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**Division:** World Wide Development
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| **Title:** | Reporting and Analysis Plan for OMB112517 : A Phase III, Open-Label, Randomized, Multicenter Trial of Ofatumumab Maintenance Treatment versus No Further Treatment in Subjects with Relapsed Chronic Lymphocytic Leukemia (CLL) who have Responded to Induction Therapy (PROLONG) |

**Compound Number:**   GSK1841157

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**Description**: Reporting and Analysis Plan for OMB112517

**Subject:** OMB112517 Reporting and Analysis Plan

**Author's Name, Title and Functional Area:**

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**Approved by:**

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_____          11 Sep 2014
DrPH                                       **Date**
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Ph.D.                                      **Date**
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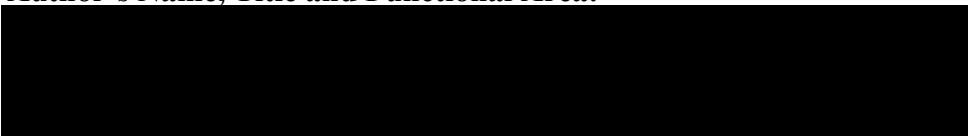| | |
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## ABBREVIATIONS

| | |
|---|---|
| AIHA | Autoimmune Hemolytic Anemia |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Concentration-time Curve |
| CBC | Complete Blood Count |
| CL | Clearance |
| CI | Confidence Interval |
| CLL | Chronic Lymphocytic Leukemia |
| CONMED | Concomitant Medication Dataset |
| Cmax | Maximum observed concentration |
| CR | Complete Response |
| CSR | Clinical Study Report |
| $C\tau$ | Observed concentration prior to next dose |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTX | Anti-cancer Therapy Dataset |
| DISCHA1 | Disease Characteristics Dataset |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Easter Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| ED-5D | EuroQoL Five-Dimension |
| EORTC QLQ-CLL-16 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia 16 item module |
| EORTC QLQC30 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 |
| GSK | GlaxoSmithKline |
| HAHA | Human Anti-human Antibodies |
| HR | Hazard Ratio |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Review Committee |
| IDSL | Integrated Data Standards Library |
| ITT | Intent to Treat |
| LLN | Lower Limit of Normal |
| MRD | Minimal Residual Disease |
| MedDRA | Medical Dictionary for Medical Affairs |
| NCI-WG | National Cancer Institute-sponsored Working Group |
| ONCTTE | Oncology Time to Event Dataset |
| ONCSURV | Oncology Survival Dataset |
| OS | Overall Survival |
| PD | Progressive Disease |

| PFS | Progression-free Survival |
| PGx | Pharmacogenetics |
| PK | Pharmacokinetics |
| PP | Per-protocol |
| PR | Partial Response |
| PRO | Patient Reported Outcome |
| PT | Preferred Term |
| RAMOS | Registration and Medication Ordering System |
| RADIO | Radiotherapy Dataset |
| RAP | Reporting and Analysis Plan |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| SRT | Safety Review Team |
| $t_{\frac{1}{2}}$ | Terminal phase half-life |
| tmax | Time of observed maximum concentration |
| TLS | Tumor Lysis Syndrone |
| TTE | Time-to-event |
| ULN | Upper Limit of Normal |
| Vss | Volume of distribution at steady state |

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# 1.    INTRODUCTION

The reporting and analysis plan (RAP) details all planned analyses for a Clinical Study Report to support a possible regulatory submission of study OMB112517.  This is a phase III, open-label, randomized, multicenter trial to evaluate efficacy and safety of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy using a parallel design.

For further information on the study design, see Protocol Amendment 05, dated 26-Aug-2014 (GlaxoSmithKline Document Number UM2008/00446/06).

The content of this RAP is based on the SOP and Information for Authors: Reporting and Analysis Plans ▮▮▮▮▮▮▮▮▮▮ effective 23 March 2011.  The RAP was written by staff of GSK.  The execution of the RAP will be undertaken by staff of GSK. The interim analysis will be undertaken by ▮▮▮▮▮▮▮▮▮

All decisions regarding final analysis, as defined in this RAP document, have been made prior to STDM Database Freeze of the study data. Interim analyses are detailed within Section 4.1, where applicable.

# 2.    STUDY OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate progression free survival (PFS) of subjects treated with ofatumumab maintenance treatment compared to no further treatment after remission induction in subjects with relapsed chronic CLL. | • PFS: defined as the interval between the date of randomization and the earliest date of disease progression or death due to any cause. |
| **Secondary** | |
| • To evaluate the improvement in response, time to next CLL treatment and overall survival in subjects receiving ofatumumab maintenance compared to nor further treatment | • Improvement in response, time to next treatment and overall survival |
| • To evaluate PFS after next-line therapy and time to progression after next-line therapy | • Progression-free survival after next-line therapy and time to progression after next-line therapy |
| • To evaluate the safety and tolerability in subjects with CLL receiving ofatumumab maintenance compared to no further treatment | •  |
| | • Incidence of and number of subjects with grade 3 and 4 infections; incidence, severity of adverse events, serious adverse events and other safety parameters; evaluation of |

| Objectives | Endpoints |
|---|---|
| | myelosuppression (anemia, neutropenia, thrombocytopenia); frequency of transfusions; incidence of Autoimmune Hemolytic Anemia (AIHA); Human Anti-Human Antibodies (HAHA); IgG, IgA, IgM serum levels. |
| • To evaluate the health related quality of life in subjects with CLL receiving ofatumumab maintenance compared to no further treatment as assessed by changes in patient reported outcome (PRO) measures relative to baseline. | • Changes in patient report outcome (PRO measures; changes in patient reported outcome (PRO) scores; improvement of ECOG performance status. |
| • To evaluate prognostic marker correlation with clinical response in subjects with CLL receiving ofatumumab maintenance compared to no further treatment | • Cytogenetics by fluorescent in situ hybridization (FISH); IgVH mutational status; β2 microglobulin; changes in complement levels. |
| • To evaluate ofatumumab pharmacokinetic parameters in subjects with CLL receiving maintenance ofatumumab every 2 months | • Plasma ofatumumab concentrations |

## 2.1.     Statistical Hypotheses

The primary endpoint for this study is progression-free-survival (PFS). The null and alternative hypotheses are designed with the goal of demonstrating the superiority of ofatumumab maintenance treatment over no further treatment after remission induction in subjects with relapsed chronic CLL. The following hypotheses will be evaluated:

H0: Distribution of the progression-free survival events for the ofatumumab maintenance treatment and for the no further treatment groups are the same (Hazard ratio is equal to 1)

H1: Distribution of the progression-free survival events for the ofatumumab maintenance treatment and for the no further treatment groups are not the same (Hazard ratio is not equal to 1)

Secondary statistical hypotheses to be tested include a comparison of time to next treatment and overall survival (OS) between the ofatumumab maintenance arm and the no further treatment arm.

## 3.     STUDY DESIGN

This is an open-label, two-arm, randomized, Phase III study of ofatumumab or no further treatment in subjects who are in CR or PR after 1 to 2 treatments for relapsed CLL.

**Screening Phase:**

Subjects will give informed consent. Blood samples, physical examination, CT scan and bone marrow examination will be performed to determine baseline disease status and study eligibility. All examinations must be performed ≤ 14 days prior to dosing, with the exception of the CT scan and bone marrow examination, which can be performed ≤ 6 weeks prior to dosing.

**Randomization and Stratification:**

Subjects will be randomized 1:1 to treatment arm A or B.

Eligible subjects will be stratified at randomization based on:

1) CR or PR at study entry

2) Number of previous induction treatments (2 vs 3)

3) Type of prior treatment : chemoimmunotherapy, only alkylating monotherapy, or other treatment

**Treatment Phase:**

Subjects randomized to treatment arm A will receive ofatumumab whereas subjects randomized to treatment arm B will receive no further treatment (i.e. observation only).

Arm A:

Ofatumumab:

• 300mg IV Week 1 followed by 1000mg IV on Week 2

• 1000mg IV (1 dose every 8 weeks for up to 2 years following the first 1000 mg

dose)

**OR**

Arm B:

• No further treatment (observation and assessments as per arm A)

Disease status assessments to determine subject response or progression will be performed approximately every 8 weeks for up to 2 years and then every 3 months for both arms according to NCI Criteria [Hallek, 2008] and will include:

• Physical examination including lymph node examination, spleen and liver measurement, and detection of constitutional symptoms

• Peripheral blood sample evaluation of complete blood count (CBC) and differential

(expressed in % and absolutes)

Monitoring and treatment of potential Tumor Lysis Syndrome (TLS) during the first cycle will be performed as per oncology standard of care.

Patient Reported Outcome (PRO) measures (EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D will be administered for completion by subjects at baseline and Cycle 4 Day 85 treatment visit and end of treatment/follow-up visits. A Health Change Questionnaire will be administered for completion by the subjects at all post baseline visits.

**Follow-up Phase:**

Survival and disease status assessments (physical examination and evaluation of peripheral blood samples) will be performed post treatment every 3 months for 5 years after last treatment.

Bone marrow examination is required for confirmation of CR at least 2 months post last treatment. MRD assessment will also be performed for subjects demonstrating CR. Subjects with negative MRD will receive follow-up MRD assessment of the peripheral blood until MRD becomes positive. CT-Scans are required for confirmation of CR and PR at least 2 months post last treatment.

Subjects demonstrating disease progression will be followed for survival status until study completion. Follow-up assessment after disease progression on treatment will assess survival status, date of next CLL therapy, type of therapy and response to therapy.

PRO measures (EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D and a Health Change Questionnaire) will be administered for completion by the subject at follow-up visits.

# 4. PLANNED ANALYSES

In line with International Conference on Harmonisation (ICH) E9 [European Agency for the Evaluation of Medicinal Products, 1998], membership of the analysis populations will be determined using the definitions in Section 6 of this RAP; this will be done prior to unblinding treatment allocation.

For the interims and the final primary analysis, treatment allocations will be unblinded and extracted from the RandAll system using GSK standard procedures. The treatment allocation will then be merged onto the study database using the randomization number (as allocated to each subject by RAMOS) to match subjects with the correct treatment allocation.

## 4.1. Interim Analyses

Two interim analyses will be performed. The first interim will assess safety endpoints. The second interim will be done to assess efficacy based on the primary endpoint, and it will also evaluate safety.

An independent data monitoring committee (IDMC) will be convened to perform an interim analysis of the safety data after 100 subjects in the maintenance arm have been on treatment for at least 6 months.

An interim analysis of the primary endpoint, PFS, will be performed when 2/3 of the total number of events have occurred (187 events).  An event is defined as when a subject has disease progression (PD) or death due to any cause during the study.   The interim analysis for PFS will be performed by an IDMC utilizing a conservative significance level of 0.001.  Performing this interim analysis with an IDMC applying conservative statistical criteria would allow for an earlier detection of clinical benefit to patients with ofatumumab maintenance and if this analysis is positive, may support a submission that enables earlier access to patients.  This interim analysis will also evaluate safety.  As the significance level was met at the interim efficacy analysis, further enrollment in the study will be discontinued.  There will be no changes to the study design, treatment, assessments, or follow-up. The interim analysis of the primary endpoint, PFS, will be conducted as described in Section 11.1, and details of the interim analysis will also be provided in the IDMC Charter.  The final analysis will be conducted at a significance level of 0.0498.

## 4.2.      Final Analyses

An analysis will take place when the total number of events (280 PFS events/deaths) is reached in the study.  An event is defined as when a subject has disease progression (PD) or death due to any cause during the study.  All available data will be analyzed and the results will be presented in a report.  Released data that are available from later visits will also be included.

An additional analysis will take place after all subjects have completed follow-up or have been withdrawn from the study.

