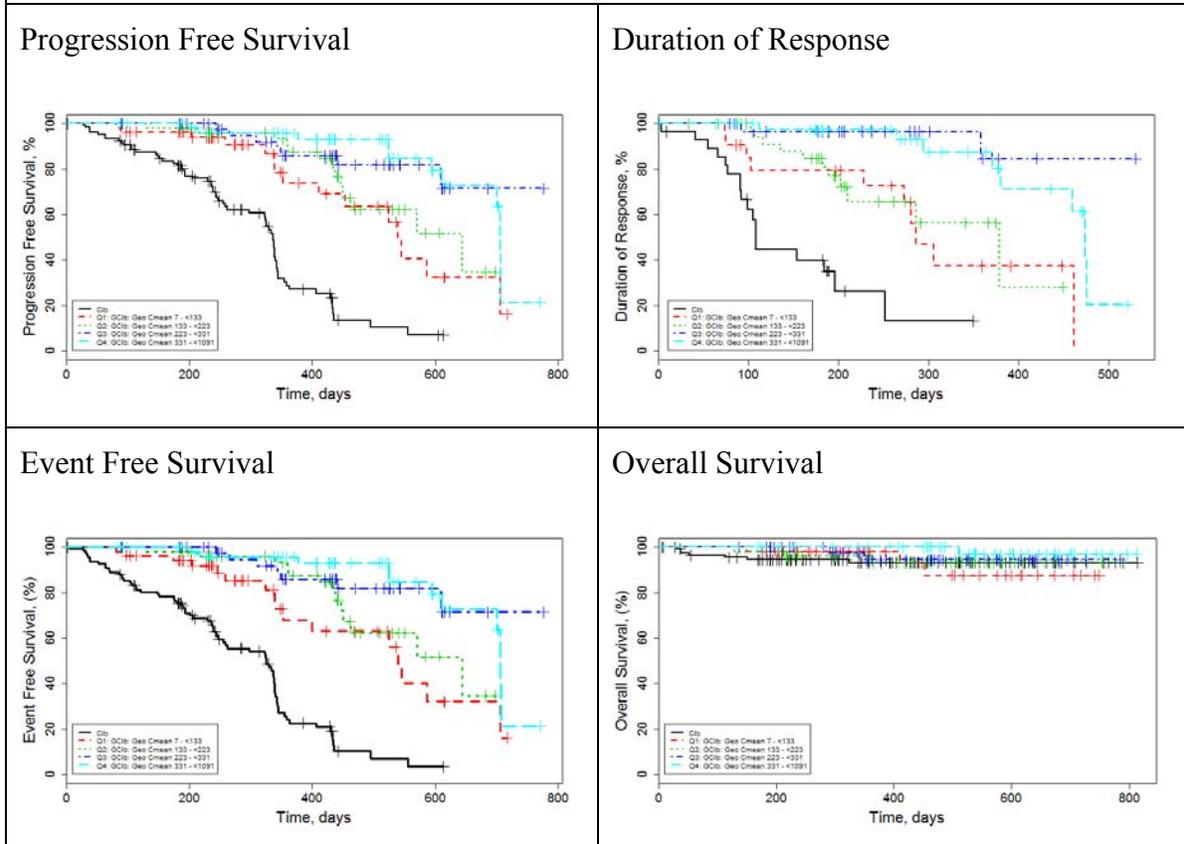
Submission	BLA125486
Submission Date	April 22, 2013
Generic Name	Obinutuzumab (Gazyva)
Reviewer	Jeffry Florian, Ph.D.
Secondary Reviewer	Nitin Mehrotra, Ph.D.
OCPB Division	DCP-5 and DPM
ORM Division	OND/ OHOP/DHP
Sponsor	Genentech
Dosing regimen	100 mg on day 1, cycle 1 900 mg on day 2, cycle 1 1000 mg on day 8, cycle 1 1000 mg on day 15, cycle 1 1000 mg on day 1, cycle 2-6
Indication	Treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)

1 SUMMARY OF FINDINGS

1.1.1 Is there evidence of an exposure-response relationship for obinutuzumab in subjects with previously untreated lymphocytic leukemia?

Yes, an exposure-response relationship was identified for obinutuzumab and progression free survival, duration of response, and event-free survival in patients with previously untreated lymphocytic leukemia (Figure 1). These exposure-response relationships provide supportive evidence of effectiveness of obinutuzumab in this patient population. No relationship was identified between overall survival and obinutuzumab exposure, however the overall number of events in either treatment at the time of data submission (9 events out of 118 subjects in the chlorambucil arm and 13 events out of 238 subjects in the obinutuzumab and chlorambucil arm). Geometric mean observed obinutuzumab C_{trough} from cycle 2 through the last cycle of treatment were used as the exposure variable while progression free survival (PFS), duration of response (DOR), event-free response (EFR), and overall survival (OS) was used as the response variables.

Figure 1. Kaplan-Meier curve for PFS, DOR, EFS, and OS by quartile of obinutuzumab exposure. For comparison, the Kaplan-Meier curve for the chlorambucil control arm is shown on each plot (black line)

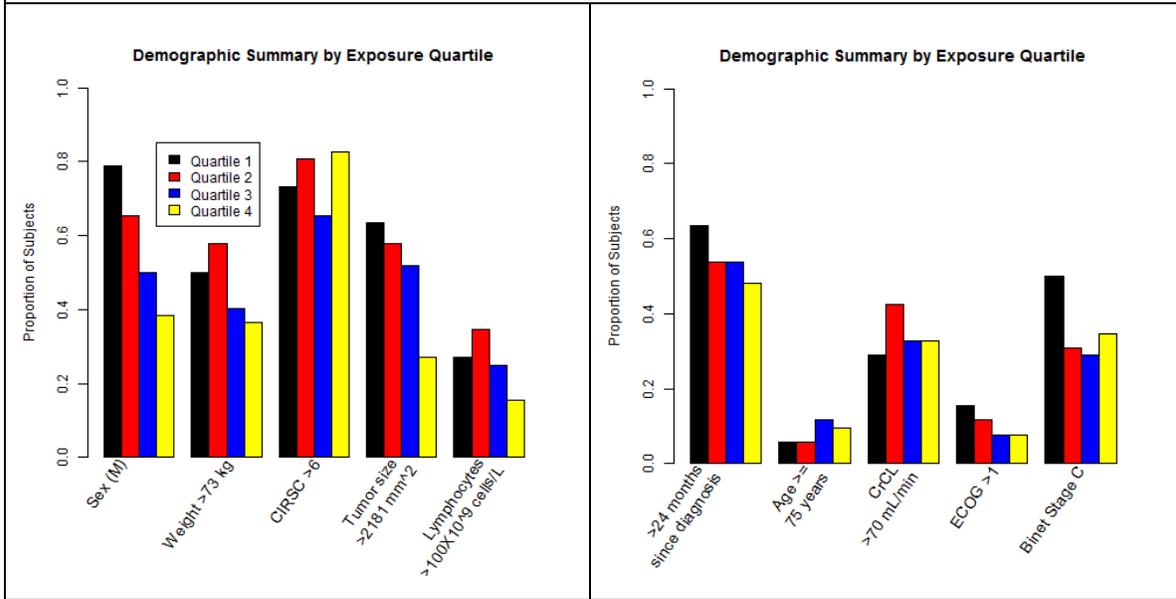


A trend of increasing effectiveness was observed between the control arm (chlorambucil) and all four quartiles of the obinutuzumab with chlorambucil (Clb) treatment arm. In addition, higher exposures appear to be associated with better PFS, with increasing PFS from the first (Q1) to the fourth (Q4) quartile. The relationship was most distinctive for exposures in the third (Q3) and fourth (Q4) quartile compared to the first (Q1) and second (Q2) quartile. This was supported by the univariate analysis that identified a decreasing hazard ratio estimate for the first (Q1) quartile compared to the Q3 and Q4, but only marginal improvement between the Q1 and Q2. However, the univariate analysis identified other potentially confounding factors that needed to be accounted as part of a multivariate analysis to better understand the impact of lower obinutuzumab exposures on PFS.

The risk factors associated with patients showed an imbalance across most obintuzumab exposure quartiles (Figure 2). There were more males, subjects with higher baseline tumor burden, subjects with higher baseline lymphocyte count in the lower exposure groups, and a longer time from diagnosis to randomization in the lowest exposure quartile (Q1) compared to the highest exposure quartile (Q4). These results are not unexpected as the population pharmacokinetic analysis identified body weight as a significant covariate for clearance and volume, and males in the Phase III study had a median body weight of

76 kg compared to 65 kg in women. Likewise, the purpose of the sponsor’s proposed cycle 1 dosing was to overcome target-mediated drug disposition by saturating available receptors. Subjects with higher circulating lymphocyte counts or tumor burden (as assessed by the 2-D sum of all lesions identified) may have more extensive disease, and by association, a greater number of target receptors to occupy before saturation.

Figure 2. Proportion of subjects in each obinutuzumab exposure quartile with the listed risk factor



Cox-proportional hazards regression after adjustment with risk factors (stratification factors for the trial such as baseline CIRS score and time from diagnosis as well as significant factors from the univariate analysis [baseline tumor size, baseline circulating lymphocytes]) indicated that the effect of obinutuzumab exposure on PFS was still significant. As shown in Table 1, the hazard of having an event is reduced approximately by 25-36% for obinutuzumab exposure in the third (Q3) and fourth (Q4) quartile compared lowest (Q1) quartile. It should be noted that the hazard ratio estimates in the multivariate analysis for obinutuzumab were higher than those in the univariate.

Table 1: Multivariate Cox-proportional hazards regression analysis for PFS

PFS	Adjustments for baseline CIRS score, time from diagnosis, baseline tumor size, baseline circulating lymphocytes	HR	CI	p-value	
	Geo Mean C _{tr} (continuous) per 100 ug/mL	0.90	0.83-0.96	0.003	
	Quartile Geo Mean C _{tr} (categorical, compared to Q1)	Q2	0.82	0.62-1.08	0.16
		Q3	0.64	0.47-0.86	0.004
		Q4	0.75	0.57-0.86	0.04

1.1.2 Is there evidence of exposure-safety relationships for obinutuzumab?

No, the available data did not identify an exposure-response relationship between obinutuzumab exposure and adverse event rate. There is evidence of increased likelihood of certain adverse events with obinutuzumab treatment compared to the control, including the percentage of subjects with grade 3 or higher cardiac events, tumor lysis syndrome, neutropenia, and thrombocytopenia. Neutropenia and thrombocytopenia, in particular, were elevated in the obinutuzumab treatment arm compared to the control arm.

Paradoxically, in the exposure-response analysis, the event rate was highest in the lowest obinutuzumab exposure quartile for grade 3-5 neutropenia and thrombocytopenia. The initial exposure-response safety assessment was based on geometric mean average exposure over the treatment duration plus 28 days after the last dose as well as the observed concentration value in closed proximity to the adverse event. In both situations, the inverse trend remained between obinutuzumab exposure and adverse event rate, though the event rates remained consistently higher than the control arm. Additional data from ongoing obinutuzumab studies will be necessary to better understand the exposure-response safety relationships between these adverse events and obinutuzumab exposures, but the current data does not suggest the need for obinutuzumab dose adjustments in CLL patients beyond the measures implemented in the Phase III trial.

Table 2: Comparison of Adverse Event Rates between Obinutuzumab Exposure Quartiles and the Control Arm from BO21004

Patients with	C1b N = 116	G-C1b N = 208			
		Q1 (N=52)	Q2 (N=52)	Q3 (N=52)	Q4 (N=52)
Grade 3+ Cardiac events	3.3%	5.8%	3.8%	0%	5.8%
Grade 3+ Tumor lysis syndrome	0%	1.9%	0%	3.8%	0%
Grade 3+ Infections	16.9%	13.5%	15.4%	9.6%	13.5%
Grade 3+ Neutropenia	17.8%	51.9%	48.1%	40.4%	28.8%
Grade 3+ Thrombocytopenia	5.1%	19.2%	19.2%	7.7%	5.8%

1.1.3 Is proposed dosing regimen appropriate? Can dose be optimized in subgroup of patients with lower efficacy?

The sponsor's proposed dosing regimen includes three components: i) splitting of the initial dose over two days (100/900 mg on day1/2 instead of 1000 mg on day 1); ii) administration of 3000 mg (1000 mg every week) in cycle 1 to overcome target-mediated

drug disposition; and iii) selection of a 1000 mg dose. The evidence supporting these components is summarized below:

i) Splitting of the initial dose over two days

In order to reduce the incidence of infusion-related reactions (IRR), the sponsor enacted a series of protocol amendments including administering corticosteroids to patients based on baseline circulating lymphocyte count, administering corticosteroids to all patients and consideration to withhold anti-hypertensives on the day of infusion, and finally, an amendment recommending splitting the initial dose over two days (100 mg on day 1 followed by 900 mg on day 2). This last protocol amendment was implemented on October 18th, 2011, though, it is not certain which, if any, of these measures were implemented in patients enrolled after this date as case report forms were not designed to capture all relevant information. However, this is the only available data for determining the impact of these protocol amendments on IRRs.

The applicant conducted an analysis by grouping patients enrolled in the time frame between the start of the trial and the various protocol amendments. In all, there were 45 subjects enrolled after the amendment for splitting the dose over two days. Overall, both the IRRs event rate and number of serious IRRs appeared to be lower in those subjects enrolled following the final amendment. While this finding is encouraging it cannot be considered definitive at this time due to the small sample sizes for each intervention and as it is uncertain if the interventions noted below were implemented in all patients enrolled following the protocol amendments. This issue should be further evaluated in future submissions that include additional phases of this trial.

