NOVARTIS

Clinical Development

# GSK1841157

Protocol OMB112517 / 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 responsed to induction therapy

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# Amendment 6

## Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound **GSK1841157**, the purpose of this protocol Amendment **06** is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of February 2016:

**480** patients have been randomized into the study in **14** countries;

7 patients in ofatumumab treatment

99 patients in study follow-up (63 for ofatumumab arm and 36 for observation arm)

191 patients in survival follow-up.

The changes described in this amended protocol require Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation.

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities.

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

**Revision Chronology**

| **GlaxoSmithKline Document Number** | **Date** | **Version** |
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| UM2008/00446/00 | 2009-JUL-14 | Original |
| UM2008/00446/01 | 2009-NOV-11 | Amendment No.: 01 |
| UM2008/00446/02 | 2009-NOV-20 | Amendment No.: 01:.(Republished) |
| Addition of baseline MRD, [redacted] post-PD PRO and clarifications | | |
| UM2008/00446/03 | 2010-MAY-21 | Amendment No. 2 |
| Added study name and clarifications, modified I/E | | |
| UM2008/00446/04 | 2013-FEB-07 | Amendment No.: 3 |
| Country specific amendment: At the request of the French regulatory agency related information from the Study Procedures Manual (SPM) was added into Section 6.4.6 | | |
| UM2008/00446/05 | 2013-DEC-17 | Amendment No. 4 |
| FDA request for additional HBV information and protocol clarifications | | |
| UM2008/00446/06 | 2014-AUG-26 | Amendment No. 5 |
| As the significance level was met at the interim analysis of efficacy, further enrollment in the study will be discontinued. | | |
| Novartis | 2016-APR-01 | Amendment No. 6 |
| Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents.<br><br>Make administrative changes to align with Novartis processes and procedures. | | |

**SPONSOR SIGNATORY**

_____ _____

[redacted] Date

[redacted],
Novartis Pharmaceuticals Corporation

# SPONSOR INFORMATION PAGE

Clinical Study Identifier: OMB112517

**Sponsor Contact Information:**

Novartis Pharmaceuticals Corporation

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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**Sponsor Serious Adverse Events (SAE) Contact Information:**

Please refer to the Study Procedures Manual.

For study conduct questions not related to patient safety, the first line of contact should be with the designated local country company contact. In the event that the designated company contact is not available please contact the medical lead.

**Regulatory Agency Identifying Number(s):**

IND number: 11, 719
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# INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol OMB112517

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

| | | |
|---|---|---|
| Investigator Name: | | |
| Investigator Address: | | |
| Investigator Phone Number: | | |
| | | |
| Investigator Signature | | Date |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADCC | Antibody-dependent cell mediated cytotoxicity |
| AE | Adverse Event |
| AIHA | Autoimmune hemolytic anemia |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| B-CLL | B-cell chronic lymphocytic leukemia |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CDC | Complement-dependent cytotoxicity |
| CL | Clearance |
| CLL | Chronic lymphocytic leukemia |
| Cmax | Maximum observed concentration |
| Cmin | Minimum observed concentration or predose (trough) concentration |
| CNS | Central nervous system |
| CR | Complete remission/response |
| eCRF | Electronic case report form |
| CRu | Complete remission/response unconfirmed |
| CT-Scan | Computed tomography scan |
| EC | Ethics committee |
| ECOG | Easter Cooperative Oncology Group |
| EOI | End of infusion |
| EORTC QLQ-C30 | European organization for research and treatment of cancer, core 30 item questionnaire |
| EORT QLQ-CLL16 | European organization for research and treatment of cancer, quality of life questionnaire chronic lymphocytic leukemia 16 item module |
| EQ-5D | Euro-QoL five dimension |
| FISH | Fluorescent in-situ hybridization |
| FL | Follicular lymphoma |
| GSK | GlaxoSmithKline |
| HAHA | Human anti-human antibodies |
| HB(V) | Hepatitis B(Virus) |
| HCG | Human chorionic gonadatropin |
| HIV | Human immunodeficiency virus |
| h | Hour(s) |
| IB | Investigator Brochure |
| IDMC | Independent data monitoring committee |
| Ig | Immunoglobulin |
| IRC | Independent review committee |
| ITT | Intent to treat |
| IWCLL | International workshop for chronic lymphocytic leukemia |
| LDH | Lactic acid dehydrogenase |
| MedDRA | Medical dictionary for regulatory activities |

| | |
|---|---|
| mAb | Monoclonal antibody |
| mL | Milliliter |
| MRD | Minimal residual disease |
| MTD | Maximum tolerated dose |
| NCI-WG | National Cancer Institute-sponsored working group |
| NONMEM | Nonlinear mixed-effects modeling approach |
| OR | Overall response |
| ORR | Overall response rate |
| nPR | Nodular partial remission/response |
| PD | Progressive disease |
| PFS | Progression free survival |
| PGx | Pharmacogenetics |
| PLL | Prolymphocytic leukemia |
| PP | Per protocol |
| PR | Partial remission/response |
| PRO | Patient reported outcome |
| RAP | Reporting and analysis plan |
| SAE | Serious adverse event |
| SD | Stable disease |
| SPM | Study procedures manual |
| t½ | Terminal half-life |
| tmax | Time at which maximum concentration is observed |
| TTP | Time to progression |
| VAS | Visual analog scale |
| vs. | Versus |
| Vss | Volume of distribution at steady state |
| WHO | World Health Organization |
| ZAP-70 | Zeta-chain-associated protein kinase 70 |

# PROTOCOL SUMMARY

## Rationale

Despite progress in therapy, chronic lymphocytic leukemia (CLL) remains incurable. Response rates are promising but remain transient and all subjects eventually relapse. There is currently no approved maintenance therapy. The objective of this study is to evaluate if maintenance therapy with ofatumumab will prolong remission duration.