# 5.      SAMPLE SIZE CONSIDERATIONS

## 5.1.      Sample Size Assumptions

The primary objective of this study is to evaluate progression-free survival (PFS) of ofatumumab maintenance treatment vs. no further treatment after remission induction in patients with relapsed CLL as determined by investigator assessment based on NCI-WG CLL criteria [Hallek, 2008]. The sample size calculation is based on the primary endpoint, PFS, using the following assumptions and was calculated using East 5.3 software:

- Exponential survival curves where the ratio of the hazard rates is constant over Time

- Median PFS for the no further treatment group is 28 months (based on REACH, Robak, et al, 2008)

- Median PFS for the ofatumumab maintenance treatment group is 39.2 months (40% improvement over the no further treatment group)

- A 1:1 stratified randomization scheme

- A 5% two-sided risk of erroneously claiming a difference in the presence of no true underlying difference (alpha level)

- An 80% chance of successfully declaring a difference in the presence of a true underlying difference (power)

- Accrual rate of 12 subjects per month

- Stratified Log-rank test for hypothesis testing

Using the above assumptions, approximately 280 total events from both treatment arms are needed for the study to attain 80% power. With a total sample size of 478 evaluable subjects, the total duration of the study will be approximately 63.5 months in order to obtain the 280 total events. Assuming a dropout rate of 10%, the total sample size for both arms combined will be about 532 and the total duration of the study will be approximately 68 months.

As the significance level was met at the interim efficacy analysis, further enrollment in the study will be discontinued.  There will be no changes to the study design, treatment, assessments, or follow-up.

## 5.2.    Sample Size Sensitivity

The robustness and sensitivity of the above sample size calculation is considered in order to assess the impact on power should the assumed median PFS vary in the ofatumumab maintenance group.  The following table shows the estimated power for different median values of PFS for the ofatumumab maintenance group.  The total number of events is 280, and the total number of evaluable subjects is 478.

| Median PFS (months) for Ofatumumab Maintenance | Median PFS (months) for No Further Treatment | Estimated Power |
|---|---|---|
| 35 | 28 | 0.47 |
| 36.4 | 28 | 0.60 |
| 39.2 | 28 | 0.80 |
| 42 | 28 | 0.92 |

## 5.3.    Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

# 6.     ANALYSIS POPULATIONS

## 6.1.     Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include subjects who are randomized in the study. This will be the primary population used for evaluation of the efficacy data for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they receive. The ITT population will also be used for all PRO analyses.

## 6.2.     Safety Population

The Safety population will include all randomized subjects. This population will be used for evaluation of all safety measurements. In the analyses, subjects will be grouped based on the treatment they received regardless of how they are randomized.

## 6.3.     Per Protocol Population

The Per-Protocol (PP) population will comprise all randomized subjects and will exclude subjects with major protocol deviations that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the results when using the ITT population. However, if the difference between the ITT and the Per-Protocol population is 10% or less, then the Per-Protocol analysis will not be performed.

Subjects who meet the following conditions will be considered as major protocol violators:

- Failure to be a PR or CR at study entry

- Received only 1 or more than 3 previous induction treatments

- Failure to demonstrate diagnosis of CLL

- Failure to satisfy the following inclusion criteria: The anti-leukemia treatment before study entry should have been for at least 3 months or 3 cycles.

- Received previous autologous or allogeneic stem cell transplantation (exclusion criteria)

- Had know transformation of CLL (e.g., Richter's transformation), prolymphocytic leukemia (PLL) or CNS involvement of CLL (exclusion criteria)

- Received prohibited therapies or procedures for CLL

## 6.4.     Pharmacokinetic Population

The Pharmacokinetic Population will consist of all subjects in the ITT population for whom a pharmacokinetic sample is obtained and analyzed.

## 6.5.    Analysis Datasets

The primary data set for efficacy will be based on the investigator response assessments. The primary data sets for safety will be based on the adverse events and the laboratory data.

The responses will be assessed by the investigators and changes in response will be determined according to the IWCLL updated NCI-WG CLL criteria (Hallek, 2008).  Data will be summarized for investigator assessed response, and statistical inference for efficacy claims will also be based on investigator assessed response data.

# 7.    TREATMENT COMPARISONS

The primary treatment comparison of interest will be ofatumumab maintenance treatment vs. no further treatment.  The primary comparison will be based on progression-free survival (PFS) when the total number of events reaches 280 in the ITT population.

The primary efficacy endpoint will serve as gatekeeper for the interpretation of treatment comparisons for the 'inferential' secondary endpoints.  If $H_0$ is rejected at the 0.001 significance level at the planned interim analysis, the conclusion will be that there is a treatment difference between ofatumumab maintenance treatment and no further treatment, and the p-values for the 'inferential' secondary endpoints may be interpreted and tested at the 0.05 significance level for the final analysis.  If $H_0$ is not rejected at the interim or final analysis, the conclusion will be that there is no difference between ofatumumab maintenance treatment and the no further treatment arm, and all other p-values will be used for descriptive ▮▮▮▮▮▮▮▮ purposes only.

The following endpoints are considered as 'inferential secondary endpoints' and will be tested and compared between the ofatumumab maintenance treatment and the no further treatment group if the primary endpoint, PFS, is significant.

1.  Time to next CLL therapy
2.  Overall survival

To control for multiplicity across the 'inferential secondary endpoints', the test of $H_0$ will be performed in a sequential manner to control the type I error at 0.05 as follows:

1-  Time to next CLL therapy
2-  Overall survival

For the primary efficacy endpoint and the inferential secondary endpoints, any p-values for the comparison of ofatumumab maintenance treatment vs no further treatment that achieve statistical significance under multiplicity adjustment will be identified in the study report as inferentially significant for confirmatory purposes.

Any other comparisons of interest between the ofatumumab maintenance treatment and the no further treatment arms for other secondary endpoints will be done at an alpha level equal to 0.05.  No multiplicity will be considered in the other secondary endpoints and any p-value that is ≤0.05 will be identified as nominally significant.

## 7.1. Data Display Treatment and Other Subgroup Descriptors

For all tabulations, Ofatumumab Maintenance and Observation (no further treatment) will be presented.

All listings will be presented by individual treatment arm.

If the sample size permits, the stratification factors will be used for subgroup analyses. The stratification factors include: CR or PR at study entry; number of previous induction treatments (2 vs 3); and type of prior treatment (chemoimmunotherapy, only alkylating monotherapy, or other treatment).

The following treatment descriptors will be used on all applicable displays:

| Treatment Group | | Data Display | Order of Treatment Groups |
|---|---|---|---|
| Code | Description | | |
| A | Ofatumumab Maintenance | Ofatumumab | 1$^{st}$ treatment column |
| B | Observation | Observation | 2$^{nd}$ treatment column |

## 8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis datasets will be created according to CDISC/ADaM standards, and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

The currently supported version of SAS will be used to perform all data analyses and to generate tables, listings, and figures. All data in the database will be presented in subject data listings. Data displays will follow the agreements proposed by the IDSL where possible.

Unless otherwise stated, continuous variables will be summarized with the following statistics: mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency counts and percentages.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment

All confidence intervals will be two-sided and will use a 95% confidence level.

Deviations from the analyses in the RAP will be identified in the CSR.

## 8.1.      Multicenter Studies

Data from all participating centers will be pooled prior to analysis.  It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would not be informative and will not be provided.  However, a summary of enrollment by center will be provided.

## 8.2.      Other Strata and Covariates

In all efficacy analyses, the tests will be stratified by the baseline stratification factors: (1) CR or PR at study entry, (2) number of previous induction treatments (2 vs 3) and (3) type of prior treatment : chemoimmunotherapy, only alkylating monotherapy, or other treatment.  The demographic summaries will document the number of subjects who fall into each stratum for the ITT population.  PFS, the primary endpoint, will also be summarized according to the stratification factors.

Subjects will be considered to fall into the respective stratification categories according to the actual data given in the eCRF.  Hence, if any misallocations took place in the stratification, it will be the actual data which will be used to determine the stratification of the subject rather than the data as recorded on RAMOS.

In addition to stratification factors, treatment arm as well as age, gender and race will be considered as covariates in the Cox regression model to assess the effect of ofatumumab maintenance treatment vs. no further treatment.

## 8.3.      Examination of Subgroups

Summary tables for PFS will be provided by the baseline stratification factors: (1) CR or PR at study entry, (2) number of previous induction treatments and (3) type of prior treatment : chemoimmunotherapy, only alkylating monotherapy, or other treatment.

Other subgroups of interest include may include age ($<70$ vs $\geq 70$), gender, race RAI/Binet Stage, ECOG (0-1 vs 2), baseline cytogenetics, cytogenetics at relapse, prognostic factors (Beta-2 microglobulin, IgVh status) , baseline lymphocyte count and MRD status.

## 8.4.      Multiple Comparisons and Multiplicity

The primary efficacy endpoint will serve as gatekeeper for the interpretation of treatment comparisons for the 'inferential' secondary endpoints.  If $H_0$ is rejected at the 0.001 significance level at the planned interim analysis, the conclusion will be that there is a treatment difference between ofatumumab maintenance treatment and no further treatment, and the p-values for the 'inferential' secondary endpoints may be interpreted and tested at the 0.05 significance level for the final analysis.  If $H_0$ is not rejected at the interim or final analysis, the conclusion will be that there is no difference between ofatumumab maintenance treatment and the no further treatment arm, and all other p-values will be used for descriptive and ████████ purposes only.

The following endpoints are considered as 'inferential secondary endpoints' and will be tested and compared between the ofatumumab maintenance treatment and the no further treatment group if the primary endpoint, PFS, is significant.

1. Time to next CLL therapy
2. Overall survival

To control for multiplicity across the 'inferential secondary endpoints', the test of $H_0$ will be performed in a sequential manner to control the type I error at 0.05 as follows:

1- Time to next CLL therapy
2- Overall survival

For the primary efficacy endpoint and the inferential secondary endpoints, any p-values for the comparison of ofatumumab maintenance treatment vs no further treatment that achieve statistical significance under multiplicity adjustment will be identified in the study report as inferentially significant for confirmatory purposes.

Any other comparisons of interest between the ofatumumab maintenance treatment and the no further treatment arms for other secondary endpoints will be done at an alpha level equal to 0.05. No multiplicity will be considered in the other secondary endpoints and any p-value that is $\leq 0.05$ will be identified as nominally significant.

# 9.     DATA HANDLING CONVENTIONS

## 9.1.     Premature Withdrawal and Missing Data

**Withdrawal**

Subjects will be observed until study completion or study withdrawal due to unacceptable adverse events(s), consent withdrawal or other reasons. All data up to time of withdrawal will be included in the analysis.

Subjects who are withdrawn prematurely from study treatment but who are not withdrawn from the study at the time of the analysis will be included in the analysis, regardless of treatment duration.

**Missing Data**

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. This data will be indicated by the use of a "blank" in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Since the period of follow-up for any subject will be dependent on efficacy and toxicity, the duration of follow-up will vary among subjects. Consequently, there will be no imputation for missing data. Randomized subjects who do not have any response data will be assumed to be non-responders and will be censored at the date associated with the last visit.

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For the PFS endpoint, subjects who are alive and have not progressed at the time of analysis will be censored at the date associated with the last visit with an adequate assessment. If a progression event occurs after an extensive lost-to-follow-up time (more than 2.5 assessment windows), the primary analysis will censor those subjects at the last date of their last visit with an adequate assessment even if subsequent information is available regarding progression or date of death.

Subjects with the designation of treatment relationship for adverse events (AE)s and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes".

There will be no other imputation for missing data other than what's described in Section 9.2 for partial dates and for missing exposure end dates.

## 9.2.    Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

### 9.2.1.    Reference Dates

There are three reference dates:

- The reference date for age is the date of screening.

- The safety reference date is the treatment start date for subjects randomized to the Ofatumumab arm, and will be used to calculate study day for safety measures. Because subjects in the observation arm do not receive treatment, the randomization date will be used as the safety reference date for subjects in this arm.

- The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics (such as time since initial diagnosis), as well as efficacy durations.