Table 3: Infusion Related Reactions at First Infusion by Infusion reaction intervention in trial BO21004

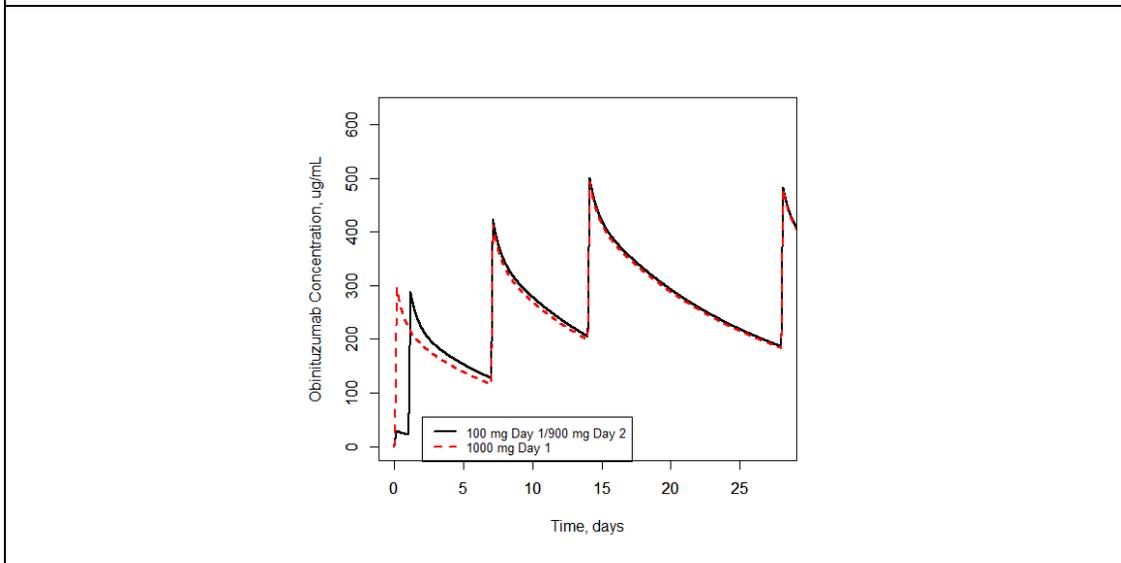
IRR Intervention	Patients Enrolled N	obinutuzumab and chlorambucil Arm (N = 240)		
		All IRRs N (%)	Serious IRRs N (%)	Grade 3-5 IRRs N (%)
1. Premedication with anti-pyretic and anti-histamine	53	47 (88.7)	5 (9.4)	9 (17.0)
2. #1 + corticosteroid pre-medication with lymphocyte count > 25x10 ⁹ /L	74	53 (71.6)	9 (12.2)	19 (25.7)
3. #1 + corticosteroid pre-medication all patients	33	23 (69.7)	8 (24.2)	10 (30.3)
4. #1 + #3 + antihypertensive drugs must be paused	35	21 (60.0)	3 (8.6)	5 (14.3)
5. # 1 + #3 + #4 + Split first Dose over 2 days (100 mg/900 mg)	45	21 (46.7)	2 (4.4)	8 (17.8)

Source: Applicant's core report for trial BO21004

In addition, the reviewer conducted a simulation analysis to determine the impact of splitting the dose as proposed by the sponsor on obinutuzumab pharmacokinetics. As expected, the primary impact of splitting the initial dose is evident over the first two days of treatment. Using pharmacokinetic parameters for a typical patient (75 kg male with CLL; see the Sponsor's Population Pharmacokinetic Model Results below), the predicted C_{tr} at the end of week 1 was 116 and 128 µg/mL for the scenario where 1000 mg was administered on day 1 or over day 1 and 2, respectively (Figure 3). By the start of cycle

2, negligible differences in obinutuzumab pharmacokinetics are expected between the two infusion strategies.

Figure 3. Simulated Obinutuzumab Exposures Over Cycle 1 For Infusion Scenarios of 1000 mg on Day 1 (red) or 100 mg Day 1 and 900 mg Day 2 (black)

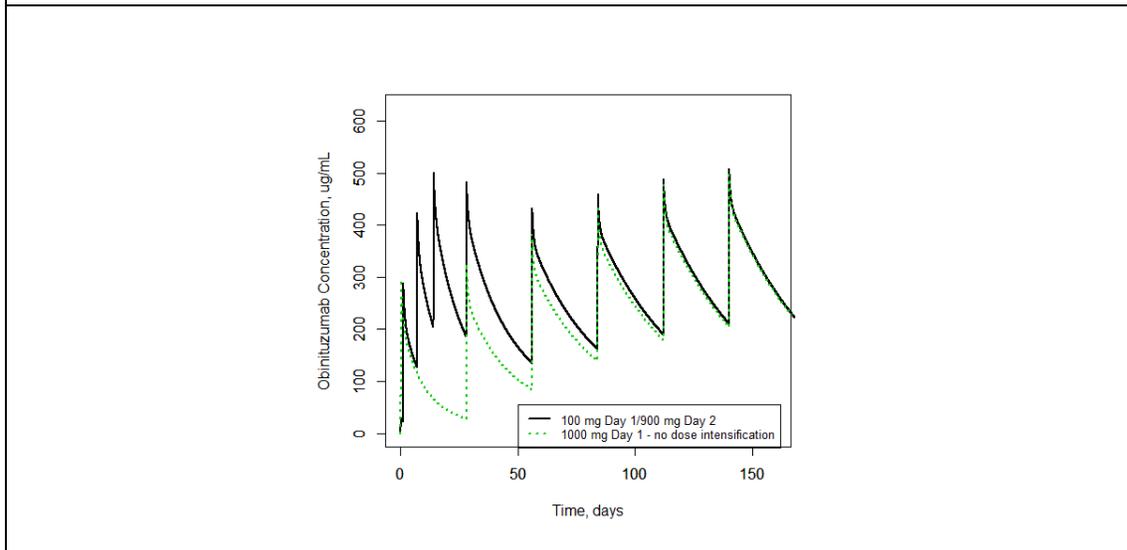


ii) Dose-intensification over cycle 1

The sponsor identified increased elimination of obinutuzumab following initial dosing, which was believed to be associated with target-mediated drug disposition. Patients with higher initial tumor burden and a higher number of CD20-positive tumor cells clear the drug faster than patients with a lower initial tumor burden. This was supported by observations from the early phase trials, the population PK modeling analysis, and is in agreement with the pharmacokinetics observed for other monoclonal antibodies (i.e., rituximab). To overcome this increased initial clearance and saturate the target early in treatment, the sponsor proposed weekly dosing of 1000 mg obinutuzumab for three weeks over the first cycle of treatment. Based on the population predicted exposures for a typical subject, this regimen is predicted to result in obinutuzumab C_{tr} exposures that are 6.6-fold higher at the beginning of cycle 2 compared to the scenario where no dose-intensification was used during cycle 1.

In addition, geometric mean C_{tr} exposures for subjects in CL21004 at the beginning of cycle 2 was 233 $\mu\text{g/mL}$, which was 39% higher than geometric mean C_{tr} at the beginning of cycle 3 (167 $\mu\text{g/mL}$). There were no differences in geometric mean C_{tr} between cycle 3 through cycle 6 (167, 160, 166, and 184 $\mu\text{g/mL}$, respectively, for cycle 3, 4, 5, and 6), supporting that the dose-intensification achieved obinutuzumab exposure at or exceeding steady state by the start of cycle 2. Without dose intensification during cycle 1, obinutuzumab exposure over the initial cycle would be substantially lower and similar exposure would not be achieved until cycle 4 or 5 of treatment (Figure 4).

Figure 4. Simulated Obinutuzumab Exposures For the Regimen Evaluated in CL21004 Versus A Regimen with No Cycle 1 Dose-Intensification



iii) Selection of the 1000 mg

Selection of 1000 mg as the treatment dose for CLL patients was based on data from studies BO20999 and BO21003 where greater tumor shrinkage was observed with higher dose of obinutuzumab (1600 mg on cycle 1 followed by 800 mg for the remaining cycles (non-Hodgkin's lymphoma [NHL]) or 1000 mg over all cycles [CLL]) compared to when patients were administered 400 mg in all cycles (NHL).

In addition, based on the exposure-response analyses above this dose resulted in improved PFS survival across all the exposure quartiles compared to that in the control arm. Also, no clear exposure-response safety relationships were identified to suggest the selected dose was excessive or should be adjusted beyond those measures currently recommended by the sponsor for handling IRRs. Despite these observations, it should be noted that the data from CL21004 is not sufficient to determine if the proposed regimen is optimal for all CLL patients. For example, a subset of patients with higher tumor burden may benefit from higher obinutuzumab doses or higher initial doses in order to saturate available receptors earlier during treatment. Also, the current analysis is based on progression free survival and should be revisited as data from other endpoints, such as overall survival, becomes available. Finally, these observations are for CLL patients, and the selected regimen may need adjustment based on the disease under evaluation (non-Hodgkin's Lymphoma may require different dosing than CLL and disease was an identified covariate in the population pharmacokinetic analysis).

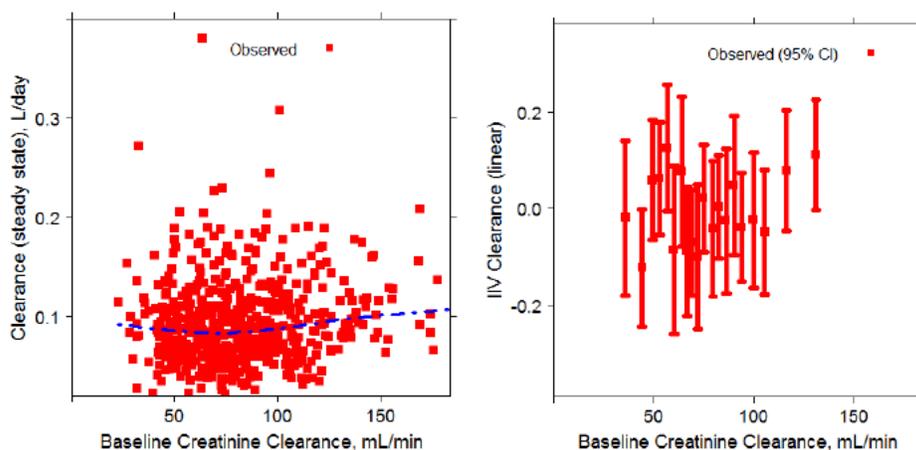
1.1.4 Should dose be adjusted for patients with renal impairment?

No dose adjustments are necessary in patients with mild or moderate renal impairment based on the population PK analysis. This is not unexpected as based on the sponsor's submitted ADME study, renal elimination of obinutuzumab is minimal. Due to the

limited number of subjects in the Phase III study with severe renal impairment (n=5), there is insufficient data to provide dosing recommendations in this population.

The sponsor evaluated the impact of renal function on exposure during their population PK analysis by evaluating whether creatinine clearance was a significant covariate on obinutuzumab clearance. Creatinine clearance for the analysis was calculated using the Cockcroft-Gault formula with values >180 mL/min capped at 180 mL/min. This population PK analysis did not identify any significant relationship between creatinine clearance and obinutuzumab clearance.

Figure 5: Effect of renal impairment on obinutuzumab clearance



The impact of renal function on obinutuzumab was further evaluated by summarizing observed obinutuzumab according to renal function category (Table 4). No difference in obinutuzumab PK was observed across categories for normal, mild, or moderate renal function. Due to the limited number of subjects with severe renal impairment in the Phase III study, there is insufficient data available to provide recommendations for subjects with severe renal impairment. Similarly, a summary of adverse event rates for renal function category are shown in Table 5. There was no trend of higher adverse event rates for any of the listed AEs across renal function categories.

Table 4: Comparison of Geometric Mean C_{tr} Between Phase III patients with normal, mild, moderate, and severe renal function based on baseline creatinine clearance (24 subjects were missing baseline CrCL data and 6 additional subjects were missing obinutuzumab concentration data)

	Normal Renal Function (n=29)	Mild Renal Impairment (n=82)	Moderate Renal Impairment (n=85)	Sever Renal Impairment (n=5)
Geometric Mean C_{tr} , ug/mL (CV%) [Median]	184 (51%) [193]	169 (93%) [203]	186 (86%) [219]	205 (43%) [202]

Population PK Clearance, L/day (CV%) [Median]	0.115 (32%) [0.115]	0.094 (36%) [0.095]	0.087 (37%) [0.088]	0.100 (37%) [0.097]
Population PK Predicted Cavg (28 days past final dose), µg·L/day (CV%) [Median]	7845 (33%) [8162]	9012 (49%) [8701]	9847 (53%) [9049]	9665 (33%) [9832]

Table 5: Comparison of Adverse Event Rates between Phase III patients with normal, mild, moderate, and severe renal impairment based on baseline CrCL

Patients with	G-C1b N = 238				
	Normal (n=29)	Mild (n=84)	Moderate (n=89)	Severe (n=5)	Missing (n=31)
Grade 3-5 Cardiac events	0%	3%	5%	0%	25%
Grade 3-5 Tumor lysis syndrome	3%	2%	1%	0%	0%
Grade 3-5 Infections	3%	17%	13%	0%	0%
Grade 3-5 Neutropenia	31%	38%	48%	40%	4%
Grade 3-5 Thrombocytopenia	14%	9%	15%	20%	0%

1.1.5 Should dose be adjusted for patients with hepatic impairment?

The available data from the Phase III trial is insufficient to inform dose adjustments in subjects with mild, moderate, or severe hepatic impairment, though the large molecular weight of obinutuzumab (150 kD) and elimination mechanism (receptor-mediated and not hepatic elimination) suggests that hepatic function should have minimal impact on obinutuzumab exposure.

Based on the population pharmacokinetic analysis, no relationship between baseline liver enzyme ALT or bilirubin and obinutuzumab clearance were observed. In addition, subjects from the Phase III trial were classified as “normal”, “mild”, and “moderate” hepatic function based on criteria proposed by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) [baseline AST and total bilirubin]. Out of the 238 Phase III patients, 2 were classified as “mild” hepatic impairment, 6 were classified

as “moderate” hepatic impairment, and 228 were classified as “normal” hepatic function (2 subjects were missing baseline laboratory information). None of the subjects were classified as “severe” hepatic impairment.

PK was available in all 8 of the subjects classified as mild or moderate impairment in and 200 of the subjects classified as having normal hepatic function. While the geometric C_{tr} measurements for subjects with moderate impairment was lower than those from subjects with normal hepatic function, the observed obinutuzumab C_{tr} was within the range observed in subjects with normal hepatic function. However, all subjects with moderate impairment were below the median for subjects with normal hepatic function. Based on the currently available data, the impact of “moderate” and “mild” hepatic impairment (and “severe” impairment) cannot be addressed with the given data.