## Objective(s)

The primary objective is to evaluate progression free survival (PFS) of ofatumumab maintenance treatment versus no further treatment after remission induction in subjects with relapsed CLL.

Secondary objectives are to evaluate clinical benefit, safety, tolerability and health-related quality of life of subjects treated with ofatumumab versus no further treatment. An additional secondary objective is to evaluate the pharmacokinetics in CLL subjects on maintenance ofatumumab.

## Study Design

This is an open-label, two-arm, randomized, Phase III study of ofatumumab or no further treatment in subjects in CR or PR after remission induction treatment for relapsed CLL.

A total of 280 events are needed for the study to have 80% power to detect a 40% difference in PFS between study arms. Subjects in CR or PR after remission induction treatment for relapsed CLL will be randomized in a 1:1 ratio to receive either ofatumumab maintenance or no further treatment in order to obtain 478 evaluable subjects (assuming a 10% drop out).

An independent data monitoring committee (IDMC) will be used for 2 interim analyses. The first interim analysis will assess safety endpoints after 100 subjects in the maintenance arm have been treated for at least 6 months. The second interim analysis of will assess efficacy of the primary endpoint, progression free survival, as well as evaluate safety and will be performed when 2/3 of the total number of events have occurred (187 events) utilizing a conservative significance level (0.001). 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 final analysis will be conducted at the significance level of 0.0498. Further details are specified in the IDMC charter.

At screening, upon informed consent, peripheral blood samples, physical assessment, CT scan (to confirm CR or PR) will be obtained to determine disease status and study eligibility. Bone marrow examination may be done ONLY to confirm CR. Refer to Appendix 1: Time and Events for complete list of screening procedures.

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

During the treatment phase, subjects will be randomized 1:1 to receive either:

Arm A: ofatumumab as infusions every 8 weeks (The first dose will be 300mg followed 1 week later by 1000 mg and 1000 mg every 8 weeks thereafter for up to 2 years) or

Arm B: No treatment (i.e. observation only)

Blood samples, lymph node examination, spleen and liver measurement, and constitutional symptoms evaluation are performed every 8 weeks throughout the treatment phase. Follow-up assessments are performed every 3 months for 5 years to evaluate survival and disease status.

A bone marrow examination is required to confirm Complete Remission (CR) at least 2 months after completion of therapy and when a subject fulfills the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) requirements for Complete Remission (CR) [Hallek, 2008]. Previous results may be used or if not available, a bone marrow exam may be done at screening. If a subject's response improves to a CR while on study, then a bone marrow examination is required to confirm CR at least 2 months after response as per the updated IWCLL NCI-WG requirements for CR [Hallek, 2008]. Additionally, CT Scans are required at screening, for confirmation of a new CR, yearly while on study, and at disease progression.

## Study Endpoints/Assessments

### Primary Endpoint:

- Progression free survival (PFS), defined as the interval from randomization until disease progression or death

### Secondary Endpoints:

#### Clinical

- Improvement in response
- Time to next treatment
- Overall survival
- Progression-free survival after next-line therapy

- Time to progression after next-line therapy
- Changes in patient reported outcome (PRO) measures
- Changes in patient reported outcome (PRO) scores
- Improvement of ECOG performance status
- B-symptoms/Constitutional symptoms/fatigue
- Incidences 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 myelosuppression (anemia, neutropenia, thrombocytopenia)
- Frequency of transfusions
- Incidence of Autoimmune Hemolytic Anemia (AIHA)
- Human Anti Human Antibodies (HAHA)
- IgG, IgA, IgM serum levels

**Disease markers**

- Minimal Residual Disease (MRD)
- B-cell monitoring
- Prognostic markers correlating with clinical response:
  - Cytogenetics by fluorescent in situ hybridization (FISH)
  - $IgV_H$ mutational status
  - β2 microglobulin
  - Changes in complement levels

**Pharmacokinetics**

- Plasma ofatumumab concentrations

# 1. INTRODUCTION

## 1.1. Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia (CLL or B-CLL) is a chronic leukemia in which peripheral, clonal B-cells progressively accumulate. The disease is a hematological neoplasm of unknown etiology, characterized by monomorphic small, round B-lymphocytes in the peripheral blood, bone marrow, and lymph nodes that aberrantly co-express T-cell (CD5+) and B-cell (CD19+, CD23+) cell surface markers, with a low expression of CD20. Over the past decade, new information suggests B-CLL originates from antigen-stimulated mature B-lymphocytes, which either avoid cell death through the effect of external signals, or die by apoptosis, but are replenished by proliferating precursor cells [Chiorazz, 2005].

Chronic Lymphocytic Leukemia is the most common type of leukemia in the western world, accounting for 40% of all leukemia types in individuals over the age of 65 [Oscier, 2004]. It is estimated that in the US alone 15,110 adults (8,750 men and 6,360 women) will be diagnosed and 4,390 adults will die of CLL in 2008 [Jemal, 2008]. CLL follows a variable clinical course with overall survival times ranging from months to decades. Median survival from diagnosis is approximately 10 years in the overall CLL population, but is only 18 months for patients with advanced disease [Nabhan, 2004]; and to 9-13 months for CLL cases refractory to fludarabine [Byrd, 2004].