### 9.2.2.    Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

### 9.2.3.    Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest

occurs prior to the efficacy reference date then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

## 9.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.

- If the reference date is before the event date then the elapsed time is the reference date minus the event date.

When reporting time to event (TTE) durations [PFS, time to next treatment, overall survival] in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

For converting all other durations (e.g., duration of adverse events, duration of exposure, age) to weeks, months or years use the following:

- To report the duration in weeks divide the number of days by 7.

- To report the duration in months use:

  (YEAR(stopdate + 1) - YEAR(startdate)) * 12 + (MONTH(stopdate + 1) - month(startdate) - 1) + (DAY(stopdate + 1) > = DAY(startdate))

- To report the duration in years use:

  intck('year', startdate, stopdate + 1) - (month(stopdate + 1) < month(startdate) or (month(stopdate + 1) = month(startdate) and day(stopdate + 1) < day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

## 9.2.5. Imputation of Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for 'slotting' data to study time periods (see Section 9.3) or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

**Adverse Events (AE):**

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

| Dataset | Date | Missing Element | Rule |
|---------|------|-----------------|------|
| Adverse Events (AE) | Start Date | day, month, and year | • No Imputation for completely missing dates |
| | | day, month | • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.<br>• Else if study treatment start date is not missing:<br>  ○ If year of start date = year of study treatment start date then<br>    • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.<br>    • Else set start date = study treatment start date.<br>  ○ Else set start date = January 1. |

| Dataset | Date | Missing Element | Rule |
|---|---|---|---|
| | | day | • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.<br>• Else if study treatment start date is not missing:<br>  o If month and year of start date = month and year of study treatment start date then<br>    • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.<br>    • Else set start date = study treatment start date.<br>  o Else set start date = 1st of month. |
| | End Date | | • No imputation for partial end dates will be performed |

**Anti-Cancer Therapy and Radiotherapy:**

Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

| Dataset | Date | Missing Element | Rule |
|---|---|---|---|
| Anti-Cancer Therapy<br><br>Radiotherapy | Start Date | day, month, and year | • No Imputation for completely missing dates |
| | | day, month | • If partial date contains a year only set to January 1st. |
| | | day | • If partial date contains a month and year set to the 1st of the month. |
| | End Date | | • No imputation for partial end dates will be performed |

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**Surgery:**

The date of surgery or procedure is generally not imputed. If the date of surgery or procedure needs to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment surgery or procedure dates maybe imputed (where applicable) to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not specific surgery or procedure date) will be stored on appropriate efficacy datasets. The category for surgical procedure variable, and not any variables that use imputed partial dates, will be used to differentiate prior, on, and follow-up surgical procedure data. The derived time in relation to treatment variables are not needed for reporting of data because the category for surgical procedure variable can be used. Therefore, imputed dates are not needed for derivation of time in relation to treatment.

| Dataset | Missing Element | Rule |
|---|---|---|
| Surgical Procedures | day, month, and year | • No Imputation for completely missing dates |
| | day, month | • If partial date contains a year only set to January 1$^{st}$. |
| | day | • If partial date contains a month and year set to the 1$^{st}$ of the month |

**Concomitant Medication and Blood and Blood Supportive Care Products:**

Impute start and end dates for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but do not permanently store the imputed start and end dates in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

| Dataset | Date | Missing Element | Rule |
|---|---|---|---|
| Concomitant Medication<br><br>Blood and Blood Supportive Care Products | Start Date | day, month, and year | • No Imputation for completely missing dates |
| | | day, month | • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1.<br>• Else if study treatment start date is not missing:<br>   ○ If year of start date = year of study treatment start date then<br>       ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.<br>       ▪ Else set start date = study treatment start date.<br>   ○ Else set start date = January 1. |
| | | day | • If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month.<br>• Else if study treatment start date is not missing:<br>   ○ If month and year of start date = month and year of study treatment start date then<br>       ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.<br>       ▪ Else set start date = study treatment start date.<br>   ○ Else set start date = 1st of month. |
| | End Date | day, month, and year | • No Imputation for completely missing dates |
| | | day, month | • If partial end date contains year only, set end date = earliest of December 31 or date of last contact. |
| | | day | • If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact (MSTONE.LCONTDT). |

**Time to Event:**

Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures dataset[s]:

| Dataset | Date | Missing Element | Rule |
|---|---|---|---|
| Anti-Cancer Therapy<br><br>Where applicable:<br><br>Radiotherapy<br><br>Surgical Procedures | Start Date | day, month, and year | • No Imputation for completely missing dates |
| | | day, month | • No imputation for missing day and month (note the eCRF should only allow for missing day) |
| | | day | • If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month).<br><br>• If partial date falls in the same month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month).<br><br>• If both rules above apply, then assign to latest of the 2 dates<br><br>• Otherwise, impute missing day to the first of the month. |
| | End Date | | • No imputation for partial end dates will be performed |

The date of new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates. If the date of new anti-cancer therapy is an imputed date, then the date of new anti-cancer therapy flag variable is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive the date of new anti-cancer therapy ensure that the date of new anti-cancer therapy flag is only set to 'D' if the derived date is imputed. For example if the date of new radiotherapy is imputed but the date of new anti-cancer therapy is prior to date of new radiotherapy and the new anti-cancer therapy date is not a partial date then the flag should be set to missing as the date used for the new anti-cancer therapy is not an imputed date.

**Covariates:**

If the algorithms for covariates (e.g., prognostic factors) include any partial dates, then the algorithms must specify the date imputation rules used in the derivations. The following imputation rules are the standard rules to be used when algorithms for covariates require date imputations.

| Variable | Example of when to impute | Rule |
|---|---|---|
| Prior anti-cancer therapy start date<br><br>Prior radiotherapy start date | • Impute to derive duration<br> o Duration of prior Therapy | • Only impute when a month and year are available but the day is missing.<br>• Impute to first day of the month.<br>• Do not store imputed date<br>• Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries) |
| Prior anti-cancer therapy end date<br><br>Prior radiotherapy end date | • Impute to derive elapsed time and duration<br> o Duration of prior Therapy<br> o Time from Last dose of prior therapy to Randomization | • Only impute when a month and year are available but the day is missing.<br>• Impute to last day of the month, also must be prior to 'start'<br> o if 'start' is the first of the month assign to 'start', else assign to 'start'-1), where 'start' is either the date of randomization or the start of study treatment.<br>• Do not store imputed date |

| Variable | Example of when to impute | Rule |
| --- | --- | --- |
| | | • Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries) |
| Any disease characteristic dates. For example:<br><br>• Date of initial diagnosis<br>• Date of last recurrence<br>• Date of last progression | • Impute to derive elapsed time<br>  o Time from initial diagnosis to randomization for use as a covariate<br>  o Time from progression on last therapy until randomization for use as a covariate | • If both month and day are missing, impute to January 1st<br>• else if day is missing, impute to first day of the month.<br>• Do not store imputed date<br>• Use only for relevant efficacy analyses (i.e. not to be used for general disease characteristic summaries) |

### 9.2.6. Imputation of Missing Exposure End Dates

In general, completely missing dates are not imputed. However, subjects in oncology trials may still be on study treatment when analyses are performed and so may have missing exposure end dates. For subjects still on study medication at the time of data cutoff, the exposure end date will be imputed to the earliest of: the date of clinical cutoff, the date of withdrawal from the study or the death date. The imputed exposure end date will be used to calculate cumulative dose and exposure duration.

### 9.2.7. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date for subjects randomized to the ofatumumab arm. For subjects randomized to the observation arm, baseline will be defined as the most recent, non-missing value prior to or on the randomization date.

For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. For subjects randomized to the observation arm, baseline will be relative to the randomization date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment (or randomization date for the observation arm) will be defined as the baseline value.

### 9.2.8.    Change from baseline

Change from baseline will be presented for safety data as described in Section 12.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

### 9.2.9.    Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report "worst case".

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

### 9.2.10.    Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

### 9.2.11.    Treatment Cycle

In order to differentiate cycle variables based on the "assessment" cycle (timeslicing/eCRF collected) versus actual treatment cycle variables based on exposure cycle start dates, treatment cycle, treatment cycle description, day with treatment cycle, day of start within treatment cycle, and day of end within treatment cycle, as appropriate, will be added to adverse events, blood and blood supportive care products, ECG, laboratory, and vital sign analysis datasets.

Treatment cycle:

- For non-planned visits/assessments select the cycle record for each subject where the dataset date variable is greater than or equal to cycle start date and less than or equal to cycle end date.

- For planned visits/assessments where Day 1 assessments are assumed to be done prior to dosing, add 1 to the cycle start date and cycle end date from the cycle dataset. For each subject, select the cycle record where the dataset date variable is

greater than or equal to the cycle start date and less than or equal to the cycle end date.

Treatment cycle description:

- Set treatment cycle description to the cycle dataset cycle description where the cycle dataset cycle is equal to the dataset treatment cycle.

Day within treatment cycle:

- For each subject, dataset date variable minus the cycle start date from the cycle dataset + 1 where the dataset date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of start within treatment cycle:

- For each subject, dataset start date variable minus the cycle start date from the cycle dataset + 1 where the dataset start date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of end within treatment cycle:

- For each subject, dataset end date variable minus the cycle start date from the cycle dataset + 1 where the dataset end date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

## 9.2.12.    Extended Loss to Follow-up or Extended Time without an Adequate Assessment

Since PFS is interval censored, extended loss to follow-up prior to PD or death increases the uncertainty when the event actually occurs. As such, PFS will be analyzed censoring for extended loss to follow-up to account for missed disease assessments prior to disease progression or death.

If 2.5 or more scheduled disease assessments are missed and are then followed by an assessment of PD or death, PFS will be censored at the last adequate assessment prior to PD or death.  An adequate assessment is defined as an assessment where the investigator determined response and components of lab and clinical parameters (blood, lymph nodes, organ and constitutional symptoms) are available. The blood laboratory tests in the definition of the "adequate assessment" are haemoglobin, platelets, ANC and lymphocytes.

If the PFS event occurred after the 1st visit up to 2 years (on-treatment or on-study period) where scheduled disease assessments are planned every 8 weeks, a 2.5 assessment window of 140 days (8 weeks + 8 weeks + 4 weeks window) will be used to determine whether there was an extended time without adequate assessment. That is, if the time

difference between PD/death and last adequate assessment is more than 140 days, then PFS will be censored at the last adequate assessment prior to PD/death.

If the PFS event occurred during the follow-up where visits are planned every 3 months for 5 years, then as 2.5 assessment window of 210 days (3 months + 3 months + 1.5 months= 7.5 months = 30 weeks) will be used to determine whether there was an extended time without adequate assessment.  This is, if the time difference between PD/death and the last adequate assessment is more than 210 days, then PFS will be censored at the last adequate assessment prior to PD/death.

The following is further explanation regarding the definition of extended lost-to-follow-up:

- 2.5 Assessment windows from last adequate assessment (prior to PFS Event assessment) to PFS Event.
    - o  If PFS Event occurred during – On-Study planned visits –
        - ▪ Visits are planned every 8 weeks after the 1st visit up to 2 years.
        - ▪ Window = 8 weeks + 8 weeks + 4 weeks = 20 weeks = **140 Days**.
    - o  If PFS Event occurred during - During Follow-Up planned visits
        - ▪ Visits are planned every 3 months for 5 years.
        - ▪ Window = 3 months + 3 months + 1.5 months = 7.5 months = 30 weeks = **210 days**.
    - o  Truncated time periods
        - ▪ First Follow-Up Assessment (3M FU) = **168 days**.
        - ▪ Second Follow-Up Assessment (6M FU) = **196 days**.
    - o  No Last Adequate Assessment is Present
        - ▪ **TTE>140** where TTE= PFS event date – Randomization date + 1
        - ▪ Will determine lost to follow-up

### 9.2.13.    Date Associated with Response

For each disease assessment after baseline, determine a date associated with the response. For complete response (CR) and partial response (PR), assign to the latest date within the disease assessments.  For progressive disease (PD), assign to the earliest assessment date associated with the progression.