Table 6: Comparison of Geometric Mean C_{tr} Between Phase III Subjects with normal, mild, and moderate hepatic function based on NCI ODWG criteria

	Normal Hepatic Function (n=200)	Mild Hepatic Impairment (n=2)	Moderate Hepatic Impairment (n=6)
Geometric Mean C_{tr}, ug/mL (CV %) [Median]	182 (85%) [214]	78; 316	102 (45%) [122]
Population PK Clearance, L/day (CV %) [Median]	0.094 (37%) [0.093]	0.115; 0.077	0.119 (32%) [0.116]

An additional analysis evaluated the rate of adverse events associated with obinutuzumab treatment and baseline hepatic function. The numbers of “mild” and “moderate” subjects were small and were grouped together for the purpose of this analysis. Adverse events were more common in subjects with baseline mild or moderate hepatic function, though this observation may be due to underlying comorbidities and not obinutuzumab exposure or due to the fact that there are only 8 patients in the mild/moderate category.

Table 7: Comparison of Adverse Event Rates between Phase III Subjects with normal, mild, and moderate hepatic function based on NCI ODWG criteria

Patients with	G-C1b N = 238	
	Normal (N=228)	Mild/Moderate (N=8)
Grade 3-5 Cardiac events	6%	13%
Grade 3-5 Tumor lysis syndrome	2%	0%
Grade 3-5 Infections	11%	25%

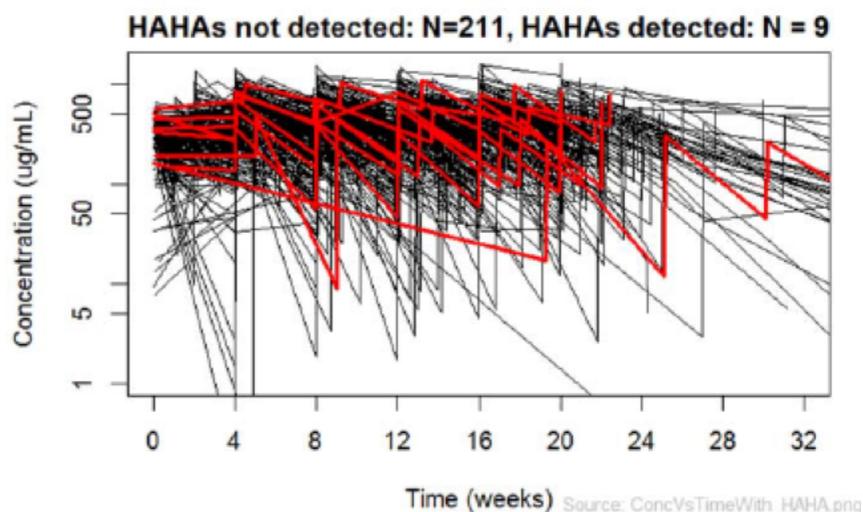
Grade 3-5 Neutropenia	36%	88%
Grade 3-5 Thrombocytopenia	11%	13%

It is recommended to continue to collect PK in ongoing or future Phase III trials to assist in addressing whether subjects with hepatic impairment are in need of dose adjustments. Other approaches, such as physiologically-based pharmacokinetic modeling, may also be utilized to inform whether any adjustments in this population are necessary.

1.1.6 What are the PK characteristics and incidence rate of anti-drug antibodies (ADA) in patients administered obinutuzumab?

In total, 7 subjects from the Phase III studies were identified as having anti-drug antibodies (ADA) 6-months or later into follow-up. Neither population PK analysis nor summary obinutuzumab pharmacokinetics (Table 8) for these seven subjects (compared to the 125 subjects with PK and confirmatory ADA results) could identify any differences in obinutuzumab exposures for subjects with ADAs. The applicant's overlay of PK data for subjects with and without ADAs (listed as HAHAs in the plot) is shown below in Figure 6. No discernible differences in the PK between subjects with and without ADAs could be identified.

Figure 6: Relationship between Observed Obinutuzumab Concentrations and Detections of ADAs



Sponsor's Population PK report, pg 98

However, given the small number of subjects in this analysis, the conclusions should be interpreted with caution and should be revisited as additional data with obinutuzumab use becomes available. In addition, as it is not known when the subjects may have developed ADAs on-treatment, a comparison of on-treatment PK between subjects with ADAs versus those without may be misleading as the ADAs may not have developed until after the final PK assessment.

Table 8: Comparison of Geometric Mean C_{tr} Between Phase III Subjects with and without ADAs

	With ADAs (n=7)	Without ADAs (n=125)
Geometric Mean C_{tr}, ug/mL (CV %) [Median]	217 (79%) [257]	236 (68%) [283]

1.2 Recommendations

Division of Pharmacometrics has reviewed this BLA from a clinical pharmacology perspective and recommends approval. The appropriateness of the obinutuzumab dose with respect to safety and efficacy should be reevaluated as data emerges in CLL subjects for overall survival and if the applicant intends to evaluate other diseases, such as non-Hodgkin’s lymphoma.

1.3 Label Statements

- 8.6 Renal Impairment**

(b) (4)

Based on population pharmacokinetic analysis of Gazyva, a baseline creatinine clearance (CLcr) >30mL/min does not affect the pharmacokinetics of Gazyva. Gazyva has not been studied in patients with a baseline CLcr <30mL/min [see Clinical Pharmacology (12.3)].

- 8.7 Hepatic Impairment**

(b) (4) Gazyva has not been studied in patients with hepatic impairment (b) (4)

- 12.3 Pharmacokinetics**

(b) (4) Based on a population pharmacokinetics (b) (4)

(b) (4)
(pop-PK) analysis, the geometric mean (CV%) (b) (4) volume of distribution of obinutuzumab at steady state is approximately 3.8 (23)

L.
The elimination of obinutuzumab is comprised (b) (4) of a linear clearance pathway and a time-dependent non-linear clearance pathway (b) (4)

As Gazyva treatment progresses, the impact of the time-dependent pathway in a manner suggesting target mediated drug disposition (TMDD). (b) (4)

—Based on a pop-PK analysis, the geometric mean (CV%) terminal obinutuzumab clearance and half-life are approximately 0.09 (46%) L/day and 28.4 (43%) days, respectively.

Special Populations:

(b) (4)

Body Weight: Volume of distribution and steady state clearance both increased with body weight, however, the expected change in exposure does not warrant a dose modification.

Renal Impairment: (b) (4) Based on the population pharmacokinetic analysis of Gazyva (b) (4), a baseline creatinine clearance (CLcr > 30 mL/min) does not affect the pharmacokinetics of Gazyva. (b) (4) Gazyva has not been studied in patients with a baseline CLcr < 30 mL/min (b) (4)

Hepatic impairment: (b) (4)
—Gazyva has not been studied in patients with hepatic impairment.

2 PERTINENT REGULATORY BACKGROUND

Obinutuzumab (also known as GA101) is a novel, humanized, Type II glycoengineered monoclonal antibody (mAb) directed against the CD20 antigen, which is found on most

malignant and benign cells of B-cell origin. Obinutuzumab was derived by humanization of the parental B Ly1 mouse antibody and subsequent glycoengineering to achieve high affinity binding to the CD20 antigen, low complement-dependent cytotoxicity activity, high direct cell death induction, high antibody-dependent cellular toxicity, and antibody-dependent cellular phagocytosis.

Obinutuzumab is being developed for the treatment of (b) (4) chronic lymphocytic leukemia (CLL) (b) (4)

Data to support the efficacy of obinutuzumab is based on a single pivotal phase 3 trial that reports that obinutuzumab plus chlorambucil (GClb) resulted in a reported IRC-assessed PFS median of 23.0 months in the GClb arm compared with 11.1 months in the Clb arm (stratified HR of 0.16 95% CI [0.11; 0.24]; p-value <0.0001 (log-rank test)). Most common ADR's ($\geq 10\%$) were infusion reactions, neutropenia, thrombocytopenia, nausea, anemia, diarrhea and pyrexia.

This application is seeking approval for obinutuzumab in combination with chlorambucil for previously untreated patients with CLL.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

The applicant developed a population pharmacokinetic model to explore the impact of intrinsic and extrinsic factors on obinutuzumab exposure in subjects with chronic lymphocytic leukemia (CLL) (b) (4). In addition, obinutuzumab time course based on estimated population pharmacokinetic parameters were used by the applicant to explore exposure-response efficacy and safety relationships in subjects with chronic lymphocyte leukemia.

3.2 Population Pharmacokinetic Model

Report 5.3.3.5 Population Pharmacokinetic Analysis of Obinutuzumab in Patients with CLL and HHL and Exposure-Efficacy and –Safety Graphical Analyses in Patients with CLL

The objectives of the analysis were population PK analysis were: 1) to build a population PK model of obinutuzumab following intravenous administration; 2) to determine post-hoc estimates of derived PK parameters; 3) to identify covariate factors that may influence disposition of obinutuzumab. The objectives of the graphical exposure-response efficacy and safety analyses were: 1) to qualitatively assess relationships between time course of drug concentrations and adverse events of interest (SAE and neutropenia); and 2) to qualitatively assess relationships between time course of drug concentrations and efficacy measures such as overall response, event-free survival, progression free survival, and overall survival.

3.2.1 Data

Obinutuzumab concentration-time, dosing, demographics and covariate data from the following studies were combined in the population PK analysis: BO20999, BO21000,

BO21003, and BO21004. An overview of these clinical trials, number of subjects, and samples is presented in Table 9. The analysis dataset contained 11784 quantifiable serum samples from 590 subjects administered obinutuzumab. A number of data points were not included in the model development (commented out in the analysis data file). Among them, 66 (0.6%) post-dose observations below quantification limit and 94 (0.8%) data points deemed as data errors (such as pre- dose concentrations and concentrations irreconcilable with the dosing history) were permanently excluded. In addition, 139 (1.2%) data points that could possibly be explained by the model although inconsistent with the expected concentration-time profiles were excluded during the model development. Demographics for these studies are summarized below in Table 10 and Table 11.

Table 9 Overview of Clinical Trials Included in Obinutuzumab Population PK Analysis

Study	Number of Subjects		Number of Concentration Values			
	Included	Excluded, later included	Included	Excluded		
				Non BQL, later included	Non BQL, not included later	Post-dose BQL
BO20999	131	2	3446	41	24	55
BO21000	134	0	3634	18	31	8
BO21003	105	1	2327	54	26	3
BO21004	220	1	2377	26	13	0
Total	590	4	11784	139	94	66

Sponsor's 1055255.pdf, pg 70

Table 10 Summary of Continuous Covariates in Obinutuzumab Population PK Analysis

Covariate	Description	Units	Overall	Study			
				20999	21000	21003	21004
N	Number of subjects		590	131	134	105	220
BSA	Body surface area	m ²	1.85 (0.208)	1.86 (0.206)	1.88 (0.221)	1.86 (0.212)	1.81 (0.195)
BW	Weight	kg	75.7 (15.2)	76.1 (15.1)	78.3 (16.7)	77.0 (15.5)	73.3 (13.9)
BMI	Body Mass Index	kg/ m ²	26.9 (4.65)	26.7 (4.63)	27.5 (5.24)	27.2 (4.29)	26.5 (4.43)
AGE	Age	years	64.9 (11.9)	63.1 (12.2)	57.1 (11.2)	61.8 (9.8)	72.1 (8.54)
BLYM	Baseline lymphocyte count	10 ⁹ /L	32.8 (63)	13.4 (27.7)	2.48 (8.81)	3.07 (12.0)	77.1 (83.2)
BBCE	Baseline B-cell count	10 ⁹ /L	31.7 (63.1)	11.8 (26.8)	1.62 (10.9)	2.43 (12.6)	75.9 (83.4)
CRCL	Calculated creatinine clearance	mL/min	82.7 (31.1)	84.8 (26.9)	99.9 (32.2)	92.9 (28.6)	66.1 (25.6)
CRCLN	Calculated normalized creatinine clearance	mL/min/ (1.73 m ²)	76.8 (25.1)	78.8 (22.7)	91.3 (24)	85.5 (21.0)	62.8 (21.5)
BSIZ	Baseline tumor load	mm ²	5820 (23300)	4480 (4470)	5560 (5130)	4420 (5740)	7450 (37500)
log(BSIZ)	Log of baseline tumor load	log (mm ²)	7.88 (1.25)	7.99 (0.962)	8.26 (0.919)	7.85 (1.07)	7.6 (1.56)

Sponsor's 1055255.pdf, pg. 72

Table 11 Summary of Categorical Covariates in Obinutuzumab Population PK Analysis