Traditional clinical staging systems devised by Rai and Binet are the simplest and still best validated means of assessing prognosis for CLL patients [Rai, 1975; Binet, 1981], however, there is substantial heterogeneity in the course of the disease within defined stages. In recent years molecular and cellular markers have been correlated with disease aggressiveness. These allow further stratification of subjects into risk groups such as: abnormal cytogenetics, CD38, ZAP-70, beta-2-microglobulin, $IgV_H$ mutational status [Oscier, 2004; Abbott, 2006; Shanafelt, 2007; Zenz, 2007]. So far, unfortunately these parameters have only limited use in determining when and what type of therapy to use [Binet, 2006]. One exception is that p53 deletion was shown to predict for non-response to purine analogues like fludarabine and for poor clinical outcome, but is not predictive for response to a particular therapy [Dohner, 1995].

The prevalence of CLL increases with age and the median age at the time of diagnosis is 65 to 70 years [Redaelli, 2004]. Approximately 50% of patients are initially asymptomatic and are observed for several years before treatment is needed, therefore more than half of patients who finally require therapy are older than 70 years.

## 1.2. Current Treatment for CLL

Over the last two decades, the treatment goal of CLL has undergone a paradigm shift changing from simple symptom palliation to attainment of maximal disease control and consequently prolonged survival [Tam, 2007]. A first generation of clinical trials assessing single agent chemotherapy was followed by a second generation of trials investigating combination chemotherapies which showed no significant difference in overall survival [Shanafelt, 2007]. Subjects receiving monotherapy or combination

chemotherapy experience a range of different levels of toxicity, with the more aggressive therapies being also more toxic and choice of therapy has to be performed as a risk based approach [Abbott, 2006]. Currently, FCR seems to be the most potent regimen, both in previously untreated and relapsed patients [Hallek, 2008; Tam 2008]. In general, as with most clinical studies, all these trials endorse strict eligibility criteria often excluding subjects older than 65 plus those with inferior organ function. This causes a limitation in assessing the suitability of these studied therapy regimen regarding their efficacy and tolerability for the treatment of unselected patients in practice of which the majority is older and in poor health.

Despite numerous studies with various therapies demonstrating overall and complete response rates in both previously untreated and relapsed or refractory CLL patients [Hallek, 2001; Huhn, 2001; O'Brien, 2001a; O'Brien, 2001b; Keating, 2002; Wierda, 2005], there is no curative treatment and the disease is marked by relentless relapse. There is no current maintenance therapy to prolong the time between relapses improving the overall quality of life or to improve overall survival.

The biological behavior of CLL is similar to follicular lymphoma (FL), wherein the disease is incurable and the clinical course is characterized by a high relapse rate. After relapse, both the response rate and progression-free survival after subsequent salvage regimens steadily decrease [Montoto, 2002]. Recently, in relapsed FL patients, maintenance treatment with the chimeric CD20 mAb, rituximab, resulted in a median PFS of 51.5 months versus 14.9 months with observation only ($p<.001$). Significantly improved PFS was noted regardless of induction treatment (CHOP vs R-CHOP). Additionally, rituximab maintenance also improved overall survival at 3 years (85% vs 77%, $p=.011$) [van Oers, 2006]. Similar results of improved PFS and overall survival with rituximab maintenance in FL patients have been noted [Forstpointner, 2006; Hochster, 2009].

While rituximab monotherapy is not very effective in previously untreated or relapsed CLL patients, possibly due to the relatively low CD20 expression on CLL cells [Byrd, 2001], a recent small phase II study with rituximab consolidation and maintenance treatment showed a significantly longer response duration in patients with minimal residual disease (MRD)-positive CLL in first remission after fludarabine induction [Del Poeta, 2008].

## 1.3. Ofatumumab

Ofatumumab is a fully human monoclonal antibody (mAb), IgG1κ, targeting a unique epitope on the CD20 molecule expressed on human B-cells, resulting in increased binding affinity to CD20, prolonged dissociation rate, and increased cell kill due to greater CDC activity and similar ADCC activity, especially in low CD20 expressing cells [Teeling, 2006]. Thus, depletion of B-cells by ofatumumab treatment may provide clinical benefits to subjects with CD20-expressing cell tumors. In B-CLL, the goal of treatment is to achieve complete abnormal B-cell depletion in the blood and to induce an objective tumor response in the lymph nodes.

In a Phase I dose-ranging trial of ofatumumab 500mg (n=3), 1000mg (n=3), or 2000mg (n=27) given weekly x 4, 50% PR was observed in the 2000mg dose amongst relapsed CLL patients [Coiffier, 2008]. Objective response significantly correlated with maximum observed concentration (Cmax), minimum observed concentration (Cmin), area under the concentration-time curve (AUC), and half-life (t½) and survival endpoints correlated with exposure. The maximum tolerated dose (MTD) was not reached and treatment was well tolerated. Adverse events were limited to grade 1-2 infusion reactions and easily managed with premedication. Grade 3-4 neutropenia occurred in only 6% of patients. Non-opportunistic grade 1-2 infections were observed in 51% of patients.

Interim analysis for the pivotal trial evaluated 154 patients with refractory CLL (Study Hx-CD20-406). In the 138 evaluable patients, approximately half (59) were refractory to both fludarabine and alemtuzumab and the other patients were refractory to fludarabine and considered inappropriate for alemtuzumab due to bulky disease of the lymph nodes. An objective response rate of approximately 50% consisting of 30 partial responses was achieved in the fludarabine and alemtuzumab refractory group and an objective response rate of approximately 44% was achieved in the fludarabine refractory group including 1 complete response and 34 partial responses. In this study, ofatumumab was generally well tolerated by the patients. The most frequently reported adverse events (>15% frequency) were pyrexia, diarrhea, fatigue, cough, neutropenia, anemia and pneumonia. There were no unexpected safety findings.