### 9.2.14.    Derived and Transformed Variables

See Section 11 for details on analyses for time to event endpoints including progression-free survival, time to next treatment, and overall survival, including censoring rules.

**Deriving and Summarizing Pharmacokinetic Parameters**

See Section 14 for derivation of PK parameters.

For the purposes of calculating summary statistics and for statistical analysis, all pharmacokinetic parameters with the exception of tmax will be $\log_e$ transformed.

Between-subject coefficient of variation (CVb%) will be calculated by the following methods, where SD is the standard deviation of the pharmacokinetic parameter data, calculated using either the raw data (untransformed) or the natural logarithm of the raw data (transformed):

Untransformed data: 100 * (SD/Mean)

Transformed data: 100 * (square root[exp(SD$^2$)-1])

**Stratification and Prognostic Factors**

In all efficacy analyses, the tests will be stratified by the baseline stratification factors: (1) CR or PR at study entry, (2) number of previous induction treatments (2 vs 3) and (3) type of prior treatment: chemoimmunotherapy, only alkylating monotherapy, or other treatment. The demographic summaries will document the number of subjects who fall into each stratum. PFS, the primary endpoint, will also be summarized according to the stratification factors. Note that it may be necessary to create an additional strata for subjects who received 1 or >3 previous induction treatments.

Subjects will be considered to fall into the respective stratification categories according to the actual data given in the eCRF. Hence, if any misallocations took place in the stratification, it will be the actual data which will be used to determine the stratification of the subject rather than the data as recorded on RAMOS.

In addition to stratification factors, treatment arm as well as age (<70 vs ≥70), gender, race, RAI stage at screening, Binet stage at screening, ECOG (0-1 vs 2), baseline cytogenetics, cytogenetics at relapse, MRD status as well as Ctau and Cmax at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 may be considered as covariates in the Cox regression model to assess the effect of ofatumumab maintenance treatment vs. no further treatment.

The following is a list of the stratification and possible prognostic variables

Treatment
      1=Ofatumumab
      0=No further treatment

Response at Study Entry
      1=CR
      0=PR

Number of Induction Therapies
      1=3 Therapies
      0=2 Therapies

Type of Prior Treatment
      2=Chemoimmunotherapy
      1=Only alkylating therapy
      0=Other

Age
      1= ≥70
      0= <70

Gender
      1=Female
      0=Male

Race
      1=White
      0=Non-white

Modified RAI Stage
      2=High Risk (stage III, IV)
      1=Intermediate Risk (stage I, II)
      0=Low Risk (Stage 0)

Binet Stage
      2=C
      1=B
      0=A

MRD Status
      1=Positive
      0=Negative

Cytogenetics (FISH)
      3= 17p-
      2= 11q-
      1= 6q- or 12q or 13q-
      0= no aberration


Note the following rules to define an aberration using 20% as a cut-off.  The same rules will also be repeated using a cut-off of 12%.

cytogenetics≥20% = YES vs. cytogenetics <20% = NO for aberrations  (12% will also be used as a cut-off )

 17p- [a] vs. 11q- [b] vs. 6q- or +12q or 13q- [c] vs no aberration [d]
[a] All subjects that have ≥20% for 17p- , disregarding the presence of any other aberrations.
[b] All subjects that have ≥20% for 11q-, absence of 17p-, disregarding the presence of any other aberrations.
[c] All subjects that have ≥20% for 6q- or +12q or 13q-, absence of 17p- or 11q.
[d] Subjects with no aberration (or less than 20% of cells).

## 9.3. Study Time Periods

Adverse events, concomitant medications, blood product, death, subject disposition, ECOG, laboratory, image data, vital signs, constitutional symptoms, lymph node examination, organ examination, biomarker, and questionnaire data (EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D) will be assigned to the treatment periods defined below. Flag variables indicating the treatment period will be added to these datasets.

**Pre-therapy** is defined as the time prior to the subject's first dose of study treatment for subjects randomized to the ofatumumab arm. For subjects randomized to the "No further treatment (observation)" arm, pre-therapy is defined as the time prior to the subject's randomization date.

**On-treatment** is defined as the time from start date/time of study treatment until the end date/time of the study treatment + 30 days for subjects randomized to the ofatumumab arm. The start date of the on-treatment phase is the date of the first dose of study drug. The end of study treatment is defined as the last dose of planned treatment. For subjects randomized to the "No further treatment (observation)" arm, on-treatment is defined as the time from randomization until the date of entry into follow-up.

There are specific rules to handle the cases where start date/time is equal to start date/time of study treatment or the start date/time is missing for different classes of data sets:

- For interventions and events, including adverse event, concomitant medications, blood product, death, and disposition, i.e., if the date/time is equal to start date/time of study treatment or time is not available and the date is equal to start date of study treatment, the flag will be set to on-treatment. If the start date is missing, and the end date/time is before start date/time of study treatment, the flag will be set to pretreatment. If start date is missing and end date/time is not before the start date/time of study treatment, or both start date and end date are missing, the flag will be set to on-treatment.

- For findings, including ECOG status ,laboratory data , imaging data , vital signs , constitutional symptoms, lymph node examination, organ examination, and biomarker if the date/time is equal to start date/time of study treatment, the flag will be set to pre-treatment. If time is not available and the date is equal to start date of study treatment, the flag will be set to pre-treatment. If the date is missing, the flag will be set to on-treatment.

**Post-treatment** is defined as any time beyond the on-treatment period.

### 9.3.1. Study Time Periods for Concomitant Medications and Blood and Blood Supportive Care Products

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time

flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- Start **relative to treatment:** Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.

- **End relative to** treatment: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').

- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start date after study treatment start date. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include concomitant medication records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER').

## 9.4.     Values of Potential Clinical Importance

### 9.4.1.     Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal

or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

### 9.4.2.    Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

| Vital Sign Parameter | Potential Clinical Importance (PCI) Range | Unit |
|---|---|---|
| Decrease from baseline Heart Rate | Decrease to <60 | bpm |
| Increase from baseline Heart Rate | Increase to >100 | bpm |

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

| Vital Sign Parameter | Potential Clinical Importance (PCI) Range | Unit |
|---|---|---|
| Increase from baseline Systolic Blood Pressure | $\geq$120 to <140 (Grade 1)<br>$\geq$140 to <160 (Grade 2)<br>$\geq$160 (Grade 3) | mmHg |
| Increase from baseline Diastolic Blood Pressure | $\geq$80 to <90 (Grade 1)<br>$\geq$90 to <100 (Grade 2)<br>$\geq$100 (Grade 3) | mmHg |

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

| Vital Sign Parameter | Potential Clinical Importance (PCI) Range | Unit |
|---|---|---|
| Increase from baseline temperature | Increase to ≥38 | Degrees C |
| Decrease from baseline Diastolic Blood Pressure | Decrease to ≤35 | Degrees C |

# 10. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the ITT population, and all summaries and data listings will use treatment labels as specified in Section 7].

The list of displays for Study Population is shown in a separate document from the RAP.

The number of subjects enrolled into the study will be summarized by investigator for the ITT population. The total number of subjects in each population specified in Section 6.2 will also be provided.

A listing of subject disposition including investigator and treatment start date will be provided for the ITT population. The number of subjects prematurely discontinuing from the study along with the reason for early study discontinuation will also be summarized and listed.

## 10.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6 will be provided. In addition, the number of subjects enrolled by investigator will be summarized by treatment group using the ITT population. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who have completed the study, are ongoing, or have discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation.

## 10.2.    Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion/exclusion deviations as well as other deviations. Protocol deviations will be classified as 'Deviations that require exclusion from per-protocol population' and 'Deviations that do not require exclusion from per-protocol population'.

Subjects who meet the following conditions will be considered as major protocol violators and will be excluded from the per-protocol population:

- Failure to be a PR or CR at study entry

- Received only 1 or more than 3 previous induction treatments

- Failure to demonstrate diagnosis of CLL

- Failure to satisfy the following inclusion criteria:  The anti-leukemia treatment before study entry should have been for at least 3 months or 3 cycles.

- Received previous autologous or allogeneic stem cell transplantation (exclusion criteria)

- Had known transformation of CLL (e.g., Richter's transformation), prolymphocytic leukemia (PLL) or CNS involvement of CLL (exclusion criteria)

- Received prohibited therapies or procedures for CLL

A separate summary and listing of inclusion/exclusion deviations will also be provided.

## 10.3.    Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized for the following categories:

- <18, 18-64, 65-74, and >=75

- <70 and >=70 years.

The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

The number of subjects enrolled by country and by site will be summarized.

Disease history and characteristics at initial diagnosis (Modified RAI stage, Binet stage) and screening (Modified RAI stage, Binet stage, time since diagnosis (years), and response to last anti-CLL treatment will be listed.  Separate summaries of disease

characteristics at initial diagnosis and screening will be provided. Medical conditions present at screening will be listed and will be summarized along with 12-lead ECG, liver and spleen organ examination, physical lymph node examination, anti-cancer therapies, and concomitant medications.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Level 1, Ingredient, and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced. A summary of pre-medications required prior to ofatumumab infusion will also be provided

Prior anti-cancer radiotherapy will be summarized and listed. Prior cancer and non-cancer related surgeries will be summarized.

The baseline stratification factors (based on actual data), will be summarized and includes: (1) CR or PR at study entry, (2) number of previous induction treatments and (3) type of prior treatment : chemoimmunotherapy, only alkylating monotherapy, or other treatment.

Summaries of baseline covariates included in Cox proportional hazards model regression analyses (see Section 11) will be provided.

## 10.4. Treatment Compliance

A listing of planned and actual treatments will be produced.

A listing of drug accountability data (date, actual dose, total volume infused) will be produced.

A summary of overall compliance for study drug based on the exposure data will be produced. Compliance will be based on the total dose of ofatumumab received (mg) divided by the total dose (mg) expected taking into account withdrawal from treatment. Therefore, the denominator is based on the total dose received during the time that a subject is actually eligible to receive drug. The calculation of overall compliance is based on the entire interval of dosing for [specify treatment(s)]. The formula for daily dose medication is compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose)]*100 where duration of study treatment is last dose-first dose +1.

For example, if the dosing period for a study is one year and during that year, a subject received 100 mg of drug each month, then the denominator (total dose expected) would be 1200mg as a total dose if the subject was actually in the study for the full year. However, if the subject discontinued treatment at the end of the 6th month, then total dose in mg expected for this case would be 600 mg.

Percentage overall compliance will be summarized using the mean, standard deviation, minimum, median, and maximum. In additional, percentage overall compliance will be categorized and summarized by <80%, 80%-105%, and >105%.

In addition, summaries of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose interruptions) will further characterize compliance. These analyses are described in Section 12.1 'Extent of Exposure'.

## 10.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient "Amoxycillin".

Blood products or blood supportive care products with onset date within the on-therapy window will be included in the summary tables. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

Concomitant medications will be summarized separately for medications with onset date within the on-therapy period and for medications with onset date within the pre-therapy period. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

## 10.6. Subsequent Anti-Cancer Therapies

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, and small molecule targeted therapy as post study treatment anti-cancer therapy will be summarized. Time from study treatment discontinuation to the first post study treatment anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy) for each subject will be provided.

# 11. EFFICACY

All efficacy analyses will be based on the ITT population as defined in Section 6 unless otherwise specified. All analyses will be presented by treatment arm.

Efficacy assessments are based on IWCLL updated NCI-WG CLL criteria (Hallek, 2008) to assess clinical activity and disease status. Primary assessments will be based on

investigator assessment. Independent Reviewer Committee assessments will be considered as supplementary for sensitivity analyses.