Covariate (NOTATION)	Level = Value	Number (Percent) of Patients				
		Total	20999	21000	21003	21004
Study (STUD)	20999 = BO20999	131 (22.2%)	131 (100%)	-	-	-
	21000= BO21000	134 (22.7%)	-	134 (100%)	-	-
	21003= BO21003	105 (17.8%)	-	-	105 (100%)	-
	21004= BO21004	220 (37.3%)	-	-	-	220 (100%)
Sex (SEX)	0 = Females	260 (44.1%)	52 (39.7%)	71 (53%)	48 (45.7%)	89 (40.5%)
	1 = Males	330 (55.9%)	79 (60.3%)	63 (47%)	57 (54.3%)	131 (59.5%)
Disease (DIS)	1 = Chronic Lymphocytic leukaemia	254 (43.1%)	30 (22.9%)	-	4 (3.8%)	220 (100%)
	2 = B-cell lymphoma, lymphoplasmacytoid lymphoma/immunocytoma, lymphoma, lymphocytic lymphoma, waldenstrom's macroglobulinaemia	286 (48.5%)	56 (42.7%)	134 (100%)	96 (91.4%)	-
	3 = diffuse large B-cell lymphoma	30 (5.1%)	26 (19.8%)	-	4 (3.8%)	-
	4 = mantle cell lymphoma	20 (3.4%)	19 (14.5%)	-	1 (1%)	-
	0 = ADA not detected	581 (98.5%)	131 (100%)	134 (100%)	105 (100%)	211 (95.9%)
1 = ADA detected	9 (1.5%)	0 (0%)	0 (0%)	0 (0%)	9 (4.1%)	
Age categories	1: Age < 65 years	265 (44.9%)	68 (51.9%)	95 (70.9%)	63 (60%)	39 (17.7%)
	2: 65 ≤ Age ≤ 75 years	197 (33.4%)	39 (29.8%)	36 (26.9%)	33 (31.4%)	89 (40.5%)
	3: Age > 75 years	128 (21.7%)	24 (18.3%)	3 (2.2%)	9 (8.6%)	92 (41.8%)
CRCL categories	1: 15 ≤ CRCL < 30 ml/min	5 (0.8%)	-	-	-	5 (2.3%)
	2: 30 ≤ CRCL < 50 ml/min	72 (12.2%)	12 (9.2%)	1 (0.7%)	2 (1.9%)	57 (25.9%)
	3: 50 ≤ CRCL < 90 ml/min	306 (51.9%)	73 (55.7%)	51 (38.1%)	54 (51.4%)	128 (58.2%)
	4: CRCL > 90 ml/min	207 (35.1%)	46 (35.1%)	82 (61.2%)	49 (46.7%)	30 (13.6%)
CRCLN categories	1: 15 ≤ CRCLN < 30 ml/min/1.73m ²	5 (0.8%)	-	-	-	5 (2.3%)
	2: 30 ≤ CRCLN < 50 ml/min/1.73m ²	74 (12.5%)	13 (9.9%)	1 (0.7%)	1 (1%)	59 (26.8%)
	3: 50 ≤ CRCLN < 90 ml/min/1.73m ²	346 (58.6%)	82 (62.6%)	62 (46.3%)	65 (61.9%)	137 (62.3%)
	4: CRCLN > 90 ml/min/1.73m ²	165 (28%)	36 (27.5%)	71 (53%)	39 (37.1%)	19 (8.6%)
Sex by disease	Females with DIS=1	103 (17.5%)	12 (9.2%)	-	2 (1.9%)	89 (40.5%)
	Males with DIS=1	151 (25.6%)	18 (13.7%)	-	2 (1.9%)	131 (59.5%)
	Females with DIS=2	140 (23.7%)	25 (19.1%)	71 (53%)	44 (41.9%)	-
	Males with DIS=2	146 (24.7%)	31 (23.7%)	63 (47%)	52 (49.5%)	-
	Females with DIS=3	11 (1.9%)	10 (7.6%)	-	1 (1%)	-
	Males with DIS=3	19 (3.2%)	16 (12.2%)	-	3 (2.9%)	-
	Females with DIS=4	6 (1%)	5 (3.8%)	-	1 (1%)	-
	Males with DIS=4	14 (2.4%)	14 (10.7%)	-	-	-
BSIZ categories	BSIZ ≤ 1750 mm ²	182 (30.8%)	34 (26%)	22 (16.4%)	34 (32.4%)	92 (41.8%)
	BSIZ > 1750 mm ²	408 (69.2%)	97 (74%)	112 (83.6%)	71 (67.6%)	128 (58.2%)

Sponsor's 1055255.pdf, pg 74-5

3.2.2 Methods

“The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, Version 7.2.0 (ICON Development Solutions). Graphical and all other statistical analyses, including evaluation of NONMEM outputs were performed using R version 2.15.2 for Windows (R project, <http://www.rproject.org/>).

Model-based simulations were performed by a combination of R and NONMEM software. The simulation R scripts created the simulation datasets and started NONMEM; NONMEM performed the simulations; the same R scripts read the NONMEM output and prepared the simulation plots and tables.

The applicant utilized a Monte-Carlo importance sampling expectation-maximization (IMPMAP) in analyzing obinutuzumab population pharmacokinetics. Some details on this method are provided below. Monte Carlo expectation-maximization (EM) methods integrate the posterior density by performing a Monte Carlo sampling over all possible individual parameters during the expectation step and then use a single iteration maximization step that is simple to compute in order to advance the fixed-effect parameters towards the maximum likelihood. The Monte Carlo methods have the advantage of not using a linearized approximation to the integral therefore providing less bias. The efficient maximization step of the EM algorithms allows them to be faster than FOCE for complex PK and PK-PD problems. The stochastic nature of the methods provides less precise and not exactly reproducible results, but it is less likely than deterministic methods to be locked into a local minimum.

The pharmacokinetics of monoclonal antibodies is usually described by a two-compartment model, either linear or with target-mediated disposition. Monoclonal antibodies that target B-cells (like rituximab) were also shown to exhibit time-dependent clearance, possibly reflecting decrease in target B-cells with time under treatment. Therefore, the modeling started with a two-compartment linear model. Then, the model with parallel linear and Michaelis-Menten elimination and the model with time-dependent clearance were tested. In the latter model, clearance was the sum of non-specific time-independent clearance (CL_{inf}) and time-dependent clearance (CL_t) that exponentially decreased with time.

Structural model refinement was driven by the data and was based on various goodness-of-fit indicators, including visual inspection of diagnostic scatter plots (observed vs. predicted concentration, conditional weighted residual vs. predicted concentration or time, histograms of individual random effects, etc.), plausibility of parameter estimates, precision of the parameter estimates, the minimum objective function value (OFV) and the number of estimated parameters.

A covariate modeling approach emphasizing parameter estimation was implemented for the covariate model development. Potential covariate-parameter relationships were identified based on scientific interest, mechanistic plausibility, exploratory analysis, and exploratory graphics, and added to the full model. The full model did not include together

the effects of several strongly correlated or collinear covariates, but only the most plausible of them.

Inferences about the covariate effects and their clinical relevance were based on the resulting parameter estimates and measures of estimation precision (asymptotic standard errors). Covariates evaluated included body weight, sex, age, AHAs, CrCL, disease status baseline tumor size, and baseline B-cell count.

The final population PK model was used to simulate the typical obinutuzumab concentration-time course and evaluate the effect of covariates in the analysis population for the dosing regimen implemented in Study BO21004 (1000 mg IV dosing every 4 weeks for 20 weeks, (140 days) with the additional 1000 mg IV doses at days 8 and 15). For the important covariates, the effect of covariates was illustrated by comparing typical concentration-time courses for various combinations of these covariates.

The final population PK model was used to calculate (using Bayesian post-hoc parameters) the individual derived PK parameters such as steady-state AUC_{τ} , C_{max} , C_{trough} , terminal half-life ($t_{1/2,term}$), and effective half-life ($t_{1/2,eff}$). Terminal half-life $t_{1/2,term} = t_{\beta}$ and effective half-life $t_{1/2,eff}$ were computed at steady-state when time-dependent clearance has already decreased to zero.

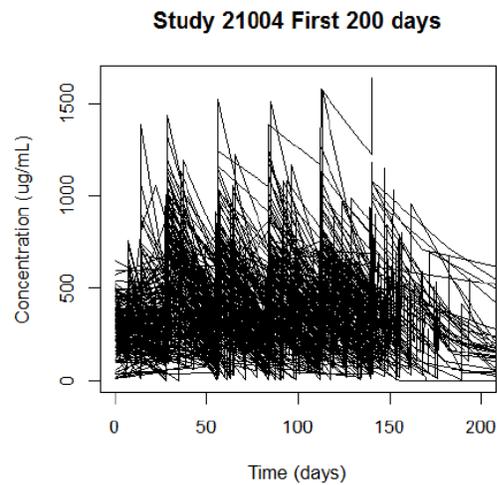
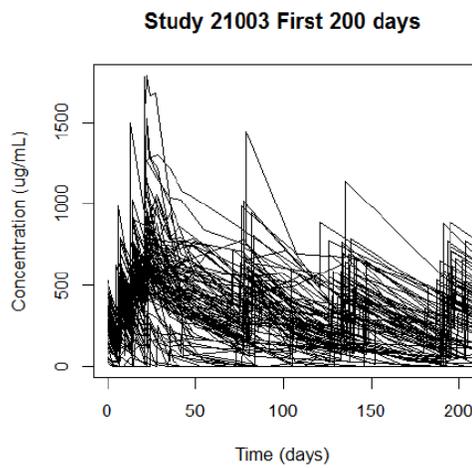
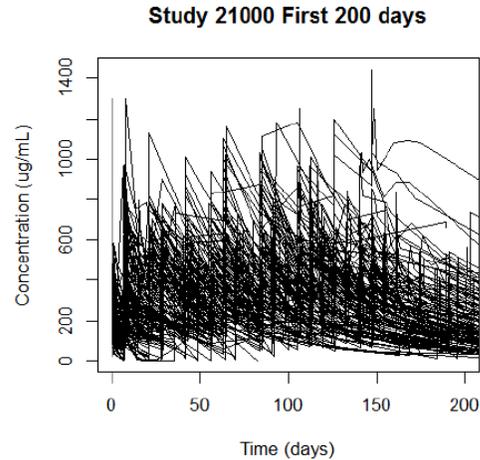
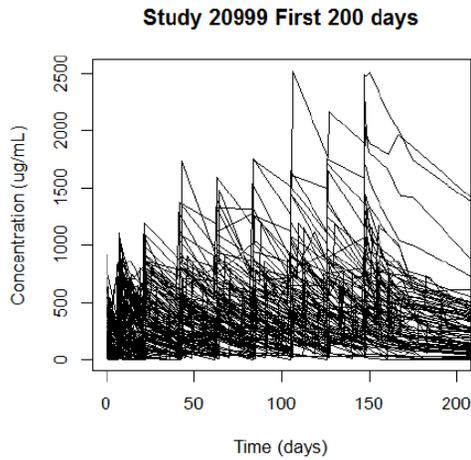
Graphical analysis of exposure-safety and exposure-efficacy relationships was conducted for CLL patients from Study BO21004. Safety analyses included any SAE, infections and infestations, gastrointestinal disorders, cardiac disorders, neoplasms, and SAE of blood and lymphatic systems. The applicant also evaluated the time of AE occurrence, dividing the AEs into early (first or second dose) and late (any dose after) SAEs. The applicant also evaluated relationships between exposure and infusion AEs, time-course of neutrophil counts, and B-cell counts. Relationships of the survival-type efficacy measures (progression free survival, disease free survival for complete responders, event free survival and overall survival) with exposure were assessed using two types of plots. First, association of the observed efficacy measures with exposure was assessed by comparing the distributions of C_{mean} and distributions of times of the observed efficacy measures, for all observed efficacy measures levels, overall and stratified by the baseline tumor size. Then, Kaplan-Meier plots that illustrate probability of survival for three exposure categories (low, medium, high) were superimposed and compared, both overall and stratified by the baseline tumor size. “

3.2.3 Results

3.2.3.1 Observed Data

Individual serum concentration time profiles, stratified by clinical study, over the first 200 days of treatment are shown below in Figure 7.

Figure 7: Obinutuzumab serum concentration time course over the first 200 days of treatment in BO20999, BO21000, BO21003, and BO21004.



Sponsor's 1055255.pdf, pg. 99-102

3.2.3.2 Population PK Parameter Estimates

The final model was a two-compartment model with time-dependent clearance. Final parameter estimates are shown in Table 12.

Table 12: Applicant's Final Obinutuzumab Population PK Model Parameter Estimates

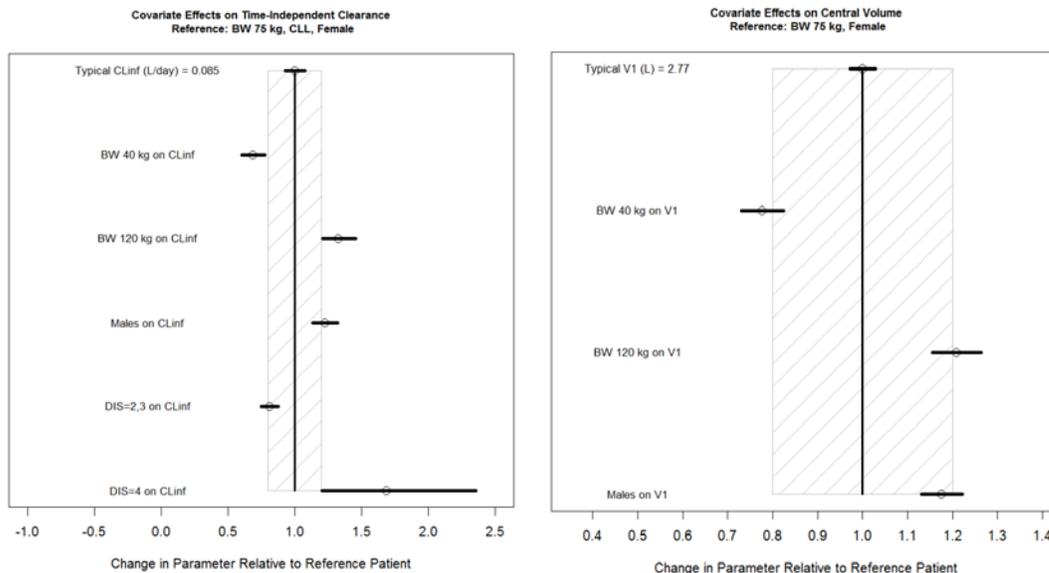
Parameter		Estimate	%RSE	95%CI		
k_{des} (1/day)	$\exp(\theta_1)$	0.0413	12.4	0.0324 - 0.0528		
CL_T (L/day)	$\exp(\theta_2)$	0.242	8.82	0.204 - 0.288		
CL_{inf} (L/day)	$\exp(\theta_3)$	0.085	3.59	0.0792 - 0.0912		
V_1 (L)	$\exp(\theta_4)$	2.77	1.43	2.69 - 2.85		
V_2 (L)	$\exp(\theta_5)$	0.965	5.56	0.865 - 1.08		
Q (L/day)	$\exp(\theta_6)$	1.29	10.4	1.05 - 1.58		
$CL_{inf,WT} = CL_{T,WT}$	θ_7	0.602	16.8	0.404 - 0.800		
$V_{1,WT}$	θ_8	0.403	12.1	0.307 - 0.499		
$CL_{T,SEX}$	$\exp(\theta_9)$	1.52	10.6	1.23 - 1.87		
$CL_{inf,SEX}$	$\exp(\theta_{10})$	1.23	3.86	1.14 - 1.32		
$V_{1,SEX}$	$\exp(\theta_{11})$	1.18	1.94	1.13 - 1.22		
$k_{des,DIS}$	$\exp(\theta_{12})$	1.87	13.6	1.44 - 2.45		
$CL_{T,DIS23} = CL_{inf,DIS23}$	$\exp(\theta_{13})$	0.811	3.85	0.752 - 0.875		
$CL_{T,DIS4} = CL_{inf,DIS4}$	$\exp(\theta_{14})$	1.68	17.1	1.20 - 2.35		
$k_{des,BSIZ < 1750}$	$\exp(\theta_{15})$	2.48	12.9	1.93 - 3.19		
Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
ω^2_{kdes}	$\Omega(1,1)$	1.64	8.53	1.37 - 1.92	CV=128%	15.7%
ω^2_{CLT}	$\Omega(2,2)$	0.982	11.1	0.769 - 1.20	CV=99.1%	20.5%
ω^2_{CLinf}	$\Omega(3,3)$	0.168	8.28	0.141 - 0.195	CV=41.0%	9.5%
ω^2_{V1}	$\Omega(4,4)$	0.0345	8.66	0.0286 - 0.0403	CV=18.6%	10.7%
ω^2_{V2}	$\Omega(5,5)$	0.391	14.6	0.279 - 0.503	CV=62.5%	30.4%
ω^2_Q	$\Omega(6,6)$	0.834	13.9	0.606 - 1.06	CV=91.3%	52.0%
ω^2_{EPS}	$\Omega(7,7)$	0.262	10.3	0.209 - 0.314	CV=51.2%	0.3%
σ^2_{prop}	$\Sigma(1,1)$	0.0324	4.43	0.0296 - 0.0352	CV=18.0%	1.6 %
$\sigma^2_{add} (\mu\text{g/mL})^2$	$\Sigma(2,2)$	0.0323	70.3	0 - 0.0769	0.180	

Parameters Q and V_2 were scaled as $(BW/75)^{3/4}$ and $(BW/75)$, respectively, where BW is body weight (kg).
SE: Standard Error; RSE: Relative Standard Error, $\%RSE=100 \cdot SE/PE$, where PE is a parameter estimate;.
95% CI: 95% confidence interval. SD: Standard Deviation; CV: coefficient of variation, $CV = 100 \cdot SD \%$.