Studies clearly indicate monoclonal antibodies (mAbs) play an important role in the treatment of CLL. Anti-CD20 mAbs with a low toxicity can be applied advantageously in subjects who cannot tolerate highly toxic treatments (i.e. advanced age), in combination with chemotherapy and as maintenance treatment. Ofatumumab preclinical data demonstrates superior CDC activity in CLL compared to rituximab. Based on this, it is suggested that ofatumumab's stronger B-cell depletion potential may translate into longer duration of treatment response.

## 1.4. Rationale

The purpose of this study is to assess the benefit of ofatumumab maintenance treatment in subjects in remission from relapsed CLL based upon:

1) the similarities in biological behavior between CLL and FL;
2) in relapsed FL, maintenance treatment with anti-CD20 MAb, rituximab is the standard of care;
3) results in a phase II study with rituximab induction and maintenance resulted in prolongation of PFS in MRD positive CLL in first remission after fludarabine;
4) ofatumumab has higher in vitro activity against CLL cells; and
5) ofatumumab has also demonstrated efficacy in refractory CLL as monotherapy (Study Hx-CD20-406).

## 1.5. Rationale for Closing Enrollment

At the start of the study, it was expected that the study would fully enroll prior to the IDMC review at 2/3 of the events. When the required number of events occurred prior to fully enrolling the study, but with the full number of evaluable subjects available, and

before the results were known, it was decided that if the primary endpoint met the predefined significance level of $p<0.001$, demonstrating clinical benefit for the ofatumumab arm, further enrollment would be discontinued. The independent data monitoring committee (IDMC) communicated that the significance level of $p<0.001$ for the primary endpoint at the interim analysis had been met. Additionally, the study had obtained the number of evaluable subjects required (the number of evaluable subjects at the time of the interim analysis was 479, with 478 evaluable required).

The conduct of the study will continue without modification, with continuation of the assessments of the efficacy and safety endpoints and no change in study design, in accordance with the IDMC recommendation. Currently, the standard of care is still observation, so that those subjects on the observation arm are receiving the standard of care and are not being jeopardized by continuation of observation. The recommendation of the IDMC was that subjects should continue in their assigned study arms without change in treatment. Additionally, the IDMC did not identify any safety concerns associated with long-term treatment with ofatumumab.

# 2. OBJECTIVES

## Primary objective:

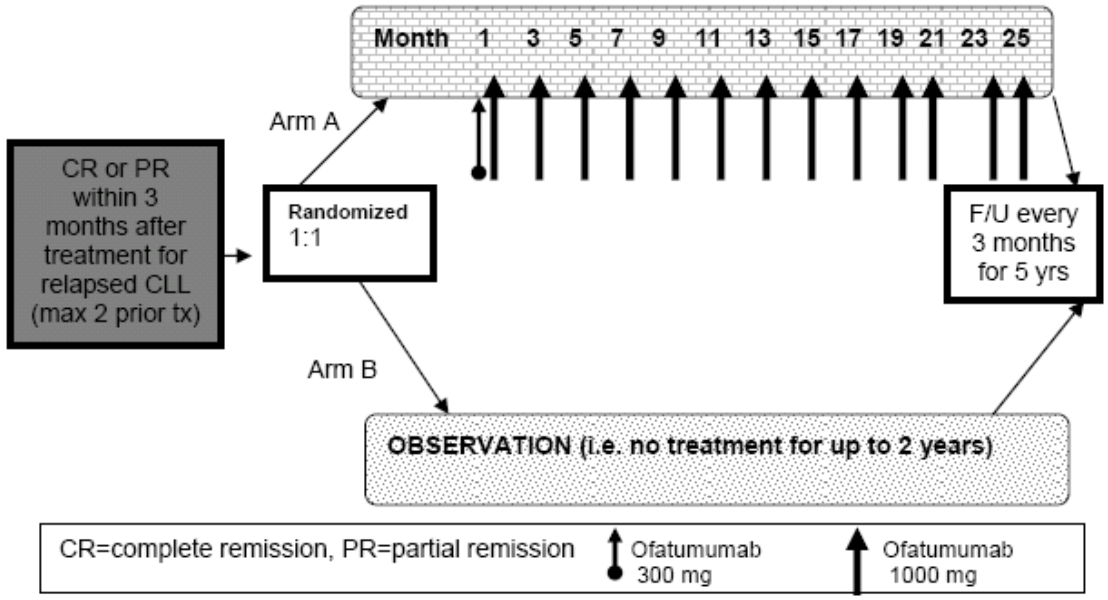
- To evaluate PFS of subjects treated with ofatumumab maintenance treatment compared to no further treatment after remission induction in subjects with relapsed chronic CLL

## Secondary objectives:

- To evaluate the improvement in response, improvement in response time to next CLL treatment and overall survival in subjects receiving ofatumumab maintenance compared to no further treatment
- To evaluate the PFS after next-line therapy and the 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
- 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
- To evaluate prognostic marker correlation with clinical response in subjects with CLL receiving ofatumumab maintenance compared to no further treatment
- To evaluate ofatumumab pharmacokinetic parameters in subjects with CLL receiving maintenance ofatumumab every 2 months

# 3. INVESTIGATIONAL PLAN

## 3.1. 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.

### 3.1.1. Screening Phase

Subjects will give informed consent. Blood samples, physical examination, CT scan and bone marrow examination will be performed to determine the study baseline. 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. At the discretion of the physician, rescreening is acceptable. Refer to Appendix 1 Time and Events for complete list of screening procedures.

### 3.1.2. 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

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

### 3.1.3. 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 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, at each treatment visit beginning with Visit 3, at last visit, and at follow-up visits. A Health Change Questionnaire will be administered for completion by the subjects at all post baseline visits, as per Section 6.5.6.