## 11.1.    Primary Efficacy Analysis

**Progression-Free Survival**

The primary endpoint, progression-free survival (PFS), is defined as the interval of time (in months) between the date of randomization and the earlier of the date of disease progression or death due to any cause.  The investigator assessment of response will be used for the primary analysis. Details on censoring are provided in Table 1.

**Note that events of disease progression determined by CT scan will be excluded from the primary analysis of PFS but will be included in a sensitivity analysis.**

The date of documented disease progression will be defined as the date of disease progression based on investigator assessment.  The date of death should be taken from the Record of Death page.  Death on study due to any cause will be included as an event for calculation of PFS.

If there is no adequate baseline assessment, the subjects will be censored at their date of randomization.  Subjects without any adequate post-baseline assessments will be censored at the date of randomization.

Subjects who progressed or died after an extended period without an adequate assessment will be censored at their date of last assessment prior to progression or death even if subsequent information is available regarding progression or death.  An adequate assessment is defined as an assessment where the investigator determined response and components of lab and clinical parameters (blood, lymph nodes, organ and constitutional symptoms) are available. The blood laboratory tests in the definition of the "adequate assessment" are haemoglobin, platelets, ANC and lymphocytes. The date of response at that assessment will be used for censoring. As the assessment schedule may change through the course of the protocol, specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in Section 9.

For subjects who receive subsequent anti-cancer therapy, the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month) the imputation rules described in Section 9 will be applies.  No imputation will be made for completely missing dates.

- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy).  The date of response at the last adequate assessment will be used as the censoring value.

- If a subject has only a baseline visit or does not have an adequate assessment that is not later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of randomization.

If a subject has not progressed, has not died or has not started new-anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the investigator determined response and components of lab and clinical parameters (blood, lymph nodes, organ and constitutional symptoms) are available. The date of response will be used as the censoring date.

The assignments for progression and censoring dates for PFS are specified in the following table

**Table 1       Assignments for Progression and Censoring Dates for PFS Analysis**

| Situation | Date of Event (Progression/Death) or Censoring | Outcome Event (Progression/Death) or Censored |
|---|---|---|
| No (or inadequate) baseline response assessment and the subject has not died | Randomization | Censored |
| No post-baseline response assessments and the subject has not died | Randomization | Censored |
| Progression documented between scheduled visits | Date of assessment of progression | Event |
| No progression (or death) | Date of last adequate assessment of response[1] | Censored |
| New anticancer treatment started (prior to documented disease progression)[2] | Date of last adequate assessment of response[1] (on or prior to starting anti-cancer therapy) | Censored |
| Death before first PD assessment (or Death at baseline or prior to any adequate assessments) | Date of death | Event |
| Death between adequate assessment visits | Date of death | Event |
| Death or progression after more than 2.5 missed visits | Date of last adequate assessment of response (prior to missed assessments) | Censored |

[1]An adequate assessment is defined as an assessment where the investigator determined response and components of lab and clinical parameters (blood, lymph nodes, organ and constitutional symptoms) are available. The blood laboratory tests in the definition of the "adequate assessment" are haemoglobin, platelets, ANC and lymphocytes.
[2]If PD and new anti-cancer therapy occur on the same day, assume that progression was documented first (i.e. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

An interim analysis of the primary endpoint, PFS, will be performed when 2/3 of the total number of events have occurred (187 events). The interim analysis for PFS will be performed by an IDMC utilizing a significance level of 0.001. The interim analysis of PFS will be conducted in the same manner as described for the final analysis. Details of the interim analysis are also provided in the IDMC Charter.

The final analysis of PFS will be based on a two-sided test with a significance level of 0.0498. The survival distributions will be estimated using Kaplan-Meier survival curves and will be compared using a stratified log-rank test. The Pike estimator [Berry, 1991] of the treatment hazard ratios (HR) will be provided, together with the 95% Confidence Interval (CI). The Pike estimator, which is a nonparametric estimator of the HR, has been specifically developed for survival data and is used as a measure of the relative survival experience of two groups. Within the range of values of the ratio of the hazard rates of interest in clinical trials, the Pike estimator is more efficient in terms of mean square error than the Cox proportional hazard method [Bernstein, 1981]

If there are a sufficient number of progressions or deaths, median PFS, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. A figure and listing of progression-free survival time will also be provided.

A supplementary table showing the details of the number at risk, number of events, and number censored with the event time will also be produced. Estimates of median PFS after 6 months, 1 year and 2 years of exposure (or observation) will also be provided.

In addition to the stratified log-rank test based on the Kaplan-Meier procedure, a Cox regression model using a stepwise procedure will be used and will include covariates for treatment, stratification factors [CR or PR at study entry; number of previous induction treatments; and type of prior treatment (chemoimmunotherapy, only alkylating monotherapy, or other treatment)] and other baseline data deemed appropriate such as age, Binet stage and baseline cytogenetics data. Treatment will remain forced in the model. An entry/removal significance level of 0.05 will be used. Analytical results will include the estimated hazard ratios along with 95% confidence intervals and associated probabilities for the effect of treatment, stratification factors, and the covariates. The hazard ratio for treatment will express the risk of experiencing disease progression or death for 'ofatumumab maintenance' vs 'observation' (i.e., no further treatment).

PFS will be evaluated for the ITT population. If the ITT population and Per Protocol population differ by more than 10%, then PFS will also be evaluated for the Per-Protocol population to check the robustness of the result when using the ITT population.

**Sensitivity Analyses for PFS**

Three sensitivity analyses of PFS will be performed.   All sensitivity analyses will be performed as described for the primary analysis of PFS.   The sensitivity analyses are specified as follows:

1.  The first sensitivity analysis will be conducted using the IRC response data as opposed to using investigator assessment of response.

2.  The second sensitivity analysis will be conducted using the investigator response data where events of progression determined by CT scan will be included in the analysis.

3.  The third sensitivity analysis will be conducted using sensitivity data generated by Perceptives where CT scan data is used to determine progression.

**Subgroup Analyses for PFS**

Subgroup analyses will be conducted for PFS for the stratification factors provided subgroups are large enough to result in meaningful analyses.  Figures displaying the survival curves will also be provided by treatment arms as well as for each of the stratification factors.  The stratification factors include the following:

1) CR or PR at study entry

2) Number of previous induction treatments (2 vs 3)

3) Type of prior treatment: chemoimmunotherapy, only alkylating monotherapy, or other treatment

PFS will also be summarized by age group (<70, >=70), gender, race, baseline MRD status (negative, positive), and cytogenetics provided the subgroups are large enough to result in a meaningful analysis.

## 11.2.    Secondary Efficacy Analyses

**Clinical Benefit:**

•  Improvement in response

Improvement in response will be assessed by calculating the percentage of subjects who change from PR at baseline to CR during the study.  Improvement in response will also be assessed by providing the frequency and percentage of subjects with negative and positive minimal residual disease (MRD).  These rates will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response at entry, number of prior treatments and type of prior treatment).  The 95% confidence intervals will also be calculated for rates in each arm.

- Overall survival

Overall survival is defined as time (in months) from the randomization date to the date of death due to any cause. For subjects who do not die, time of death will be censored at the date of last contact. Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test. The same analysis will be conducted as described for the primary endpoint, PFS.

The analysis of overall survival will be performed when the second interim analysis for PFS takes place as well as at the end of the study. Subjects will be followed for 5 years after the 2 year treatment period.

- Time to next therapy

Time to next therapy is defined as the time (in months) from the randomization date to the date of receiving the next CLL treatment. For subjects who do not receive another CLL therapy, time of next therapy will be censored at the date of last contact. The same analysis will be conducted as described for the primary endpoint, PFS.

The analysis of time to next therapy will be performed when the second interim analysis for PFS takes place as well as at the end of the study.

- Progression-free survival after next-line therapy

This endpoint will be defined as the time (in months) from randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy. Analysis of this endpoint will only include subjects who received next-line therapy and subjects who died prior to receiving next-line therapy. Subjects who receive next-line therapy and who do not have progression or death after next-line therapy will be censored at their last date of contact. If a subject dies prior to next-line therapy, this will count as an event. ████████████████████████████████████████████████████████████████████████████

- Time to progression after next-line therapy

This endpoint will be defined as time (in months) from progression following randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy. Analysis of this endpoint will only include subjects who received next-line therapy and who also had PD prior to receiving next-line therapy. Subjects with PD who died prior to receiving next-line therapy will also be included. Subjects who receive next-line therapy with a PD prior to receiving next line therapy and who do not have progression or death after next-line therapy will be censored at their last date of contact. If a subject dies prior to next-line therapy, this will count as an event. ████████████████████████████████████████████████████████████████

- Changes in patient reported outcome scores

Area under the curve (AUC) of change from baseline over time in the EORTC QLQ-C30, EORTC QLQ-CLL16 domain scores and total scores as well as the EQ-5D utility and VAS scores will be evaluated. Details of the methods used to evaluate changes in PRO domain and total scores will be provided in the Health Outcomes section of the RAP.

- Improvement of ECOG performance status

Improvement is defined as a decrease from baseline by at least one step on the ECOG performance status scale (improvement categorized as yes or no). The proportion of subjects with improvement will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response at entry, number of prior treatments and type of prior treatment).

- B-symptoms/Constitutional symptoms

The proportion of subjects with no night sweats, no weight loss, no fever and no extreme fatigue will be summarized and compared to the proportion of subjects with at least one of the following: night sweats, weight loss, fever or extreme fatigue. The proportions will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response at entry, number of prior treatments and type of prior treatment).

- Incidences of and number of subjects with grade 3 and 4 infections

The number and percentage of subjects with grade 3, 4 and 5 infections will be summarized by treatment group.

- Evaluation of myelosuppression (anemia, neutropenia, thrombocytopenia)

The number and percentage of subjects with myelosuppression will be summarized by treatment group.

- Frequency of transfusions

The number and percentage of subjects who receive blood transfusions during the study will be provided by treatment group.

- Incidence of Autoimmune Hemolytic Anemia (AIHA)

The number and percentage of subjects with autoimmune hemolytic anemia during the study will be provided by treatment group. The proportion of subjects with AIHA will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response at entry, number of prior treatments and type of prior treatment).

- Human Anti-Human Antibodies (HAHA)

HAHA sample analysis will be conducted by a contract research organization using a validated assay. The number and percentage of subjects with positive and negative

HAHA results will be provided for each HAHA timepoint. A summary table with the overall HAHA assessment for each subject, considering ofatumumab concentration at the time of each HAHA sample collection, will be provided. A listing of HAHA results with the ofatumumab concentration at that time will be provided

- IgG, IgA, IgM

Summaries of IgG, IgA, and IgM will be provided at scheduled visits for actual values as well as for change from baseline.

**Disease Markers:**

- Minimal Residual Disease (MRD)

The number and percentage of subjects with positive and negative MRD will be provided at each timepoint. The proportion of subjects with negative MRD and positive MRD will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response at entry, number of prior treatments and type of prior treatment). An analysis of the time to first MRD positivity for subjects who were MRD negative at baseline will also be provided using Kaplan-Meier methodology.

- B-cell monitoring

The change and percent change of $CD5^+CD19^+$ and $CD5^-CD19^+$ from baseline will be summarized to assess the treatment effect, to monitor the normal B-cell population, and to follow their recovery. In addition, frequency and percentage of subjects with complete B-cell depletion and near-complete B-cell depletion will be summarized. Complete B-cell depletion is defined as the absolute value of $CD5^+CD19^+$ and $CD5^-CD19^+$ both equal to zero cells/uL. Near complete B-cell depletion is defined as the sum of the absolute value of $CD5^+CD19^+$ and $CD5^-CD19^+$ <5 cells/uL.