Sponsor's 1055255.pdf, pg 80

The covariates retained in the final model were: body weight on clearance and volume parameters; sex on CL_T , CL_{inf} , and V_1 ; disease type on k_{des} , CL_T , and CL_{inf} ; and baseline tumor size on k_{des} . The dependence of clearance parameters on weight was consistent with allometric scaling (the power coefficient was estimated at 0.602). The power coefficient of dependence of central volume on weight (estimated at 0.403) was lower than would be expected from allometric scaling. The parameters k_{des} and CL_T influenced the initial decline of clearance rather than the steady state value. Decline of clearance defined by k_{des} value was much faster for patients with NHL (DIS=2, 3, and 4). High tumor size (above 1750 mm² at baseline) was associated with slower decline in time-dependent clearance consistent with longer time needed to saturate the target. The initial value of time-dependent clearance was higher in male patients. Both the time-dependent and time-independent parts of clearance were slightly lower in patients with BCL and DLBCL (DIS=2, 3) and were much higher in patients with MCL (DIS=4) compared to patients with CLL (DIS=1). The impact of identified covariates on time-independent clearance and volume of distribution are shown below Figure 8.

Figure 8: Impact of Significant Covariates on Obinutuzumab Clearance and Volume of Distribution



Sponsor's 1055255.pdf, pg 163-4

Reviewer's comments: In general, the sponsor's population PK analysis is reasonable. The reviewer's independent assessment using the same methodology resulted in identification of the same model structure and similar covariates. The PK for obinutuzumab was characterized by two-compartment pharmacokinetics with a clearance that decreased to a lower value over time. The rate of convergence for the initial clearance to steady state clearance was dependent upon total tumor burden and disease type, which is further supportive that the non-linear clearance is due to target-mediated drug disposition. The reviewer's concern regarding the nonlinear clearance parameterization is that accurate parameter estimates may be difficult to obtain, particularly in cases with sparse sampling (CL21004) and that the rate of decline to steady state clearance is based on time from initial dosing rather than time above a saturating concentration. This assumption means that if dosing was delayed (or more spread out dosing) in a subject, the subject would still be predicted to attain steady state clearance at the same time as a subject receiving treatment at typical dosing times. This latter item cannot be addressed with the available data and is more a limit on whether the model would predict obinutuzumab PK with changes to the dosing interval.

The population PK analysis also identified body weight and sex as significant covariates on clearance and volume. The power law coefficients for both clearance and volume (0.6 and 0.4, respectively) were both lower than typical allometric scaling coefficients (typical scaling coefficients of 0.75 and 1 were included for intercompartment clearance and peripheral volume). It is unclear how sex may have been a direct contributor to obinutuzumab pharmacokinetics given that the drug is administered intravenously and has limited renal or hepatic contribution to its elimination. Alternatively, the identification of sex as a significant covariate may be due to the sparse PK sampling (mostly peak and trough samples with intensive sampling over one or two cycles in

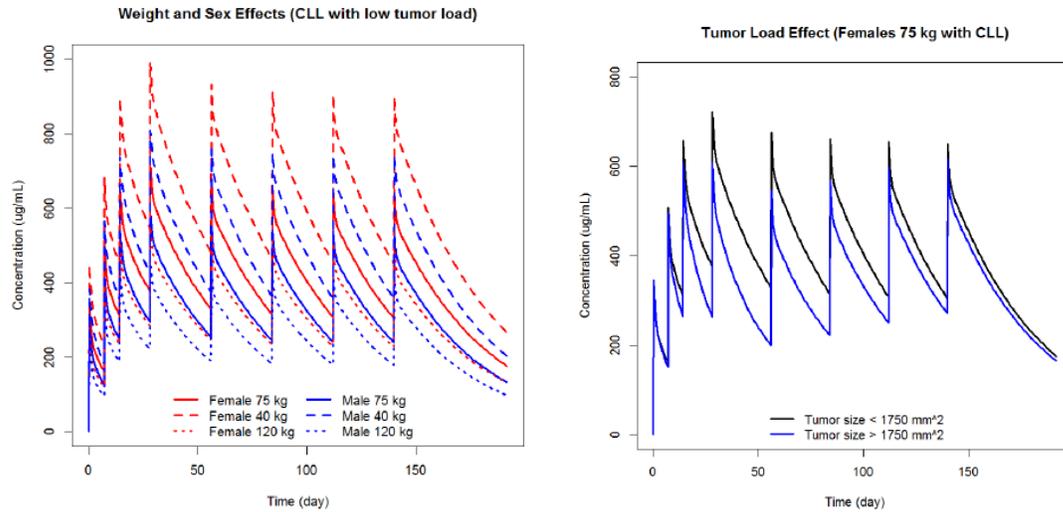
earlier Phase I and II trials) and/or the impact of other factors such as tumor burden and TMDD. This is further supported by the direction of the covariate effect for sex which is in the same direction as that of higher body weight (i.e., both higher body weight and male gender was associated with a higher clearance value).

Finally, the identification of body weight (and sex) as significant covariates for obinutuzumab pharmacokinetics, combined with it being a fixed-dose intravenous regimen, suggests that body weight dosing may ensure more consistent exposure in patients. There was approximately 25% higher and 20% lower clearance in subjects with body weight 120 and 40 kg compared to a 75 kg individual. In addition, the sponsor's and reviewer's exposure-response efficacy analysis suggests that subjects in the higher exposure quartile (predominantly lower body weight and female) were more likely to respond than subjects in the lowest exposure quartile (higher body weight and male). However, all exposure quartiles exceeded that observed in the control arm and no relationships between obinutuzumab exposure and safety were identified from CL21004. In addition, there are other confounding factors that influence obinutuzumab pharmacokinetics such as available receptors (tumor burden and possibly circulating lymphocyte count) that may be of similar or greater significance on obinutuzumab pharmacokinetics than body weight. As such, there are no current recommendations for weight-based dosing at this time, though the need for weight-based dosing or therapeutic drug monitoring should continue to be evaluated as additional data from obinutuzumab in CLL patients (b) (4) becomes available.

3.2.4 Simulation Results

The effects of covariates on typical concentration-time courses following 1000 mg IV doses on days 0, 8, 15, 28, 56, 84, 112, and 140 (dosing regimen of the pivotal study BO21004) for various combinations of important covariates are illustrated in Figure 9. Typical concentration-time courses for 75 kg female and male patients, and also female and male patients with median weight (among Study BO21004 patients stratified by sex; 67.7 kg for females and 79.7 kg for males) display 20% lower exposure in males. Simulations for baseline tumor size show divergent predictions that converge later in treatment, in agreement with where tumor size was included as a covariate in the population PK model (covariate on k_{des} and not on clearance or volume of distribution). Summary statistics for conditional predictions based on the dosing regimen in BO21004 are shown below in Table 13.

Figure 9: Model-Based Simulation of Typical Concentration-Time Course by Weight and Sex (left) and Tumor Size (right) for the Regimen Administered in BO21004



Sponsor's 1055255-pop-pk.pdf, pg. 227-9

Table 13: Summary Statistics for Condition Predictions of PK Parameters at Cycle 6 for the Dosing Regimen Used in Study BO21004

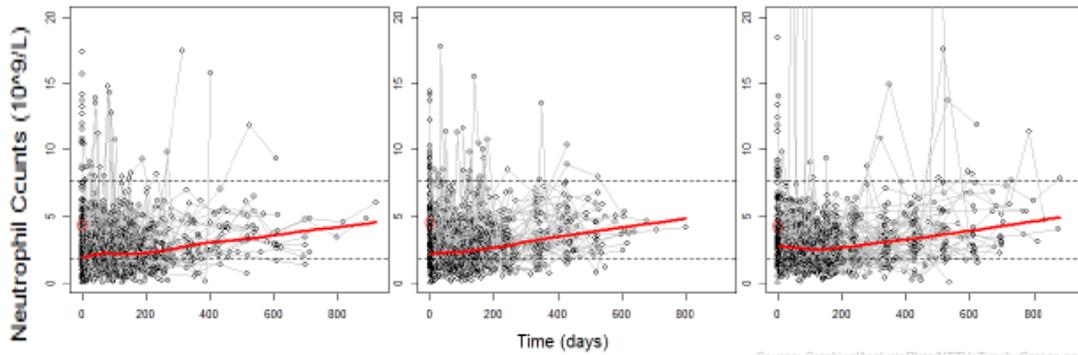
	Statistic	Study			
		20999	21000	21003	21004
C_{max} ($\mu\text{g/mL}$)	Mean (SD)	575.2 (237.7)	561.7 (170)	632.4 (224.6)	510.6 (178.6)
	Median (Range)	543 (120.1-1455.8)	524.9 (154.8-1049)	600.9 (211.2-1326.3)	472.5 (201.4-1429.3)
	Geometric Mean (CV)	527.4 (0.43)	536.8 (0.31)	591.8 (0.38)	481.7 (0.34)
C_{trough} ($\mu\text{g/mL}$)	Mean (SD)	309 (204.6)	321.8 (143)	384.6 (208.2)	250.5 (154.3)
	Median (Range)	290.5 (0.2-1154.8)	286.6 (4.8-756.1)	373.1 (0-981.1)	223.9 (7.3-1179.9)
	Geometric Mean (CV)	224.7 (1.07)	287.2 (0.56)	294.2 (1.15)	203.1 (0.72)
AUC_{τ} ($\mu\text{g/mL}^*$ day)	Mean (SD)	11832 (6306)	11816 (4372)	13844 (6139)	10113 (4720)
	Median (Range)	11009 (622-36520)	10800 (1258-24670)	13173 (847-31990)	9300 (2159-36460)
	Geometric Mean (CV)	10062 (0.63)	11008 (0.4)	12220 (0.57)	9073 (0.48)
$t_{1/2,term}$ (day)	Mean (SD)	33.4 (14.1)	41.7 (17)	41.9 (17.8)	30.4 (12.1)
	Median (Range)	32.9 (4.3-80.8)	38.2 (15.2-143.8)	38.1 (9.9-93.7)	29 (11.3-102.1)
	Geometric Mean (CV)	30.3 (0.47)	39.2 (0.34)	38.1 (0.45)	28.5 (0.35)
$t_{1/2,eff}$ (day)	Mean (SD)	33.2 (14.0)	41.3 (16.9)	41.8 (17.8)	30.2 (12.1)
	Median (Range)	32.8 (4.3-80.8)	38.0 (15.1-143.6)	37.9 (9.8-93.7)	28.9 (11.1-102)
	Geometric Mean (CV)	30.1 (0.47)	38.8 (0.34)	38.0 (0.45)	28.3 (0.35)

Sponsor's 1055255-pop-pk.pdf, pg. 82

3.2.4.1 Safety Analyses

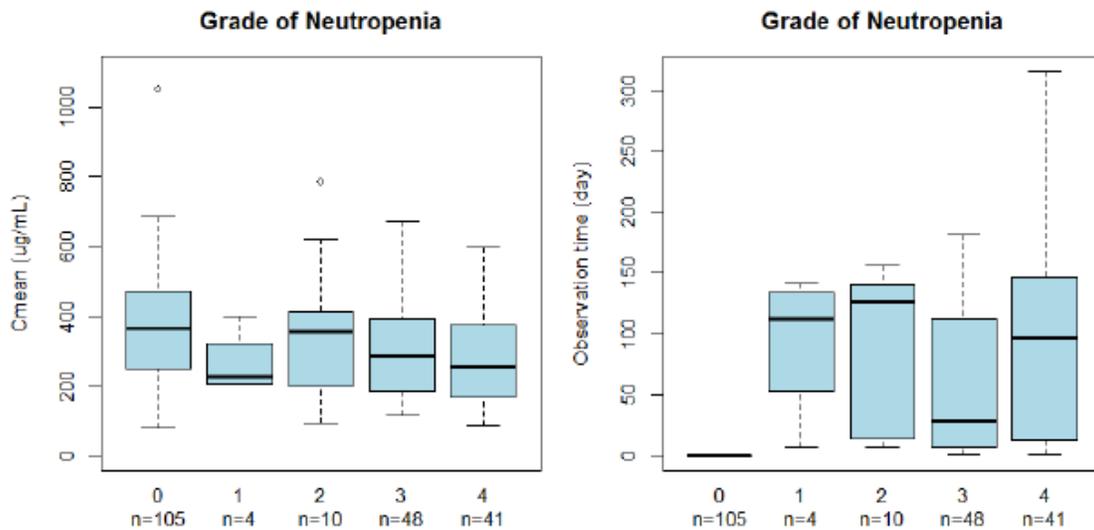
The results of the graphical analysis indicated that the occurrence of the SAEs (late, early, system organ class) was not correlated with obinutuzumab concentration or cumulative exposure. Infusion-related AEs could not be correlated with first-dose C_{max} . The graphical analysis performed to assess the relationship between the observed values of the neutrophil counts and obinutuzumab exposure (C_{mean}) has not indicated any differences between the exposure groups. There were no associations of the observed grade of neutropenia with exposure based on the applicant's analysis (Figure 10 and Figure 11).