### 3.1.4. 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.

A bone marrow examination is required to confirm Complete Remission (CR) at least 2 months after completion of therapy and when a subject fulfills the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) requirements for Complete Remission (CR) [Hallek, 2008]. Previous results may be used or if not available, a bone marrow exam may be done at screening. If a subject's response improves to a CR while on study, then a bone marrow examination is required to confirm CR at least 2 months after response as per the updated IWCLL NCI-WG requirements for CR [Hallek, 2008].

Additionally, CT Scans are required yearly while on study, including during follow-up, and at disease progression, whenever that may occur.

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. It is acceptable for the information for survival follow-up visits to be collected remotely (via telephone, email), as necessary. The frequency of the survival follow-up visits should be per local standard of care, suggested every 3 months for CLL. Minimally, this should be collected at least annually.

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, as per Section 6.5.6.

Please refer to Section 6: Study Assessments and Procedures for detailed assessment instructions.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with additional administrative and detailed technical information.

## 3.2. Discussion of Design and Dose Rationale

As discussed in the rationale, CLL is characterized by relapse and there is currently no approved maintenance therapy. This study will evaluate the use of ofatumumab as maintenance treatment in second/third line CLL. Subjects will be randomized to receive either ofatumumab or no treatment in a 1:1 ratio to provide a direct comparison of treatment versus observation, the current standard of care.

The study does not utilize a placebo and is not blinded as the infusion reactions to ofatumumab would not maintain the blind. As the endpoints of the study are objective, this will not affect the interpretation of the study.

The design of the study is considered sufficient at 80% power to detect a clinically meaningful difference in maintenance treatment vs no treatment.

With the current treatment options, patients receiving chemoimmunotherapy (i.e. FCR) have the longest PFS. For patients not naïve to rituximab, this PFS represents a median of 28 months [Wierda, 2005] and a 40% increase of this PFS would be 39.2 months.

The proposed ofatumumab dose and schedule in this study was selected based on several considerations: preclinical data with ofatumumab and clinical population pharmacokinetic modeling and simulation, prior clinical experience with rituximab, and prior clinical experience with ofatumumab.

An initial dose of 300 mg of ofatumumab is given in Week 1 to minimize infusion-related events before introducing the higher dose at Week 2 to provide higher ofatumumab concentrations.

Preclinical data suggest that ofatumumab plasma concentrations >10 μg/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as suppress tumor cell growth in Daudi tumor-bearing SCID mice [Bleeker, 2008]. Ofatumumab concentrations above 50 μg/mL were sufficient for complete B-cell depletion. Recovery of $CD20^+$ cells in peripheral blood and lymph nodes was detected when plasma ofatumumab concentrations had dropped below 5-10 μg/mL. Thus, a potential clinical target in developing ofatumumab dosing regimens is prolonged maintenance of plasma concentrations >10 μg/mL.

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

Prior clinical experience with rituximab suggests that prolonged administration schedules enhance response duration in patients with non-Hodgkin's lymphoma [Collins-Burow, 2007; van Oers, 2007]. Various dosing regimens have been examined as maintenance therapy, including administration of single infusions every two months, and safety has been demonstrated for up to two years of maintenance therapy. Two Phase II studies have examined maintenance therapy with rituximab in patients with CLL, one examining four weekly infusions of 375 $mg/m^2$ every six months for up to two years in patients with objective response or stable disease after initial rituximab treatment [Hainsworth, 2003] and one examining four monthly infusions of 375 $mg/m^2$ followed by twelve monthly infusions of 150 $mg/m^2$ in patients with CR or PR positive for minimal residual disease after fludarabine/rituximab treatment [Del Poeta, 2008]. These studies suggest that prolonged administration schedules enhance response duration in patients with CLL. The existing clinical experience with maintenance rituximab suggests that administration of an anti-CD20 monoclonal antibody should be tolerated for up to two years.

Prior clinical experience in a Phase I/II trial of ofatumumab in patients with relapsed or refractory CLL (Study Hx-CD20-402) suggested that a total dose of 6500 mg (weekly doses of 500, 2000, 2000, and 2000 mg) was effective and tolerated [Coiffier, 2008]. In the pivotal trial in patients with refractory CLL (Study Hx-CD20-406), ofatumumab was given as an initial infusion of 300 mg, followed by seven 2000 mg infusions at weekly intervals, followed five weeks later by 2000 mg infusions every four weeks for four

doses. This initial high-dose/intense regimen followed by monthly high-dose infusions was tolerated, suggesting that 1000 mg ofatumumab every two months for two years should be tolerated. Adverse events in previous trials had been primarily infusion-related events on the day of the first infusion; therefore, the prolonged treatment schedule in Study OMB112517 is not expected to affect the overall safety profile.

# 4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

## 4.1. Number of Subjects

Subjects who meet all the following inclusion/exclusion criteria will be eligible for randomization into the study. The original plan was for approximately 583 subjects to be screened (with 532 randomized) to obtain 478 evaluable subjects (assuming 10% screen failure and 10% drop out rates). All evaluable subjects were obtained, and as the significance level was met at the interim efficacy of analysis, further enrollment will be stopped.