Tables that will be provided are:

- Summary of $CD5^+CD19^+$ counts over time
- Summary of $CD5^-CD19^+$ counts over time
- Summary of $CD5^+CD19^+$ change from baseline (counts and percentage)
- Summary of $CD5^+CD19^+$ percent change from baseline (counts and percentage)
- Summary of $CD5^-CD19^+$ change from baseline (counts and percentage)
- Summary of $CD5^-CD19^+$ percent change from baseline (counts and percentage)
- Summary of subjects with complete B-cell depletion Summary of subjects with near-complete B-cell depletion
- Prognostic markers correlating with clinical response

Cox-regression will be used to explore the relationship between PFS and the following explanatory variables: treatment group, cytogenetics (analyzed by FISH) at baseline,

IgVH mutational status at baseline, β2 microglobulin at baseline, baseline CD20 and baseline complement level. Ctau and Cmax at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 4 and cytogenetics at relapse may also be considered as possible explanatory variables in the model.

## 11.3. Other Efficacy Analyses

### 11.3.1. Concordance Analysis of Progression-Free Survival Timings

An assessment of the concordance between Investigator assessment of progression and

IRC Assessment of progression will be provided for both arms. The calculation will be based on the percent agreement (the proportion of progression outcomes that agree or match across both IRC and Investigator Assessments).

### 11.3.2. Number of Events of Progression During Treatment and During Follow-up

The number and percentage of subjects with progression (based on Investigator assessment) during the treatment period and also during follow-up will be summarized for both treatment arms.

## 12. SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the Safety population as defined in Section 6 and summaries will include all events or assessments collected during the study. All the analyses will be performed by treatment arm.

The list of displays for the Safety Analyses is shown in a separate document from the RAP.

## 12.1. Extent of Exposure

The dose (mg) and duration of exposure to ofatumumab in hours will be summarized by each infusion using summary statistics mean, standard deviation, median, minimum value, and maximum. The total number of infusions administered will also be summarised with mean, median, standard deviation, minimum, and maximum. The number and percentage of subjects who received infusions will be reported.

The frequency of infusion interruptions and incomplete infusions will also be provided.

## 12.2. Adverse Events

All SAEs and AEs regardless of relationship to investigational product will be collected from the first dose of investigational product to 60 days after the last dose of investigational product and will be documented on the eCRF. All SAEs and AEs for subjects not receiving treatment (observation) will be collected for the same duration time (i.e. Visit 1 until 60 days after last visit, up to Visit 14). Only SAEs will be reported from 60 days after the last dose of investigational product or last treatment/observation visit to

the end of the follow-up period. All SAEs regardless of causality will be collected until the end of the follow-up period.

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose delays/ interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

A summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate should not be included in this table). The summary will be displayed by SOC and PT.

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.

- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary table will be displayed in descending order of total incidence by PT only.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

Adverse events will be summarized and listed separately during the study and up to 60 days after the last dosing.

The following adverse event tables will also be provided for events occurring from the

start of treatment until 60 days after last dosing:

- All adverse events, all serious adverse events (including deaths) for the following:
  - Secondary malignancies
  - Cardiac events
  - Small bowel Obstruction
- All infusion reactions reported as AEs, SAEs and leading to withdrawal
- All infections reported as adverse events, all serious infections reported as adverse events
- All mucocutaneous adverse events, all serious mucocutaneous adverse events
- All decreased neutrophil count/ hemoglobin count/ and platelet count adverse events, all serious decreased neutrophil count/ hemoglobin count/ and platelet count adverse events
- All autoimmune hematologic complication adverse events, all serious autoimmune hematologic complication adverse events
- All tumor lysis syndrome adverse events, all serious tumor lysis syndrome adverse events

The relationship between MedDRA SOC, PT, and Verbatim will be displayed.

Summaries based on the following covariates will be provided for all AEs:

- Gender
- Age: <70 vs. ≥70 years
- Race: White, vs. non-white.

Additionally, summaries for adverse events sorted by preferred terms (in descending order of incidence of 'Any OFA' arm) will also be provided for AE, SAE, drug-related AE, SAE, fatal AE, AE leading to permanently discontinuation of study treatment, AE leading to dose interruption/delay, mucocutaneous reaction AE, serious mucocutaneous reaction AE, autoimmune hematologic complication AE, serious autoimmune hematologic complication AE and AE by subgroup.

The following subject listings will be provided:

- Relationship of AE system organ class, preferred terms and verbatim text
- Subject numbers for individual AE (by system organ class and preferred term)
- All AEs (by preferred term and verbatim text).
- AEs leading to permanent discontinuation of study treatment
- Liver chemistry adverse events for subjects with at least one liver event.

## 12.3.    Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

The events of special interest include

- Infusion related AEs

- Infections

- Mucocutaneous reactions

- AEs associated with decreased neutrophil, hemoglobin or platelet count

- Prolonged and late-onset neutropenia

- Autoimmune Hematologic Complication Adverse Events

- Tumor Lysis Syndrome (TLS)

Summaries of the number and percentage of subjects with these events will be provided for each type of event separately.

**Infusion related AEs**

Infusion reactions will be summarized using the preferred terms from the AE dataset.

The process for defining and reporting the infusion reactions is the following:

1) Select the candidate AEs

For each infusion, only AEs occur during and within 24 hours following the end of infusion will be included as candidate AEs.

If the AE onset date is available but the onset time is missing, then the AE will be included if it occurs on the same day as the infusion and the day following the infusion.

2) The list of candidate events based on the above criteria will be reviewed by the GSK clinical and safety review team to select the final set of terms for inclusion in the analysis tables.  This will be conducted at the Preferred Term (PT) level.

**Infections**

Summaries of infections will be based on treatment period and follow-up period pooled together by each grade and will be provided for grade 3, 4 and 5, respectively, as well as all infections regardless of grades.

In addition, the following summaries will be presented:

1) Summary of worst-grade infections by Binet stage and Rai stage and by neutrophil grade at baseline.

2) Summary of type of infections by all infections, all respiratory tract infections, lower respiratory tract infections, upper respiratory tract infections, sepsis and other infections.

3) Summary for drug-related infections

4) Summary of infections for subjects with baseline neutropenia.

## Mucocutaneous Reactions

An overview of mucocutaneous reactions and a summary of will be provided.

A summary of all mucocutaneous reactions and all serious mucocutaneous reactions

within 60 days after the last ofatumumab dose will also be provided.

A subject listing of all mucocutaneous reactions will be provided

## AEs Associated with Decreased neutrophil count/hemoglobin count/platelet count

A summary of AEs associated with decreased neutrophil count;  a summary of AEs associated with decreased hemoglobin count;  a summary of AEs associated with decreased platelet count; and a summary of AEs associated with other cytopenias will be provided.

In addition, mucocutaneous reactions reported as adverse events will be summarized and listed separately.

## Prolonged and late-onset neutropenia

Prolonged neutropenia is defined as Grade 3/4 neutropenia that occurred during the treatment period and was not resolved at least 42 days post the last dosing date.

Late-onset neutropenia is defined as Grade 3/4 neurtopenia starting at least 42 days after the last treatment dose.

## Autoimmune Hematologic Complication Adverse Events

A summary of all autoimmune hematologic complication adverse events and all serious autoimmune hematologic complication adverse events reported within 60 days after the last ofatumumab dose will also be provided.

A subject listing of all events will be provided.

## Tumor Lysis Syndrome (TLS)

Laboratory TLS, calculated using the following criteria will be summarized:

| Metabolic Abnormality | Criteria for Laboratory TLS | Criteria for Clinical TLS |
|---|---|---|
| Hyperuricemia | Uric acid >8.0 mg/dl | |
| Hyperphosphatemia | Phosphorus >4.5 mg/dl | |
| Hyperkalemia | Potassium >6.0 mmol/l | Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia |
| Hypocalcemia | Corrected calcium <7.0 mg/dl or ionized calcium <1.12 mg/dl | Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm,Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia |
| Acute kidney injury | NA | Increase in serum Creatinine level of 0.3 mg/dl (or a single value >1.5x ULN) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hours |

In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

The corrected calcium level in mg/dL = measured calcium level in mg/d + 0.8x (4 – albumin in g/dl).

Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome.

A listing of subjects with TLS (reported as an adverse event and subjects with laboratory TLS) will be provided.

## 12.4. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of medication (>60 days or ≤60 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. SAEs will be summarized up to 60 days after last infusion. Separate summaries will also be provided for study treatment-related SAEs, fatal SAEs and study treatment related fatal SAEs. The summary tables will be displayed in descending order of total incidence OR incidence by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs

- Non-Fatal SAEs.

## 12.5. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation of Study Treatment

- AEs leading to Withdrawal from the Study

- AEs Leading to Dose Interruptions/Delays

- AEs Leadings to Dose Reductions

## 12.6.    Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

## 12.7.    Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized for each parameter by scheduled assessment.   The proportion of subjects with values outside the reference range for each of these laboratory parameters will be summarized by scheduled assessment and overall at any post-baseline assessment.

The CTCAE v4.0 / IWCLL Grading Scale for Hematological Toxicity will be used to programmatically assign grades to the laboratory values.  The laboratory values will be summarized by frequency and percentage of subjects at each time interval by maximum grade.  The worst grade per subject per time interval will be reported along with the worst grade per subject.

Summary statistics of laboratory values and changes from baseline at each assessed time interval will include count, mean, median, standard deviation, minimum, and maximum. Baseline is defined as the assessment closest to but prior to first dose (e.g. day 1 if available otherwise screening).

Summaries of subject shifts in grade will be provided.  These summaries will display the number and percentage of subjects with a maximum grade during each assessment time based on their baseline grade.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia

Separate summary tables for hematology and chemistry laboratory tests will be produced.

Detailed derivation of baseline assessment is specified in Section 9.2.7.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

The hepatobiliary laboratory values will also be summarized.

Listings for lab data for subjects with abnormalities of potential clinical concern will be provided. Figures for median hemoglobin/neutrophil count/platelet count for all subjects, and for all subjects excluding those who received blood supportive care products over time will also be generated.

### 12.7.1.    Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided.

Possible Hy's law cases are defined as any elevated ALT>3×ULN and total bilirubin≥2×ULN (≥35% direct birlirubin; bilirubin fractionation required); ALT>8 XULN; ALT ≥5XULN for more than 2 weeks.

### 12.8.    Other Safety Measures

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

### Vital Signs

Vital sign data, as well as change from baseline, will be summarized for each parameter by scheduled assessment.  Summary statistics of values and changes from baseline at each assessed time interval will include count, mean, median, standard deviation, minimum, and maximum.  Baseline is defined as the assessment closest to but prior to first dose without time (e.g., Day 1 if available otherwise screening).

 Summaries of increases in each vital sign at each planned assessment time and the worst-case post baseline value will be produced.  Increases will be categorized as follows:

- Systolic Blood Pressure:  'Any Grade Increase', 'Increase to Grade 2 (140-159)' and 'Increase to Grade 3 (≥160)'

- Diastolic Blood Pressure: 'Any Grade Increase', , 'Increase to Grade 2 (90-99)', 'Increase to Grade 3 (≥100)'

- Heart Rate: 'Decrease to <60', 'Increase to > 100'

- Temperature: 'Decrease to ≤35', 'Increase to ≥38'

Summaries of shift from baseline values for each planned assessment time and the worst-case post baseline will be provided for all vital signs.  Shifts will be categorized at baseline and each planned assessment times as follows:

- Systolic Blood Pressure:  '<120', '120-139', '140-159', '≥160'

- Diastolic Blood Pressure: '<80', '80-89', '90-99', '≥100'

- Heart Rate: '<60', '60-100', '>100'

- Temperature: '≤35', '36-37', '≥38'

Vital signs (blood pressure, heart rate, temperature, respiration rate, and weight) will be listed for each subject.

## Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

## ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings at screening/baseline will be provided.

## Organ Examination

The number and percentage of subjects with normal or enlarged organs based on liver and spleen examination by palpation/CT scan will be summarized by scheduled visits.

A supporting listing will also be provided.

# 13.     HEALTH OUTCOMES ANALYSES

All analyses described in this section will be performed using the ITT population. Data from all questionnaires, including translated versions, will be pooled for analysis.

The EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D should be administered at baseline and at treatment clinic visits; Days 1 and 85, and follow-up visits post treatment; every 3 months through Month 60. The Health Change Questionnaire should be administered at all the aforementioned post-baseline visits. If a subject demonstrates disease progression, the measures should be completed at the progression visit and again one time after determination of progression. If a subject in PD will be available and willing, post-PD questionnaires may be administered through the date that would correspond to the subject's Month 60 visit. If a subject withdraws from the study then the PRO questionnaires should be administered at the point of withdrawal.

## 13.1.     Patient Reported Constitutional Symptoms ('B-Symptoms') Score

**Background:**

The EORTC QLQ-C30 and QLQ-CLL16 module include items asking about symptoms due to CLL and other problems commonly associated with CLL or its treatment, such as

increase risk of infections. To provide a clear indication of the change in constitutional or 'B'-symptoms, ████████████████████████████████████████████████████████, namely, need to rest (C30 item 10), felt weak (C30 item 12), tired (C30 item 18), weight loss (CLL item 31), temperature changes (CLL item 35), night sweats (CLL item 36) lethargic (CLL item 39), slowed down (CLL item 40). This endpoint labeled as 'B-symptoms' score is proposed to provide patient reported data that might be supportive of the 'B-symptoms' clinician rating as well as record improvement in symptoms with each therapy. ███████████ ████████████████████████████████████████████████████ ████████████████████████

**Calculation of patient reported B-symptoms score**
Since the psychometric validation has not been conducted at the time of RAP development, ████████████████████████████████████████████████ ████████████████████████████████████

**Calculating the 'fatigue' subscore:**

There are five items, namely, need to rest (C30 item 10), felt weak (C30 item 12), tired (C30 item 18), lethargic (CLL item 39) and slowed down (CLL item 40) that are reflective of 'extreme fatigue' (one of the four B-symptoms). The fatigue subscore is therefore calculated as follows:

    a.    Compute the mean if at least 3 of the 5 items have a score of 3 or more. XEF = Mean of (Q10, Q12, Q18, Q39, Q40)

    b.    Carry out a linear transformation to convert to a 0-100 scale: TEF = (XEF - 1) / 3 *100

    c.    If less than 3 of the items have a valid score treat the scale as missing.

**Calculating the 'weight loss', 'fever' and 'night sweats' subscores**
Since there is only one item reflective for each of the three B-symptoms (weight loss, night sweats and fever), each of these items are treated individually. Therefore, a subscore for each of the three items will be calculated if the subject scored 3 or more for that item. These scores then should be linearly transformed to a 0-100 scale as follows:

- WL: Weight Loss (item 31) WL = (Q31 - 1) / 3 * 100
- TC: Temperature changes (item 35) TC = (Q35 - 1) / 3 * 100
- NS: Night sweats (item 36) NS = (Q36 – 1) / 3 * 100

If a subject does not respond to any one of the 3 items (QLQ-CLL item 31, QLQ-CLL item 35 and QLQ-CLL item 36), the score for that item will be deemed 'missing'.

Depending on the number of subscores reported, the B-symptom score will be calculated as a mean of those sub-scores

**Summaries and Analyses:**

Changes from baseline scores over time in patient reported B-symptoms score will be analyzed with a repeated measures analysis of covariance (ANCOVA). Analyses will be carried out using PROC MXED in SAS: baseline score, age group, performance status, and Binet stage, time, treatment, baseline by time, and treatment by time interaction will be fitted as fixed effects, and time will be treated as the repeated variable within subject. Restricted maximum likelihood (REML) will be used to estimate the parameters of the model. An unstructured variance-covariance matrix in the repeated measures model will be used. The model may be modified if required in order to obtain convergence.

Treatment comparisons, including estimated treatment difference, 95% confidence intervals and associated p-values will be provided.

## 13.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia 16 item module (EORTC QLQ-CLL 16)

**Background:**

Subjects respond to the items on a four point Likert scale ranging from 1 *'Not at all'* to 4 *'Very much'* and are asked to think back over the past week when responding to 12 of the items and the past four weeks for the remaining four items which are all included in the hypothesized Infection domain.

Hypothesized scoring for the QLQ-CLL16 module has been recommended but thus far has not been validated. QLQ-CLL16 domain scores will also be developed based upon the recommendations of the authors and, ███████████████████████
███████████████████████████████████████

**Summaries and Analyses:**

The same analyses for each domain will be conducted as described for patient reported B-symptoms.

**Scoring procedure for the EORTC QLQ-CLL16**

The QLQ- CLL16 module includes 16 items, consisting of 4 multi-item scales and 2 single-items. The following section is the scoring algorithms for the scales described in a similar fashion to the scoring for the EORTC QLQ-C30.

For the multi-item scales and single-item scales a high score is equivalent to worse or more symptoms/problems.

**Multi-item Scales**
**FA: Fatigue Scale:** Items 39, 40

a. Compute the mean if at least one item has a valid score. XFA = Mean of (Q39, Q40)
b. Carry out a linear transformation to convert to a 0-100 scale: $FA = (XFA - 1) / 3 * 100$

c. If both items do not have a valid score treat the scale as missing.

**TSE: Treatment Side Effects Scale:** Items 31, 32, 35, 37
a. Compute the mean if at least 2 of the items have a valid score. XTSE = Mean of (Q31, Q32, Q35, Q37)
b. Carry out a linear transformation to convert to a 0-100 scale: TSE = (XTSE - 1) / 3 * 100
c. If less than 2 of the items have a valid score treat the scale as missing.

**DSE: Disease Effects Scale:** Items 33, 34, 36, 38
a. Compute the mean if at least 2 of the items have a valid score. XDSE = Mean of (Q33, Q34, Q36, Q38)
b. Carry out a linear transformation to convert to a 0-100 scale: DSE = (XDSE - 1) / 3 * 100
c. If less than 2 of the items have a valid score treat the scale as missing.

**IN: Infection Scale:** Items 43, 44, 45, 46
a. Compute the mean if at least 2 of the items have a valid score. XIN = Mean of (Q43, Q44, Q45, Q46)
b. Carry out a linear transformation to convert to a 0-100 scale: IN = (XIN - 1) / 3 * 100
c. If less than 2 of the items have a valid score treat the scale as missing.

**B. Single-item Scales**, Items 41 and 42
These items are treated individually and should be linearly transformed to a 0-100 scale.
**SP:** Social problems (item 41) SP = (Q41 - 1) / 3 * 100
**FH:** Future health (item 42) FH = (Q42 - 1) / 3 * 100

## 13.3. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30)

**Background:**

The 30 items of the EORTC QLQ-C30 are scored in the following domains: Physical Functioning (5 items), Role Functioning (2 items), Emotional Functioning (4 items), Cognitive Functioning (2 items), Social Functioning (2 items), Pain (2 items), Fatigue (3 items), Nausea and Vomiting (2 items). There are also five single item symptom scores (Insomnia, Loss of Appetite, Constipation, Diarrhea, and Dyspnea), a single item asking about Financial Difficulties and a global health status/quality of life domain consisting of two items. Subjects respond to the items on a four point Likert scale ranging from 1 '*Not at all*' to 4 '*Very much*' and are asked to think back over the past week when responding to the items.

**Summaries and Analyses:**
The same analyses for each domain will be conducted as described for patient reported B-symptoms.

**Scoring method:**

|  | Scale | Question numbers |
|---|---|---|
| Global health status/QOL | QL | 29,30 |
| Functional Scales |  |  |
| Physical functioning | PF | 1 to 5 |
| Role functioning | RF | 6,7 |
| Emotional functioning | EF | 21 to 24 |
| Cognitive functioning | CF | 20, 25 |
| Social functioning | SF | 26, 27 |
| Symptom Scales/items |  |  |
| Fatigue | FA | 10, 12, 18 |
| Nausea and vomiting | NV | 14, 15 |
| Pain | PA | 9, 19 |
| Dyspnoea | DY | 8 |
| Insomnia | SL | 11 |
| Appetite loss | AP | 13 |
| Constipation | CO | 16 |
| Diarrhoea | DI | 17 |
| Financial difficulties | FI | 28 |

If items $I_1$, $I_2$, $I_3$,…, $I_n$ are included in a scale, the procedure is as follows:

- Raw score
  Calculate the raw score. Raw Score=RS=$( I_1 + I_2 + I_3 +… + I_n )$/n

- Linear transformation
  Apply the linear transformation to 0-100 to obtain the score S,
  Functional scales: S = {1-(RS-1)/range} x 100
  Symptom scales/items: S = {(RS-1)/range} x 100
  Global health status/QoL: S = {(RS-1)/range}} x 100

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored to 1 to 4, giving range = 3. The expectations are the items contributing to the global health status /QoL, which are 7–point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have range = 1.

## 13.4.   EuroQoL Five-Dimension (EQ-5D)

**Background:**

The EQ-5D is comprised of a 5-item health status measure and a visual analogue rating scale/feeling thermometer. These components are administered independently which results in the derivation of two utility measures. It is a simple, effective, validated and globally accepted generic instrument which is being used in this study as a two part measure (part one is the five dimensional Health State Classification and part two is the visual analogue scale 'Thermometer') [EuroQol, 1990] .

The first utility value will be derived from the five domains of the EQ-5D in those countries where a scoring algorithm has been developed and the second utility value will be derived from the feeling thermometer.

**Summaries and Analyses:**

The same analyses for each domain will be conducted as described for patient reported B-symptoms.

Using the five dimensional Health State Classification [EuroQol EQ-5D User Guide,1992], subjects are asked to respond to five questions on different aspects of their health status that assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is responded to on a three-point scale which indicates the level of impairment (level 1 = no problem; level 2 = some or moderate problem(s) and level 3 = unable, or extreme problems). This generates a unique description of the subjects' health status, which is valued between zero (representing death) and one (representing perfect health) according to the methodology developed by the authors [EuroQol EQ-5D User Guide,1992]. Negative health status describes health state worse than death. Details of the method for calculating this score are provided in Section 13.5.

The five dimensional Health State Classification is also being used to generate descriptive data from the questionnaire which will be used to profile subjects at the visits they fill out the questionnaire. The differences in subjects' health status at each point with respect to baseline should be calculated.

As well as completing the five dimensional Health State Classification to generate a single health status index and a health profile, subjects are asked to rate their current health status using the visual analogue scale 'Thermometer'. The 'Thermometer' has endpoints of 100 (best imaginable health state) and 0 (worse imaginable health state). The subject rates their current health state by drawing a line from the box marked 'Your health state today' to the appropriate point on the 'Thermometer' scale. If subjects are visually impaired it is appropriate for the investigator to read aloud the instructions within the questionnaire and to record the responses on behalf of the subject.

## 13.5. Health Change Questionnaire

The health Change Questionnaire (HCQ) used is a nine item scale that asks the patient to rate change in status since beginning treatment on this study. Scale choices are :

A great deal better
Moderately better
A little better
Almost the same, hardly any better
Unchanged
Almost the same, hardly any worse
A little worse
Moderately worse
A great deal worse

A summary of the percentage of subjects in each category will be provided.

# 14. PHARMACOKINETIC ANALYSES

The reconciliation of the pharmacokinetic Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Data Sciences - Oncology, GlaxoSmithKline.

The merge of pharmacokinetic concentration data and CRF data to generate a dataset with actual blood sampling times, actual time relative to dosing, and concentrations will be performed after DBF by, or under the direct auspices of, Oncology Quantitative Sciences (Programmer), GlaxoSmithKline.  Analysis datasets will be created according to CDISC/ADaM standards.

Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Oncology Quantitative Sciences (Statistician), GlaxoSmithKline.

Unless otherwise stated, all tables, figures and listings in this section will be based on the Pharmacokinetic population, and all summaries, figures and data listings will use treatment labels as specified in Section 7.