Figure 10: Neutrophil Counts over Time by Obinutuzumab Exposure (C_{mean})



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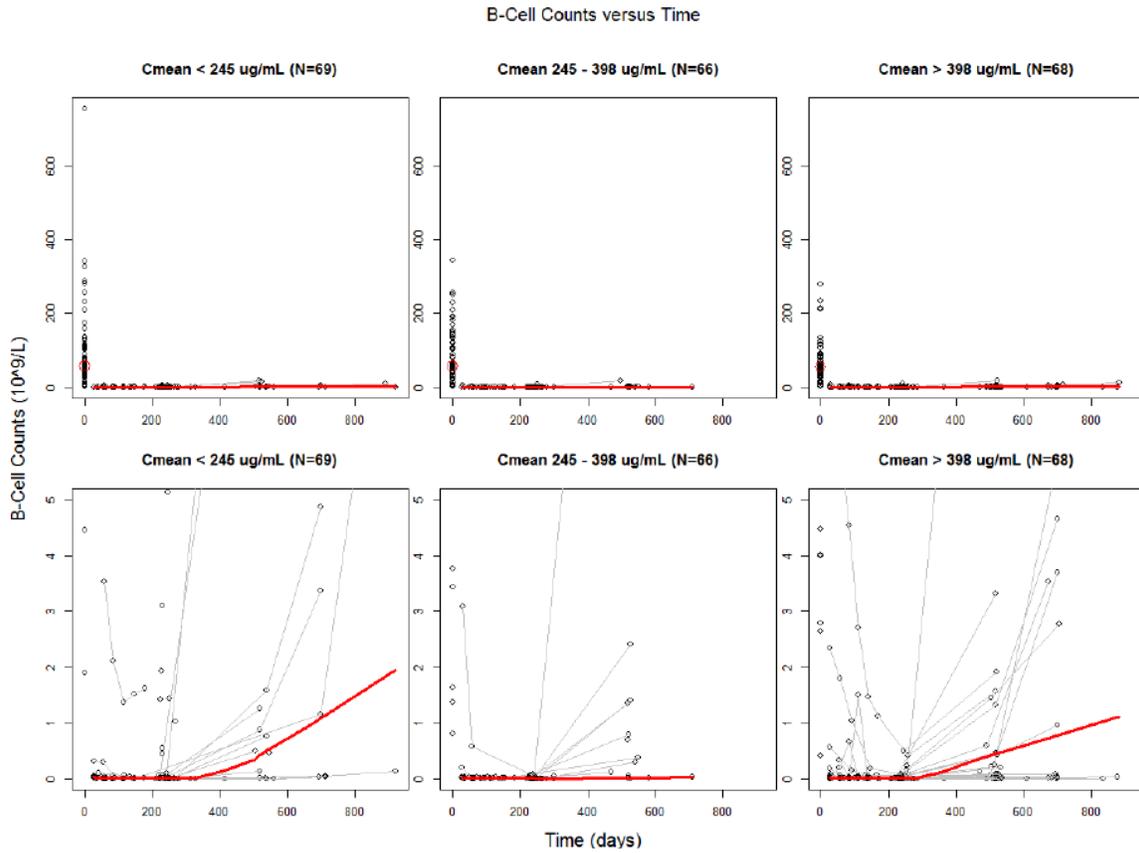
Figure 11: Neutrophil Grade versus Exposure and Time to Neutropenia Grade (BO21004)



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The graphical analysis performed to assess the relationship between the observed values of the B-cell counts and obinutuzumab exposure (C_{mean}) indicated that in all the exposure groups B-cell counts declined from their baseline values to nearly zero after start of drug administration, and stayed at those levels as long as they were measured.

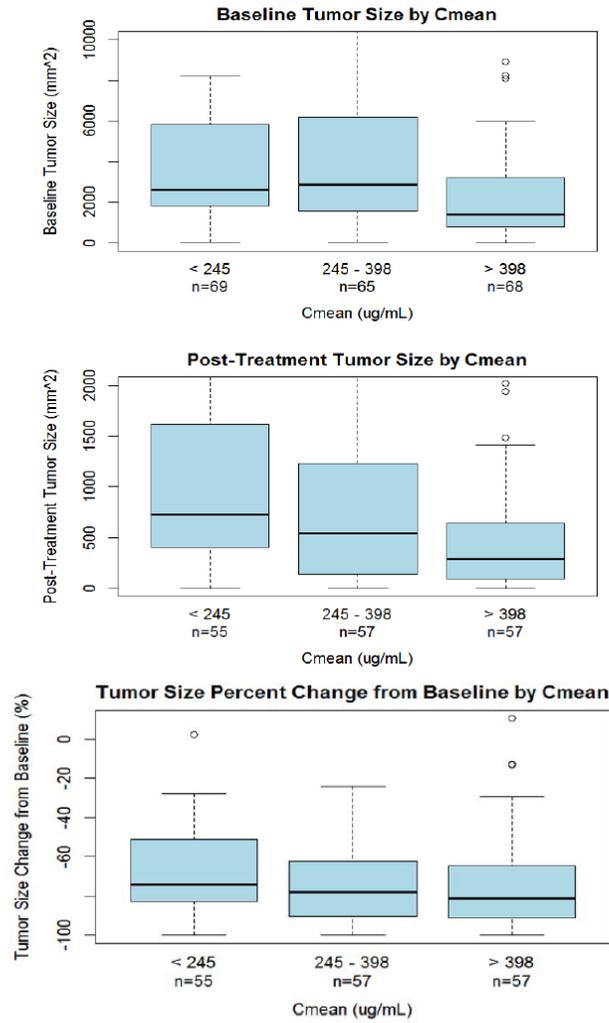
Figure 12: B-Cell Counts over Time by Obinutuzumab Exposure (C_{mean}) (bottom row has an adjusted y-axis scale of same data)



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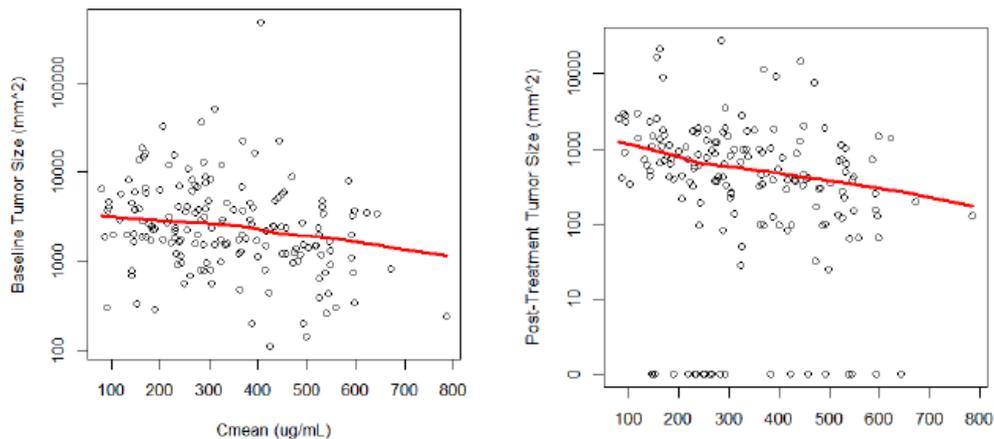
The graphical analysis performed to assess the relationship between the observed tumor size values and obinutuzumab exposure suggested that patients with a higher tumor size at baseline had a lower exposure and that patients with lower exposure have higher post-treatment tumor size (Figure 13 and Figure 14). However, the interaction between the target and the PK of obinutuzumab makes it difficult to determine if the lower absolute effect is due to a lower exposure, to a higher tumor size at baseline or to both.

Figure 13: Tumor Size at Baseline and Post-Treatment versus Obinutuzumab Exposures



Sponsors 1055255-pop-pk.pdf, pg 249-50

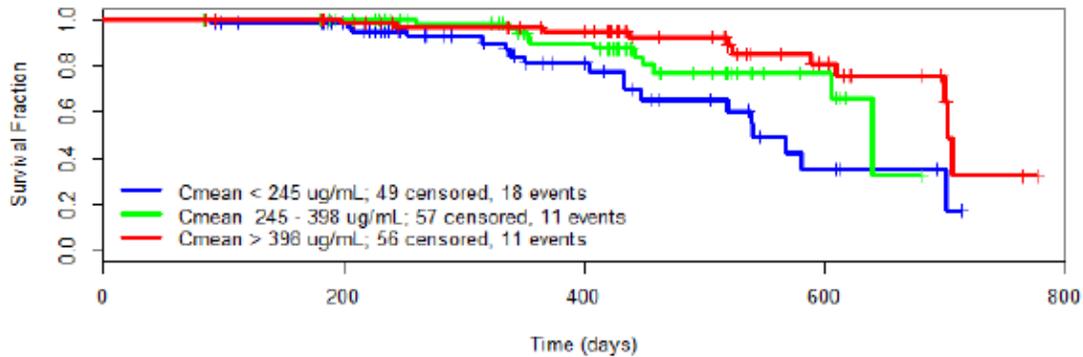
Figure 14: Relationship between Baseline and Post-treatment Tumor Size and Obinutuzumab Exposures



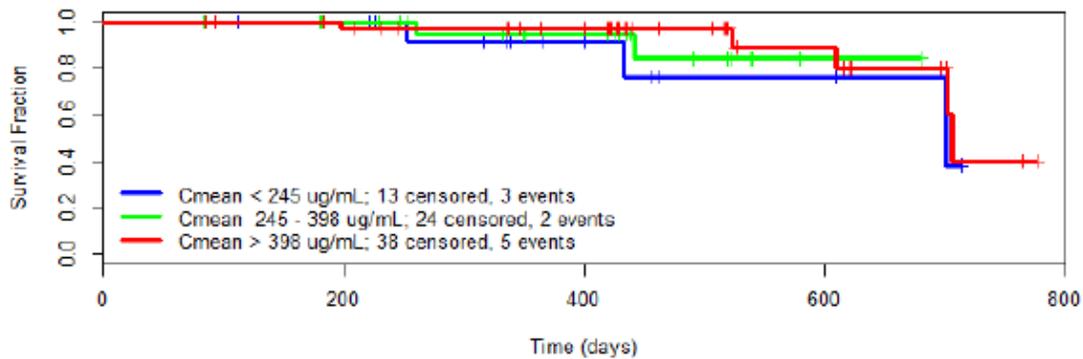
Sponsors 1055255-pop-pk.pdf, pg 251

Event-free survival and progression-free survival data were nearly identical as they differed by only one patient who had an event-free survival event but had not progressed. Therefore, this discussion is focused on the progression-free survival, which was the primary efficacy measure. Kaplan-Meier plots suggested that higher exposure was associated with longer progression free survival, though the impact of exposure was less in subjects with tumor sizes greater than 1750 mm² (Figure 15).

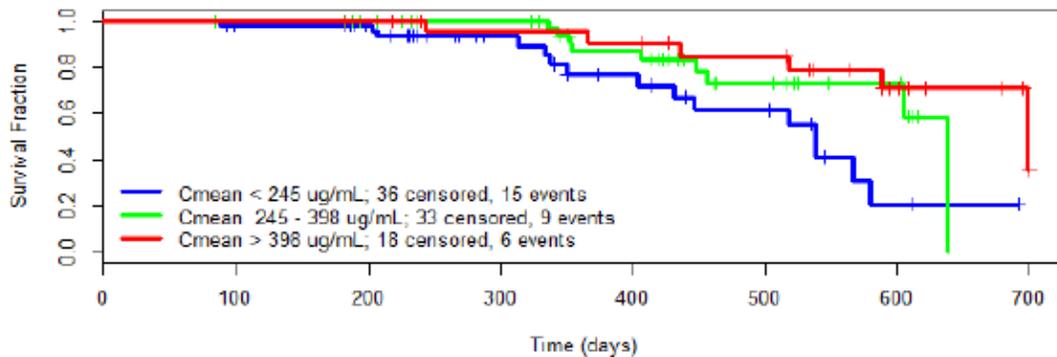
Figure 15: Kaplan-Meier Plot for Progression-Free Survival by Exposure Group and Tumor Size



**Kaplan-Meier Plot for Progression Free Survival
Tumor size < 1750 mm²**



**Kaplan-Meier Plot for Progression Free Survival
Tumor size > 1750 mm²**



Sponsors 1055255-pop-pk.pdf, pg. 266

Reviewer's comment: Similar to the sponsor, the reviewer's safety analysis with respect to neutropenia grade did not indicate a relationship between obinutuzumab exposure and neutropenia event rate or grade. Obinutuzumab exposures trended lower in subjects with grade 3+ neutropenia, and this observation should be reassessed as additional data from other obinutuzumab trials becomes available.

B-cell count and tumor size decreased following obinutuzumab treatment. B-cell count decreased rapidly following initiation of treatment and remained suppressed throughout treatment. No clear relationship between the rate of B-cell count decline or duration of suppression and obinutuzumab exposure could be identified. There was a trend of higher obinutuzumab exposure in subjects with small baseline tumor burden as well as those subjects with lower post-treatment tumor size. This illustrates the confounding nature of obinutuzumab exposure with response as patients with higher initial tumor burden would be expected to have a greater number of receptors to occupy and increased TMDD. Whether the lower obinutuzumab exposure is due to a higher baseline tumor burden or due to other factors cannot be determined from the available data. Finally, the sponsor's analysis of progression free survival and obinutuzumab exposure demonstrated that higher obinutuzumab C_{mean} exposures were associated with increased PFS. Upon further analysis, the sponsor demonstrated this increase was predominantly in subjects with higher baseline tumor burden ($>1750 \text{ mm}^2$). This again, demonstrates the confounded nature of obinutuzumab exposure with respect to tumor burden. These two factors, as well as other baseline factors, are explored in the reviewer's PFS exposure-response analysis above.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The reviewer performed an additional analysis to evaluate the impact of renal and hepatic function on obinutuzumab exposure. In addition, the reviewer evaluated the exposure-response efficacy relationship for progression free survival (PFS) and baseline factors that were predictive of treatment response.