## 4.2. Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Adults with documented diagnosis of CLL based on the modified IWCLL updated NCI-WG guidelines [Hallek, 2008]
2. At least PR according to the revised 2008 NCI-WG CLL criteria within 3 months of the response assessment after the last dose of $2^{nd}/3^{rd}$ line treatment
3. The anti-leukemic treatment before study entry should have been for at least 3 months or 3 cycles
4. ECOG Performance Status of 0-2
5. Signed written informed consent prior to performing any study-specific procedures

**French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

## 4.3. Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Known primary or secondary fludarabine-refractory subjects, defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months [Hallek, 2008]
2. Prior maintenance therapy
3. Known transformation of CLL (e.g. Richter's transformation), prolymphocytic leukemia (PLL), or CNS involvement of CLL

4. Active Autoimmune Hemolytic Anemia (AIHA) requiring treatment except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
5. Previous autologous or allogeneic stem cell transplantation
6. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis B or C
   (Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded*.)
7. Other past or current malignancy (with the exception of basal cell carcinoma of the skin or in situ carcinoma of the cervix or breast) unless the tumor was successfully treated with curative intent at least 2 years prior to trial entry except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
8. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to screening, congestive heart failure, and arrhythmia requiring therapy, with the exception of extra systoles or minor conduction abnormalities except if in the opinion of the investigator it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
9. History of significant cerebrovascular disease or event with symptoms or sequelae
10. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator contraindicates participation in this study
11. Other anti-leukemic use of medications including glucocorticoids
12. Known HIV positive
13. Screening laboratory values:
    - Platelets<50 x $10^9$/L
    - Neutrophils<1.0 x $10^9$/L
    - Creatinine > 1.5 times upper normal limit (unless normal creatinine clearance)
    - Total bilirubin > 1.5 times upper normal limit (unless due to liver involvement of CLL or Gilbert's syndrome)
    - Alanine Aminotransferase (ALT) > 2.5 times upper normal limit (unless due to liver involvement of CLL)
    - Alkaline phosphatase >2.5 times upper normal limit
14. Known or suspected hypersensitivity to ofatumumab that in the opinion of the investigator or medical lead contraindicates study participation

15. Subjects who have received treatment with any non-marketed drug substance or experimental therapy within 5-terminal half-lives or 4 weeks whichever is longer prior to first dose of study medication or currently participating in any other interventional clinical study
    *Note: Participation in any other interventional clinical study after disease progression during post PD follow-up is permitted*
16. Lactating women, women with a positive pregnancy test at Visit 1 or women (of childbearing potential) as well as men with partners of childbearing potential, who are not willing to use adequate contraception from study start through one year following last ofatumumab dose. Adequate contraception is defined as abstinence, oral hormonal birth control, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device, and male partner sterilization if male partner is sole partner for that subject. For females in the USA, the use of a double barrier method is also considered adequate (condom or occlusive cap plus spermicidal agent).

* If HBV DNA is negative, subject may be included but must undergo HBV DNA monitoring (see Section 6.3.4). Prophylactic antiviral therapy may be initiated at the discretion of the investigator. Consult with a physician experienced in the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.

## 4.4. Withdrawal Criteria

Subjects may be withdrawn from investigational product at any time if it is the wish of the subject (or their legally acceptable representative) for any reason, the investigator judges it necessary due to medical reasons including disease progression or the subject becomes pregnant. (See also Section 8.3.5.) The subject will be evaluated for disease status and survival per the follow-up visit schedule outlined in Section 3.1.4.

Furthermore, a subject may withdraw from study participation (i.e., withdraw consent) at any time for any reason. The reason for withdrawal from study participation must be documented in the eCRF.

The investigator must make every effort to perform and document the following in the eCRF:

- Disease assessment
- Hematology and Chemistry
- Physical examination, vital signs and body weight assessment
- Response Assessment
- AE/SAE Assessment
- Concomitant Medication assessment
- Subject completion of PRO measures (EORTC QLQ-C30, EORTC QLQ-CLL16, EQ-5D and the Health Change Questionnaire)

For data collection purposes, subjects are considered as completing the study if they have died during the treatment or follow-up phases, are lost to follow-up, or withdraw consent.

# 5. STUDY TREATMENTS

## 5.1. Investigational Product and Reference Therapy

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request. Adequate precautions must be taken to avoid direct contact with the investigational product.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Please refer to the SPM for detailed instructions related to:

- storage conditions
- infusion preparation
- premedication
- dosing schedule
- handling of infusion reactions
- observations required during infusions

### 5.1.1. Ofatumumab

The investigational medical product, ofatumumab, is a clear liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously on day 1 (300mg) and day 8 (1000mg) in the first cycle, followed by infusions of 1000mg every 2 months.

The ofatumumab infusions will be prepared in 1000 mL sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/mL and 1 mg/mL ofatumumab concentration for the first and subsequent infusions, respectively. Please refer to the SPM for instruction correct preparation of the investigational medical product.

#### 5.1.1.1. Ofatumumab Pre-Medication

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment as detailed in Table 1:

**Table 1 Pre-medication Requirements prior to Ofatumumab Infusions**

| Infusion # | Acetaminophen (po) or equivalent | Antihistamine (iv or po) diphenhydramine or equivalent | Glucocorticoid (iv) prednisolone or equivalent[1] |
|---|---|---|---|
| 1st | 1000 mg | 50 mg | 50 mg |
| 2nd | 1000 mg | 50 mg | 50 mg |
| 3rd -Nth | 1000 mg | 50 mg | 0 – 50 mg[2] |

1. Please refer to the SPM for glucocorticoid equivalent doses.
2. If the 2nd infusion has been completed without the subject experiencing any grade = 3 AEs, pre-medication with glucocorticoid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

#### 5.1.1.2. Ofatumumab Treatment Schedule

Please refer to the study procedures manual for the preparation of the ofatumumab infusion.

**First Infusion of 300mg Ofatumumab**

The initial rate of the first infusion of 300mg ofatumumab (0.3mg/mL) should be 12mL/hour (hr). If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/hr, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.5 hours.