## 14.1. Drug Concentration Measures

Concentrations of ofatumumab in plasma will be listed by actual relative time and summarized by nominal time. Standard summary statistics will be calculated (i.e., mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document GUI_51487, "Non-Compartmental Analysis of Pharmacokinetic Data", for more information regarding the handling of ofatumumab plasma concentrations below the assay's lower limit of quantification (NQ).

Individual plasma concentration-time profiles and median/mean profiles by treatment group will be plotted using actual elapsed time for individual plots and nominal time for median/mean profiles. Each of the figures will contain one plot on the untransformed scale (i.e., a linear plot) and one plot on the log-transformed scale (i.e., log-linear plot).

Any concentration data excluded from the derivation of pharmacokinetic parameters by CPMS should be omitted from any figures and summaries and flagged with an asterisk in the relevant data listings, with a footnote to indicate that these values have been omitted from subsequent analyses.

## 14.2. Deriving and Summarizing Pharmacokinetic Parameters

For subjects in the active treatment group, the pharmacokinetic parameters $C\tau$ and Cmax will be determined directly from the concentration-time data and will be extracted from the dataset by the Programmer. At each visit, the pre-dose sample will correspond to $C\tau$ and the 0.5 hr after the end of infusion sample will correspond to Cmax. For the purpose of summarizing geometric mean $C\tau$ values, original NQ values will be imputed to half

the BQL (50 ng/mL).   In addition, concentrations at 3 and 6 months after last dose will be extracted from the data by the programmer and labelled as C3mos and C6mos.

Other pharmacokinetic parameters will be derived based on the population pharmacokinetic analysis (Section 14.3).

All derived pharmacokinetic parameters will be listed. For each of these parameters, the following summary statistics will be calculated for each study occasion for which pharmacokinetic parameters were calculated:  median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean, and standard deviation of logarithmically transformed data. All pharmacokinetic parameters will be reported to at least three significant digits, but to no more significant digits than the precision of the original data.

## 14.3.      Population Pharmacokinetic Analyses

The population pharmacokinetic model reported in GlaxoSmithKline Document Number 2012N156806_00 for ofatumumab monotherapy will be used to generate *post hoc* ofatumumab pharmacokinetic parameter estimates for the individual subjects in Study OMB112517 using the NONMEM software.  BIN will be initialized based on the geometric mean baseline $CD5^+CD19^+$ cell counts in Study OMB112517.  Since Study OMB112517 is being conducted in subjects with relapsed CLL, this *post hoc* parameter estimation will be performed both with and without the scaling of BOND; in the previous model, BOND was scaled for relapsed/refractory CLL and was not scaled for fludarabine-refractory CLL.

Based on the individual *post hoc* parameters, dosing information, and sample collection times, ofatumumab plasma concentrations at the time of sample collection will be predicted for each subject.  If there is evidence of bias, further model refinement may be needed. Model evaluation will consist of comparison of model-predicted and observed concentrations.

Based on the individual *post hoc* parameters, derived pharmacokinetic parameter values (e.g., CL, Vss, t½, AUC(0-τ)) will be generated on certain dosing occasions, data permitting.

## 14.4.      Statistical Analyses

Ofatumumab concentration-time data and pharmacokinetic parameter values will be listed for each subject and summarized by dosing occasion using descriptive statistics as described in Section 14.1 and Section 14.2.

The following tables and listings will be created:

- Summary of Plasma Ofatumumab Concentration-Time Data

- Summary of Derived Plasma Ofatumumab Pharmacokinetic Parameter Data

- Listing of Derived Plasma Ofatumumab Pharmacokinetic Parameter Data

- Listing of Plasma Ofatumumab Concentration-Time Data

Additionally, the figures listed below will also be provided:

- Mean Plasma Ofatumumab Concentration-Time Plot

- Median Plasma Ofatumumab Concentration-Time Plot

- Individual Plasma Ofatumumab Concentration-Time Plots

- Geometric Mean CL over Time

- Geometric Mean Targeted-Mediated CL over Time

- Median Ofatumumab Cmax over Time Plot by response categories

- Median Ofatumumab $C\tau$ over Time Plot by response categories
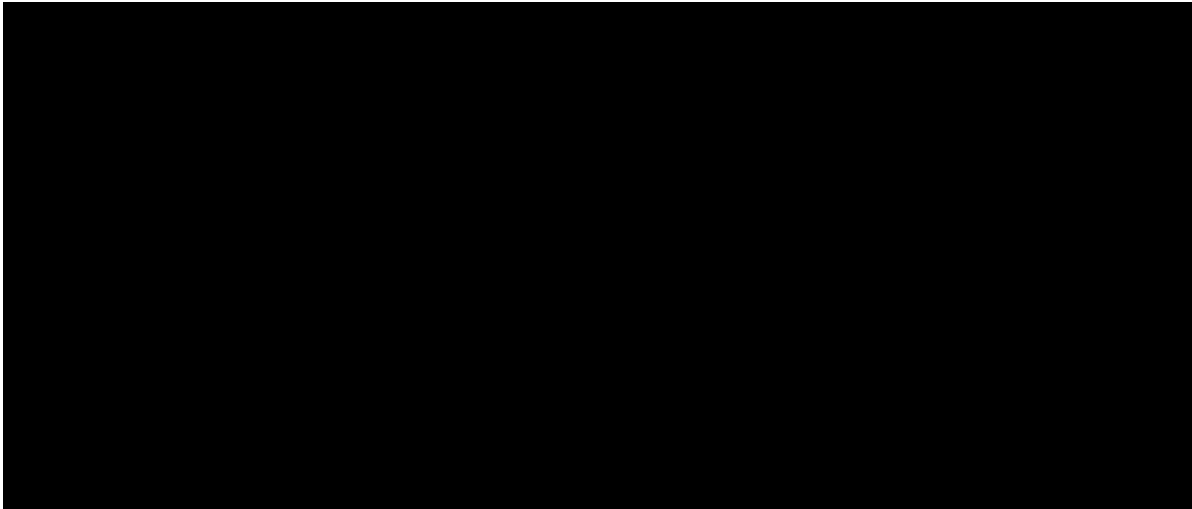
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# 17.     ATTACHMENTS

## 17.1.     Table of Contents for Data Display Specifications

The table of contents for the data displays as well as the data display specifications will be available as a separate document from the RAP.

# NOVARTIS

Clinical Development

Ofatumumab/Arzerra®

OMB157C2301 / NCT01039376

**A phase III, open label, randomized, multicenter trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy**

**Statistical Analysis Plan (SAP) – analysis based on 280 PFS events**

| | |
|---|---|
| Author: | |
| Document type: | SAP Documentation |
| Document status: | Final |
| Release date: | 02- June-2017 |
| Number of pages: | 25 |

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| bid | bis in diem/twice a day |
| CLL | chronic lymphocytic leukemia |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| FAS | Full Analysis Set |
| eCRF | Electronic Case Report Form |
| HR | Hazard Ratio |
| IVR | Interactive Voice Response |
| IWR | Interactive Web Response |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| mPFS | Median Progression Free Survival |
| NCI | National Cancer Institute |
| o.d. | Once Daily |
| OS | Overall Survival |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PRO | Patient-reported Outcomes |
| qd | Qua'que di'e / once a day |
| QoL | Quality of Life |
| RAP | Reporting and Analysis Process |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1      Introduction

OMB157C2301 (OMB112517)  is a Phase III, open-label, randomized, multicenter trial to evaluate efficacy and safety of ofatumumab (OFA) maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy using a parallel design.

**Background:** The primary endpoint has been met at the protocol-defined interim analysis that was triggered after 187 events were observed (data cut-off date on June, 19 2014). OFA maintenance demonstrated a significant improvement in PFS ($p<0.0001$) as assessed by the investigator over Obs (OFA maintenance: median [mPFS] of 29.4 months, Obs: mPFS of 15.2 months; HR 0.50; 95% CI 0.38, 0.66). A 120 day Safety update has been performed (safety update data cut-off (28-Feb-2015)).

Statistical Analyses Plan (SAP) for the current planned analysis is based on the efficacy and safety data collected up to 20-Feb-2017, the cut-off date when 280 PFS events or death occurred in the study. The analysis results will be used for descriptive purpose only. In particular supportive analysis to the primary endpoint will be provided.

All analyses that were done for the interim CSR (Dated 11-Sep-2014, Document # 2014N213614_00) will be done for this analysis _**except**_ the following outputs (see Table 1).

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Besides that, the following outputs will be added (Table 3.0929 , Table 3.1800, Table 3.0421) on Table of content (TOC) for this analysis based on 280 PFS events (see Appendix 1).

- Summary of SAEs before or after start of next anticancer therapy (Table 3.0929)
- Time since last treatment with Ofatumumab for patients who have not started next anticancer therapy (Table 3.1800)
- Summary of Fatal SAE (Table 3.0421)

All the data rules will follow the interim CSR ones. The TOC for the  analysis based on 280 PFS events is documented in a separate document, attached for reference in Appendix 1.

# 2 Appendix 1

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Clinical Development

Ofatumumab/Arzerra®

OMB157C2301 / NCT01039376

# A phase III, open label, randomized, multicenter trial of ofatumumab maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy

## Statistical Analysis Plan (SAP) – Final Analysis

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## List of abbreviations

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| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| bid | bis in diem/twice a day |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| FAS | Full Analysis Set |
| eCRF | Electronic Case Report Form |
| IVR | Interactive Voice Response |
| IWR | Interactive Web Response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| o.d. | Once Daily |
| OS | Overall Survival |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PRO | Patient-reported Outcomes |
| qd | Qua'que di'e / once a day |
| QoL | Quality of Life |
| RAP | Report and Analysis Process |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1      Introduction

OMB157C2301 (OMB112517) is a Phase III, open-label, randomized, multicenter trial to evaluate efficacy and safety of ofatumumab (OFA) maintenance treatment versus no further treatment in subjects with relapsed chronic lymphocytic leukemia (CLL) who have responded to induction therapy using a parallel design.

**Background:** The primary endpoint has been met at the protocol-defined interim analysis that was triggered after 187 events were observed (data cut-off date on June, 19 2014). OFA maintenance demonstrated a significant improvement in PFS (p<0.0001) as assessed by the investigator over Obs (OFA maintenance: median [mPFS] of 29.4 months, Obs: mPFS of 15.2 months; HR 0.50; 95% CI 0.38, 0.66). A 120 day Safety update has been performed (safety update data cut-off (28-Feb-2015)).

Then, a planned analysis has been performed based on efficacy and safety data collected up to 20-Feb-2017, the cut-off date when 280 PFS events or death occurred in the study. The analysis of PFS based on investigator-assessment showed an estimated 45% risk reduction in the OFA maintenance arm compared to the Obs arm (Hazard ratio: 0.55 with 95% CI: 0.43,0.70). The median PFS times (95% CI) are 34.17 months (29.70, 38.01) and 16.89 months (12.98, 20.37) respectively for OFA maintenance arm and Obs arm.

**Analysis Plan:** The current version of the statistical analysis plan (SAP) for the final analysis is based on data collected up to last patient last visit. All the analysis conventions will follow the previous SAP (published on 02-Jun-2017 and addendum on 11-Jan-2018). Final analysis of PFS was performed at protocol defined 280 events and will not be updated. The analysis results will be used for descriptive purpose only.

The population pharmacokinetic analyses ███████████████████████████████████████ using the established PopPK model [GlaxoSmithKline Document Number 2012N156806_002] will not be repeated, as the PopPK model takes into account data from Cycle 1 Week1, Cycle 1 week 9 and Cycle 4. The majority of this data was already available at the time of the data cut-off 19-Jun-2014 and described in the PopPK report [GlaxoSmithKline Document Number 2014N215557_00] in the interim CSR.

In case psychometric validation of B-symptoms score and QLQ-CLL16 domain scores will be performed, this would be documented in separate document and will not be part of the final analysis CSR.

 The table below contains the list of outputs that will be produced for this final analysis.

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