4.2 Objectives

Analysis objectives are:

1. To evaluate the effect of renal/hepatic impairment on obinutuzumab PK using the population PK model
2. To analyze the exposure-response relationships for progression free survival (PFS)
3. To analyze the exposure-response safety relationships for infusion-related reactions from BO21004 for

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 14.

Table 14: Analysis Data Sets

Study Number	Name	Link to EDR
popPK	poppk.xpt; imp25ctl.txt, imp25lst.txt	\\cber-fs3\M\CTD_Submissions\STN12548

		6\0000\m5\datasets\pop-pk\analysis
BO21004	aex.xpt, medt.xpt, lapbexpt.xpt, labpfacs.xpt, labpmrd.xpt, lab41raw.xpt, tumraph.xpt, cicrc.xpt, demoext.xpt, comorb.xpt, event.xpt, pconpk.xpt, efex.xpt, event3a.xpt	\\cber- fs3\M\CTD_Submissions\STN12548 6\0000\m5\datasets\bo21004\bo21004 -randomized

4.3.2 Software

Population pharmacokinetics modeling was performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with R (version 2.13.1).

4.3.3 Population PK model

The sponsor's population pharmacokinetic model was found satisfactory by the reviewer's assessment. No additional changes to the model shown above were made, though the model structure was used to perform simulations for various dosing scenarios including predicted profiles for a typical patient if the day 1 1000 mg dose was administered all on day one or split between day 1 and day 2 (900 mg on day 1 and 100 mg on day 2). Likewise, the model was also used to compare obinutuzumab profiles for scenarios where dose intensification was not used during cycle one of treatment. These simulations are summarized as part of the response to Question 1.1.3 above.

4.4 Results

4.4.1 Impact of Renal Impairment on Obinutuzumab PK

The sponsor evaluated creatinine clearance (CrCL) as part of their population PK covariate analysis and found that it was not a covariate for obinutuzumab clearance. The reviewer repeated this analysis as part of the evaluation of the applicant's population PK modeling, and agrees with the conclusion. This is not unexpected as based on the sponsor's submitted ADME study, renal elimination of obinutuzumab is minimal. As shown in Figure 5 and Table 4, no significant effect of mild or moderate renal function could be identified on obinutuzumab exposures. The obinutuzumab exposure in subjects with severe renal impairment was limited (n=5), though the observations suggest that obinutuzumab were not markedly different in these subjects. However, due to the limited number of subjects in the Phase III study with severe renal impairment (n=5), there is insufficient data to provide dosing recommendations in this population.

4.4.2 Impact of Hepatic Impairment on Obinutuzumab PK

The reviewer conducted a covariate analysis to evaluate the effect of hepatic function as a preliminary analysis based on subjects from CL21004. In all, there were 8 subjects classified as 'mild' or 'moderate' hepatic impairment according to the National Cancer Institute Criteria and 200 subjects with normal hepatic function. While the geometric C_{tr} measurements for subjects with moderate impairment was lower than those from subjects with normal hepatic function, the observed obinutuzumab C_{tr} was within the range observed in subjects with normal hepatic function (Table 6). However, all subjects with

moderate impairment were below the median for subjects with normal hepatic function. Based on the currently available data, the impact of “moderate” and “mild” hepatic impairment (and “severe” impairment) cannot be addressed with the given data. This analysis is further limited by the use of NCI criteria, which utilizes only baseline AST and bilirubin for categorizing baselines into hepatic function categories.

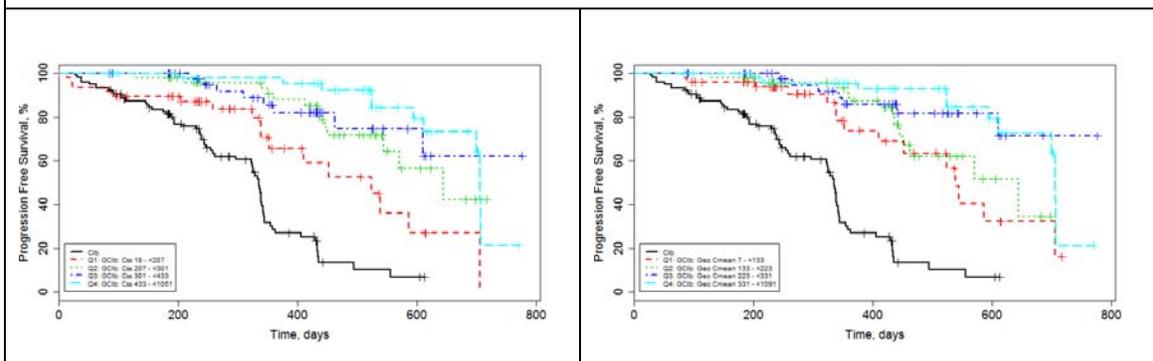
4.4.3 Exposure-response Analysis for PFS

For exposure-response analysis, exposure metrics including geometric mean C_{tr} at cycle 2 through 6 and average concentration (C_{avg} ; average concentration from the start of the last dose through 28 days) were obtained based on observed data or from the final population PK model, respectively.

The reviewer’s analysis confirmed the sponsor’s exposure-response findings of a relationship between C_{avg} and PFS with longer PFS in those subjects in higher exposure quartile. The median days to PFS in the highest exposure quartile was 706 days, could not be calculated due to too few events in the third quartile, 644 days in the second quartile, and 524 in the lowest (first) quartile. By comparison, the median time to PFS in the control arm was 333 days.

As the population PK predictions are based on sparse sampling and as the developed population pharmacokinetic model includes a time-dependent clearance, the reviewer also evaluated relationships between observed geometric mean C_{tr} between cycle 2 and 6 from patients with one or more obinutuzumab concentrations available from CL21004. As shown in Figure 16, the relationship between PFS and geometric mean C_{tr} was similar to that identified for C_{avg} . The median time to PFS was 706 days in the fourth (highest) quartile, could not be calculated due to too few events in the third quartile, 644 days in the second quartile, and 539 days in the lowest (first quartile). For both exposure metrics, all four obinutuzumab exposure quartiles exceeded the PFS observed in the control arm.

Figure 16. Kaplan-Meier curve for PFS Based on C_{avg} and Geometric Mean C_{tr} Over Cycles 2-6. For comparison, the Kaplan-Meier curve for the chlorambucil control arm is shown on each plot (black line)



An analysis of risk factors associated with lower exposure was conducted and the results are shown in Table 15. There were more males, subjects with higher baseline tumor burden, subjects with higher baseline lymphocyte count in the lower exposure groups, and a longer time from diagnosis to randomization in the lowest exposure quartile (Q1) compared to the highest exposure quartile (Q4). These results are not unexpected as the population pharmacokinetic analysis identified body weight as a significant covariate for

clearance and volume, and males in the Phase III study had a median body weight of 76 kg compared to 65 kg in women. Likewise, the purpose of the sponsor's proposed cycle 1 dosing was to overcome target-mediated drug disposition by saturating available receptors. Subjects with higher circulating lymphocyte counts or tumor burden (as assessed by the 2-D sum of all lesions identified) may have more extensive disease, and by association, a greater number of target receptors to occupy before saturation.

Table 15: Risk factors in Each Obinutuzumab Quartile

Patients Covariate	G-C1b N = 240			
	Q1 (n=52)	Q2 (n=52)	Q3 (n=52)	Q4 (n=52)
Male	79%	65%	48%	40%
Body weight > 73 kg	50%	60%	38%	37%
CIRS Score >6	73%	77%	69%	83%
Baseline Tumor Volume >2200 mm ³	65%	58%	46%	31%
Baseline Lymphocytes >25 X 10 ⁹ cells/L	81%	85%	77%	62%
Date since diagnosis >24 months	63%	54%	54%	48%
Age >= 75 years	38%	54%	44%	48%
Creatinine Clearance >70 mL/min	29%	40%	34%	33%
Dose adjustments	71%	62%	60%	40%

Univariate Cox-proportional hazards regression analyses with data from the Phase 3 trial indicated that geometric mean C_{tr}, baseline tumor burden, baseline lymphocyte count, and baseline cytogenetics were significant factors for PFS (Table 16).

Table 16: Univariate Cox-proportional hazards regression analysis for PFS*

Univariate Tested	HR	CI	p-value	
Geo Mean C_{tr} (continuous) per 100 ug/mL	0.67	0.54-0.84	<0.001	
Quartile Geo Mean C_{tr} (categorical, compared to Q1)	Q2	0.75	0.35-1.61	0.46
	Q3	0.34	0.14-0.84	0.02
	Q4	0.30	0.14-0.68	0.004
Baseline lymphocyte (>100x10⁹ cells/L compared to <100x10⁹ cells/L)	2.70	1.51-4.84	<0.001	
Total tumor lesion size (>2181)	0.40	1.34-4.67	0.004	

mm² compared to <2181 mm²)				
Baseline cytogenetics (normal compared to 17p negative)		0.37	1.09-6.63	0.03
Binet stage (categorical, compared to stage A)	B	1.59	0.69-3.67	0.28
	C	1.64	0.69-3.89	0.26
Time between diagnosis to randomization (compared to <12 months)	13-24 months	1.00	0.52-1.91	0.99
	>24 months	1.10	0.50-2.46	0.81
Baseline CIRS score >6		0.77	0.42-1.42	0.41
Body weight		0.99	0.97-1.01	0.32
Sex (Male compared to female)		1.41	0.79-2.49	0.24
Age		1.01	0.98-1.05	0.42
CrCL (<50 mL/min compared to >50 mL/min)		0.78	0.43-1.42	0.41
ECOG Score >1		0.31	0.08-1.29	0.11

** For the analysis with concentration, a subset (N=208) was used since 30 subjects did not have concentration data at or after cycle 2. Likewise, for the analysis with tumor size, a subset (N=227) was used since records of tumor size at baseline for 11 patients were missing.*

Further analysis was performed to investigate the influence of obinutuzumab exposure on PFS after adjustment of significant factors found from the univariate analysis. As shown in Table 1, the effect of obinutuzumab exposure on PFS was still significant after adjustment for those factors. The hazard ratio (HR) for PFS is reduced by approximately 10% for every 100 µg/mL increase in obinutuzumab geometric mean C_{tr}.

4.4.4 Exposure-response Safety Analysis for Infusion Related Reactions

An exposure-response safety analysis evaluated whether there was a relationship between infusion-related adverse events and observed post-infusion obinutuzumab concentration (C_{max}). No significant trend was identified between the likelihood of infusion-related adverse events and obinutuzumab concentration, but there was a trend of lower obinutuzumab C_{max} in subjects listed as having a grade 3 or 4 infusion-related adverse event (Table 17). This trend should be interpreted with caution as only 56% of subjects with grade 3 or 4 infusion-related adverse events had obinutuzumab PK collected post-infusion compared to 89% of subjects with grade 0-2 infusion-related adverse events. Similar trends are observed if instead population predicted C_{max} is used in the analysis, though the percentage of subjects with 3 or 4 infusion-related adverse events and obinutuzumab exposure data available is unchanged. The incidence of severe (grade 3 or 4) infusion-related adverse events did not appear to be more common in subjects with high baseline circulating lymphocytes counts (>100 x 10⁹ cells/L) or high initial tumor size (>2181 mm²). Subjects with high baseline circulating lymphocyte counts comprised 24% of the population and 26% of the subjects with grade 3 or 4 infusion-related adverse events (13/50). Likewise, subjects with high initial tumor size comprised 50% of the

population and 52% of the subjects with grade 3 or 4 infusion-related adverse events (25/48; 2 subjects with missing size data).

Table 17: Summary of Infusion-Related Adverse Events in the Obinutuzumab Treatment Arm, Percentage of Subjects with Obinutuzumab Samples, and Summary Pharmacokinetic Parameters (C_{max})

Infusion Reaction Adverse Event Grade (n)	Grade 0 (n=76)	Grade 1 (n=43)	Grade 2 (n=71)	Grade 3 (n=40)	Grade 4 (n=10)
Percentage with Observed PK (n)	67 (88%)	38 (88%)	64 (90%)	26 (65%)	2 (20%)
Geometric Observed Post-Infusion Mean C_{max} , ug/mL (CV%) [Median]	282 (56%) [293]	273 (53%) [323]	232 (78%) [285]	194 (78%) [194]	102 (107%) [133]
Percentage with Predicted PK (n)	72 (95%)	41 (95%)	66 (93%)	26 (65%)	2 (20%)
Geometric Predicted Post-Infusion Mean C_{max} , ug/mL (CV%) [Median]	313 (22%) [308]	313 (26%) [330]	292 (30%) [294]	228 (69%) [252]	252 (32%) [259]

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER_Analysis.R	Exposure-response analysis code for safety and efficacy Summary tables for renal and hepatic impairment	Obinutuzumab_BLA125486S0000_JAF/ER Analyses
BLA125486_PopPK.R Run100.mod, run100.lst sdtab100, patab100, cotab100, catab100	Population PK analysis control stream and outputs for obinutuzumab	Obinutuzumab_BLA125486S0000_JAF/PPK Analyses/Final Model

Simulation_Dose_Scenario.R	R code for simulating various obinutuzumab dosing scenarios (split dosing, no dose-intensification, etc.)	Obinutuzumab_BLA125486S0000_JAF/ PPK Analyses/Final Model
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4.3 Cover sheet and OCPB Filing/Review Form

See filing memo posted in DARRTs by JA Grillo on 06/03/2013.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO
09/20/2013