**Table 2 Infusion rate at 1st Ofatumumab (300 mg) infusion**

| Time | mL/hour |
|---|---|
| 0 – 30 minutes | 12 |
| 31 – 60 minutes | 25 |
| 61 – 90 minutes | 50 |
| 91 – 120 minutes | 100 |
| 121 - 150 minutes | 200 |
| 151 - 180 minutes | 300 |
| 181+ minutes | 400 |

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hr before the pause, the infusion should be restarted at 12 mL/hour. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

**Subsequent infusions of 1000mg Ofatumumab**

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of 1000 mg (1mg/mL) can start at a rate of 25 mL/hr and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 3. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 2.

**Table 3 Infusion rate at subsequent Ofatumumab (1000 mg) infusion**

| Time | mL/hour |
|---|---|
| 0 – 30 minutes | 25 |
| 31 – 60 minutes | 50 |
| 61 – 90 minutes | 100 |
| 91 – 120 minutes | 200 |
| 121+ minutes | 400 |

Subsequent infusions=2nd and 3-14th infusions

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary. For details please refer to the SPM.

Dose reductions or modifications of ofatumumab are not permitted with the exception of those initiated for patient safety (i.e. due to infusion reactions). If a dose delay is required for ofatumumab, due to but not limited to adverse events, dosing may resume at physician discretion, and if the patient is still considered to be in remission.

#### 5.1.1.3. Management of Infusion Reactions

##### *5.1.1.3.1. Mild and Moderate Intensity Adverse Events (Grade 1 and 2)*

If the investigator judges the AE to be related to the infusion, the infusion may be temporarily slowed or interrupted.

When the subject's condition is stable, the infusion can be restarted according to the judgment of the investigator.

Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12mL/hr before the pause, the infusion should be restarted at 12mL/hr.

Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in Table 2 and Table 3 (i.e. not more than doubled and no earlier than every 30 minutes).

#### *5.1.1.3.2. Severe Intensity Adverse Events (Grade ≥3)*

If the investigator judges a grade ≥3 AE to be related to the infusion, the infusion must be interrupted and the appropriate clinical intervention begun. When the AE decreases to grade <3, the investigator may restart the infusion.

Upon restarting the infusion, the infusion rate must be 12mL/hr for the first infusion or 25mL/hr for subsequent infusions, and may subsequently be increased according to the judgment of the investigator, as described in Table 2 and Table 3 (i.e. not more than doubled and no earlier than every 30 minutes).

If the severity of the AE does not resolve to grade <3 despite adequate clinical intervention, or the same AE increases to grade =3 on three occasions during one infusion, the subject should be withdrawn from treatment.

## 5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule (see Section 3.1.2). Please refer to the SPM for detailed instruction.

## 5.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study.

## 5.4. Prohibited Concomitant Medication or Therapies

- Anti-cancer medication not part of the protocol treatment (e.g. alkylating agents, anti-metabolites, purine analogues, other monoclonal antibodies, and other medications including glucocorticoids)
- Any non-marketed drug substance or experimental therapy

  Note: Glucocorticoids given for other indications such as exacerbations of asthma or as premedication for ofatumumab infusions are allowed.

# 6. STUDY ASSESSMENTS AND PROCEDURES

Please refer to Appendix 1 Time and Events

## 6.1. Clinical Assessments

### 6.1.1. Demographics

At screening, date of birth, sex, and race/ethnicity is collected.

### 6.1.2. Disease Characteristics and Medical History

At screening, relevant medical history is collected including:

- Date of initial CLL diagnosis
- Rai and Binet staging at diagnosis and screening
- Listing of relevant past and current diseases

### 6.1.3. Previous CLL Therapy

Prior treatment of CLL will be recorded including name of therapy, start and end date, dosing information, response and duration of response.

### 6.1.4. Height and Weight

Height (without shoes) will be measured at screening and recorded in the eCRF. Body weight (without shoes) will be measured at screening and throughout treatment and follow-up phases and recorded on the eCRF.

### 6.1.5. Physical Examination

A general physical examination is required at the screening visit and at visits during the study. This physical will include general appearance including examination of the following: skin, palpation of the lymph nodes, extremities, abdomen including determination of hepatomegaly, respiratory, cardiovascular, musculoskeletal, and neurological systems.

### 6.1.6. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) is required at screening. The investigator will perform an overall interpretation of the ECG or may delegate this task to a cardiologist, if applicable. Additional ECGs may be obtained as clinically warranted at the discretion of the PI or delegate.

### 6.1.7. Vital Signs

Vital signs including temperature, blood pressure (BP), and pulse are documented per Appendix 1 Time and Events and during ofatumumab intravenous infusions. Temperatures for individual subjects must be measured using the same method at all visits.

### 6.1.8. Concomitant Medication

Any medication other than the trial drug is considered concomitant medication (apart from protocol defined premedication given prior to the infusions of ofatumumab) and will be documented, including the following information:

- Indication

- Dose information
- Start date
- Stop date of administration or ongoing at study termination

Of note: Intravenous gamma globulin, prophylactic antibiotics, and G-CSF may be given per local standard of care, at the physician's discretion.

### 6.1.9. ECOG Performance Status

An Eastern Cooperative Oncology Group (ECOG) Performance Status value is required at screening and throughout treatment and follow-up phases, to evaluate daily living abilities. Please refer to SPM for definitions of the ECOG performance status.

### 6.1.10. Constitutional Symptoms (B-Symptoms)

Assessment for the presence of the following symptoms will be performed at screening and at each visit:

- night sweats without signs of infection
- unintentional weight loss ≥ 10% within the previous 6 months
- recurrent, unexplained fever of greater than 100.5°F for 2 weeks without signs of infection
- extreme fatigue

### 6.1.11. Lymph Node and Organ Examination

A physical lymph node and organ (spleen and liver) examination will be performed at screening and throughout the trial as part of disease status assessment.