SARAH J SCHRIEBER
09/20/2013

JEFFRY FLORIAN
09/20/2013

NITIN MEHROTRA
09/21/2013

JULIE M BULLOCK
09/25/2013

Office of Clinical Pharmacology New Drug Application Filing and Review Form

General Information About the Submission

BLA Number:	125486\0	SDN:	1
Sponsor:	Genentech, Inc.	Date of Submission	4/23/2013
Brand Name:	GAZYVA	Generic Name:	obinutuzumab
Drug Class:	CD20-directed cytolytic antibody		
Dosage Form:	1000 mg/40mL (25mg/mL) single use vial		
Dosing Regimen:	C1D1: 100 mg @ 25 mg/hr; C1D2: 900 mg titrate 50-400 mg/hr @ 30 min intervals; and C1D8, C1D15, C2-6D1: 1000 mg titrate 100-400 mg/hr @ 30 min intervals		
Route of Administration:	Intravenous Infusion following dilution in 250 mL NS		
Indication:	In combination with chlorambucil for previously untreated patients with CLL.		
OCP Division:	DCP5	OND Division:	DHP
OCP Reviewer:	Joseph Grillo, Pharm.D.		
OCP Team Leader:	Julie Bullock, Pharm. D.		
PM Reviewer:	Jeffrey Florian, Ph.D.		
PM Team Leader:	Nitin Mehrotra, Ph.D.		
GG Reviewer:	Christian Grimstein		
GG Team Leader:	Rosane Charlab Orbach		
Priority Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	PDUFA Due Date	12/20/2013
OCP Review Due Date:	9/9/2013	OND Division Due Date:	9/20/2013

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	<input checked="" type="checkbox"/>		
Tabular Listing of All Human Studies	<input checked="" type="checkbox"/>		
Human PK & BP Summary	<input checked="" type="checkbox"/>		
Labeling	<input checked="" type="checkbox"/>		
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/>	4	3-obinutuzumab and 1-Rituximab
I. Clinical Pharmacology			
Mass balance:	<input type="checkbox"/>		
Isozyme characterization:	<input type="checkbox"/>		
Blood/plasma ratio:	<input type="checkbox"/>		
Plasma protein binding:	<input type="checkbox"/>		
Pharmacokinetics (e.g., Phase I) -	<input type="checkbox"/>		
<i>Healthy Volunteers:</i>			
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		
<i>Patients:</i>			
single dose:	<input checked="" type="checkbox"/>	4	
multiple dose:	<input checked="" type="checkbox"/>		
Dose proportionality -			
fasting / non-fasting single dose:	<input checked="" type="checkbox"/>		
fasting / non-fasting multiple dose:	<input checked="" type="checkbox"/>		
Drug-drug interaction studies -			
In-vivo effects on primary drug:	<input type="checkbox"/>		
In-vivo effects of primary drug:	<input type="checkbox"/>		
Concomitant therapy:	<input checked="" type="checkbox"/>		Descriptive comparison of exposure of monotherapy vs. CHOP or bendamustine in BO21000. No analysis of Chlorambucil
In-vitro:	<input type="checkbox"/>		
Subpopulation studies -			

	ethnicity:	<input checked="" type="checkbox"/>		Japanese
	gender:	<input checked="" type="checkbox"/>		Pop-PK
	pediatrics:	<input type="checkbox"/>		Waiver
	geriatrics:	<input checked="" type="checkbox"/>		Pop-PK
	renal impairment:	<input checked="" type="checkbox"/>		Pop-PK
	hepatic impairment:	<input type="checkbox"/>		
PD -	Phase 2:	<input type="checkbox"/>		
	Phase 3:	<input type="checkbox"/>		
PK/PD -	Phase 1/2, proof of concept:	<input checked="" type="checkbox"/>		
	Phase 3 clinical trial:	<input checked="" type="checkbox"/>	1	ER & ES
Population Analyses -	Data rich:	<input checked="" type="checkbox"/>	1	
	Data sparse:	<input checked="" type="checkbox"/>		
QT evaluation:		<input type="checkbox"/>		Dedicated QT planned
II. Biopharmaceutics				
	Absolute bioavailability:	<input type="checkbox"/>		
	Relative bioavailability -			
	solution as reference:	<input type="checkbox"/>		
	alternate formulation as reference:	<input type="checkbox"/>		
	Bioequivalence studies -			
	traditional design:	<input type="checkbox"/>		
	replicate design:	<input type="checkbox"/>		
	Food-drug interaction studies:	<input type="checkbox"/>		
	Bio-waiver request based on BCS	<input type="checkbox"/>		
	BCS class	<input type="checkbox"/>		
	Alcohol induced dose-dumping	<input type="checkbox"/>		
III. Other CPB Studies				
	Genotype/phenotype studies	<input type="checkbox"/>		
	Immunogenicity Testing	<input checked="" type="checkbox"/>	3	
	Chronopharmacokinetics	<input type="checkbox"/>		
	Pediatric development plan	<input checked="" type="checkbox"/>		Waiver
	Literature References	<input checked="" type="checkbox"/>	86	
Total Number of Studies			13	

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			limited
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		NCA data missing
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Waiver
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X			

Is the Clinical Pharmacology Section of the Application Fileable?

- Yes
 No

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant:

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- In your clinical pharmacology summary you state "NCA was used to analyze the obinutuzumab concentration data in serum samples in the following studies: BO20999, BO21003, BO21000 (only first-line follicular NHL [fNHL] patients) and JO21900;

however we are unable to locate the electronic data set files for the PK parameters derived from this analysis. Please identify the location of these files or submit them within 10 business days with appropriate identification and demographic variables included. These file may be submitted in CDISK or SAS file transport (.xpt) format.

- We note the November 29, 2011 type C meeting where you proposed to evaluate the effect of obinutuzumab on the QT/QTc interval in patients with previously untreated, low tumor-burden indolent NHL in a substudy of Study BO25454; however, we are unable to find your assessment of other available data (i.e., in vitro data and ECG data from submitted P1-P3 trials) relative to this issue. If such an analysis was submitted please identify the location or submit an addendum to your clinical pharmacology summary within 10 business days addressing this issue. In addition, please provide an update regarding the status and timeline for the conduct and submission of the QT/QTc substudy of Study BO25454.
- While we note your hypothesis, in section 3.9 of your clinical pharmacology summary, that an interaction between chlorambucil and obinutuzumab is “highly unlikely,” we are unable to locate any in vitro or clinical data in your submission that directly supports it. If such information was submitted please identify the location or submit additional supporting information and analyses, if they exist, as an addendum to your clinical pharmacology summary within 10 business days.

Signatures:

Joseph Grillo, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Julie M. Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Clinical Pharmacology - NDA Filing Memo

NDA: 1254860 Original Submission **IND:** 104405
Compound: GAZYVA (Obinutuzumab) Injection for intravenous infusion
Sponsor: Genentech, Inc.
Filing Date: April 22, 2013
Reviewer: Joseph Grillo, Pharm.D.

GAZYVA (also known as Obinutuzumab, GA101 and RO5072759) is a recombinant monoclonal humanized and glycoengineered Type II CD20 antibody of the IgG1 isotype. The sponsor states that obinutuzumab specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant preB and mature B lymphocytes while sparing haemopoietic stem cells, other normal plasma cells and tissues. This application is seeking approval for obinutuzumab in combination with chlorambucil for previously untreated patients with CLL.

Data to support the efficacy of obinutuzumab in combination with chlorambucil (Clb) in previously untreated chronic lymphocytic leukemia (CLL) patients are based on a single pivotal Phase III trial (Trial BO21004/CLL11). Treatment of obinutuzumab plus chlorambucil resulted in a reported IRC-assessed PFS median of 23.0 months in the GC1b arm compared with 11.1 months in the Clb arm (stratified HR of 0.16 95% CI [0.11; 0.24]; p-value <0.0001 (log-rank test)). The incidence of all grade adverse events, Grade 3-5 adverse events, serious adverse events (SAEs) and adverse events leading to withdrawal from treatment was higher in the GC1b arm compared to the Clb arm. The sponsor states that the difference between the treatment arms in adverse events, Grade 3-5 adverse events and SAEs was mainly due to infusion-related reactions (IRRs), primarily occurring during the first infusion of obinutuzumab. The most common adverse reactions (incidence $\geq 10\%$) were: infusion reactions, neutropenia, thrombocytopenia, nausea, anemia, diarrhea and pyrexia.

Data from two clinical studies (BO20999 and BO21003), in NHL, CLL and diffuse large B-cell lymphoma (DLBCL) patients, were used in conjunction with a pharmacokinetic (PK) model of obinutuzumab to define the recommended dose which was used in the pivotal Phase III Study BO21004/CLL11. The goal was to saturate the target as early and quickly as possible and reduced impact of TMDD in the majority of patients, and to maintain this saturation over the complete treatment period, while minimizing adverse events. The sponsor reports that based on this analysis, a total dose of 3000 mg obinutuzumab in Cycle 1 was considered suitable, both to maximize the potential to saturate the target for all patients regardless of tumor burden, and to achieve consistent and higher plasma concentrations. The C1D1 dose is split over 2 days to minimize the impact of IRRs on first obinutuzumab infusion.

Five clinical studies of obinutuzumab administered as a single agent (Phase I/II BO20999, Phase I/II BO21003, and Phase I JO21900 trials) or in combination with chemotherapy (Phase Ib BO21000 and Phase III pivotal BO21004/CLL11 trials) in CD20-positive malignant disease were used to characterize the PK/PD of obinutuzumab. Phase I Dose escalation trials explored doses from 50 mg to 2000 mg (BO20999 and BO21003 trials). The relevant clinical trials employed a serum sampling scheme which was primarily designed to enable the development of a population PK (pop-PK) model, although sufficient samples were obtained from trials BO20999, BO21003 and BO21000 to enable non-compartmental analysis (NCA). A validated enzyme-linked immunosorbent assays (ELISA) was used to measure obinutuzumab plasma concentrations in these trials.

The NCA analysis reported that increased doses of obinutuzumab led to increases in serum obinutuzumab concentrations. The C_{max} and AUC for 50-200 mg doses of obinutuzumab were less than dose proportional; however, a trend towards dose proportionality was reported for doses 400-2000 mg. Due to low patient numbers and disease heterogeneity, no meaningful conclusions could be made regarding dose proportionality. An accumulation ratio (~200%) in exposure between C1D1 and C1D8 was observed dose escalation phase 1 trials. Trough concentrations did not appear to increase further between C2-C8 in CLL patients receiving a 1000 mg obinutuzumab dose in a phase 1 trial. Similar accumulation findings were reported from an analysis of pre and post infusion concentrations in the pivotal P3 trial. The reported V_{dss} and $t_{1/2}$ of obinutuzumab in the P1 trials was ~5 L and ~25 days respectively. Protein binding was not assessed.

Using pop-PK modeling on a dataset pooled from four clinical trials (BO20999, BO21003, BO21000 and BO21004/CLL11) in CLL and NHL patients the sponsor reports that at the start of treatment, the obinutuzumab time-dependent clearance is estimated at 0.242 L/day (95% confidence interval [CI]: 0.204-0.288 L/day), which was 2.85 times higher than steady-state clearance (0.0850 L/day, 95% CI: 0.0792-0.0912 L/day). Time-dependent clearance declined with a half-life of 17 days, and concentrations approached steady-state levels after approximately 4 months of dosing. At the end of treatment (Cycle 6 day 1) the elimination $t_{1/2}$ is reported to be approximately 30.4 days.

Pop-PK modeling results also report that the obinutuzumab steady-state clearance and central volume increased with body weight and male sex. At the same dose, patients with high baseline tumor size were reported to have lower exposure. In addition, the PK of obinutuzumab were reported to be independent of age and renal function. The sponsor concludes that, for CLL patients, the pop-PK identified demographic differences in steady-state exposure were within 30%, and they were deemed to be not clinically relevant for the proposed 1000 mg IV dosing regimen in CLL patients. No differences were reported in serum obinutuzumab concentrations between Japanese subjects (JO21900) and Western European subjects (BO20999). No dedicated trials have been performed to investigate the impact of hepatic impairment or renal impairment on the PK of obinutuzumab. The sponsor states that PK and PD data from trial BO21000 (combined with CHOP or bendamustine) were similar to those observed in the monotherapy trials BO20999 and BO21003. The potential for an interaction between chlorambucil and obinutuzumab has not been evaluated.

The primary pharmacodynamic effect of obinutuzumab in clinical trials was measured by monitoring depletion of B cells and subsequent recovery in the peripheral blood. In CLL patients, the sponsor reports that a rapid and complete depletion in B cell counts was observed immediately following the initiation of treatment with obinutuzumab at all doses (50-2000 mg). Recovery of B cells was observed within 12-18 months of follow up in 13 (33%) of patients without progressive disease and 5 (13%) with progressive disease. Exposure-response analysis of pivotal trial BO21004 reports that patients with higher exposure appeared to have a better clinical response compared to patients with lower exposure, and this finding remained after stratification for baseline tumor size. There was no relationship reported between C_{max} following the first dose of obinutuzumab and the occurrence or grade of the serious adverse events (SAEs) that occurred between the first and second doses. There was no relationship reported between exposure (cumulative AUC up to the time of SAE and C_{mean}) and the occurrence of mid- and long-term SAEs following treatment initiation. No exposure-response relationships were reported for neutrophil count or neutropenia grade.

All clinical studies of obinutuzumab also included plasma sampling to test for HAHA against obinutuzumab. The sponsor states that in the early clinical studies (BO20999, BO21000, BO21003 and JO21900), a highly sensitive HAHA ELISA assay for the detection of anti-obinutuzumab antibodies in serum samples with low obinutuzumab concentrations was used. However, due to the generally high obinutuzumab serum concentrations in patient samples and the limited drug tolerance of the first generation assay there remained a potential for false negative results. Therefore, a second generation ELISA with improved drug tolerance was developed for use in the pivotal trial. In trial BO21004/CLL11, a total of 7 patients out of the 64 patients (11%) who had samples assessed using the second generation assay with improved drug tolerance had positive HAHA results at, or after, the 6-month follow-up visit. The sponsor states that neither PK parameters nor clinical response were notably affected. However, given the limited number of patients assessed at the time of the Stage 1a analysis, no definitive conclusion on the incidence of HAHA positivity and their clinical consequences can be made. No patients were reported to have HAHA above the lower limit of detection during follow-up in any of the supporting trials or populations.

During pharmaceutical development, three different manufacturing processes were established for obinutuzumab (i.e., from (b) (4)). (b) (4)

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/s/

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05/30/2013

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06/03/2013