Lymph nodes evaluation requires physical exam recording the diameter in two planes of the largest palpable node in each of the following sites: cervical, axillary, supraclavicular, inguinal and femoral. Lymphadenopathy is defined as lymph nodes with the largest diameter greater than 1.5 cm.

Liver and spleen size is assessed by physical exam and documented as 'cm' under the costal margin.

### 6.1.12. Pre-treatment Computed Tomography (CT) Scans

All subjects must have a CT scan with contrast of the thorax, abdomen, and pelvis performed at screening to confirm remission status. CT scans performed within 6 weeks prior to entering the study and collected according to defined standards can be used as screening CT scans. Clinical staging is independent of CT scan results.

### 6.1.13. Pre-treatment Bone Marrow Examination

Unilateral bone marrow aspirate smear and a suitable bone marrow biopsy will be performed at baseline (or within 6 weeks prior to entering the study) ONLY to confirm

CR. A pathologist at a central laboratory will evaluate the biopsy and smear. Details regarding collection of bone marrow samples are provided in a separate procedure manual.

## 6.2. Efficacy

### 6.2.1. Definition of Response

While subjects will be entering the study in remission, changes in status to disease progression or even from PR to CR will be determined according to the definitions of response in the IWCLL updated NCI-WG guidelines [Hallek, 2008] and documented at visits outlined in the time and events table. For a tabular summary of all criteria of response definition in CLL patients see Appendix 2. The IWCLL updated NCI-WG guidelines should be applied in the context of clinical judgment and determination of disease progression is at the physician's discretion.

#### 6.2.1.1. Complete Remission (CR)

CR requires all of the following criteria as assessed at least 2 months after therapy or at the earliest 2 months after beginning this maintenance protocol (i.e. ofatumumab treatment/observation):

Peripheral blood lymphocytes (evaluated by blood and differential count) below 4x109 (4000/μL)

Absence of significant lymphadenopathy (e.g. lymph nodes > 1.5 cm diameter).

No hepatomegaly or splenomegaly.

Absence of constitutional symptoms

Blood counts above the following values:

a. Neutrophils > 1.5 x $10^9$/L*

b. Platelets > 100 x $10^9$/L*

c. Hemoglobin > 11.0 g/dL (6.8mmol/L)**

*without need for exogenous growth factors
**without red blood cell transfusion or need for exogenous erythropoietin

Bone marrow aspirate and biopsy should be performed at least 2 months after the final treatment and if clinical and laboratory results listed above in Section 6.2.1.1 (items 1 to 5) demonstrated that a CR has been achieved. The marrow sample should be analyzed by flow cytometry to demonstrate that the marrow is free of clonal CLL cells. Cases with residual CLL cells by conventional flow cytometry are defined as PR.

To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If lymphoid nodules can be found, immunohistochemistry analysis should be performed to assess if nodules are comprised primarily of T-cells or lymphocytes

other than CLL cells or of CLL cells. If marrow is hypocellular, repeat after 4-6 weeks, provided the blood counts have recovered (as defined in Section 6.2.1.1 item 5). Marrow biopsies should be compared with any pretreatment marrow. In some cases, it is necessary to postpone the marrow biopsy until after all other criteria to define a CR have been satisfied, however, this time interval should not exceed 6 months after treatment.

Subjects who fulfill all the preceding criteria for CR (Section 6.2.1.1 items 1 to 6) but have persistent anemia, thrombocytopenia or neutropenia, apparently unrelated to CLL but related to drug toxicity, should be considered as CR with incomplete bone marrow recovery.

#### 6.2.1.2. Partial Remission (PR)

PR is defined by the criteria described in Section 6.2.1.2 items 1, 2, and /or 3 (if abnormal prior to therapy), as well as one or more of the features listed in item 4. To define a PR at least one of these parameters needs to be documented for a minimal duration of 2 months. Constitutional symptoms persisting for more than 1 month should also be documented.

1. A decrease in the number of peripheral blood lymphocytes by 50% or more from the value prior to therapy
2. Reduction in lymphadenopathy as defined by:

- A decreased lymph node size by below 50% or more either in the sum product of up to 6 lymph nodes or in the largest diameter one of the enlarged lymph node(s) detected prior to therapy
- No increase in any lymph node and no new lymph nodes. In small lymph nodes (<2cm), an increase of <25% is not considered to be significant

3. A decrease in the noted pre treatment enlargement of liver or spleen by 50% or more
4. The blood count should show at least one of the following results:

- Neutrophils more than 1.5 x $10^9$/L (1500/μL) *
- Platelet counts greater than 100 x $10^9$/L (100,000/μL) or 50% improvement over baseline*
- Hemoglobin greater than 110g/L (11.0g/dL, 6.8mmol/L) or 50% improvement over baseline **

**without need for exogenous growth factors*

*** without red blood cell transfusion or need for exogenous erythropoietin.*

#### 6.2.1.3. Progressive Disease (PD)

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

1. Lymphadenopathy. Progression of lymphadenopathy, if one of the following is observed:

- Appearance of new lesion such as enlarged lymph nodes (>1.5cm), splenomegaly, hepatomegaly or other organ infiltrates
- An increase by 50% or more in greatest determined diameter of any previous site.

An increase by 50% or more in the previously noted enlargement of the liver or spleen or *de novo* appearance of hepatomegaly or splenomegaly

An increase by 50% or more in the numbers of blood lymphocytes with at least 5000 B-lymphocytes per microliter ($5.0 \times 10^9$/L).

Transformation to a more aggressive histology (e.g. Richter's transformation).

Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL

- During therapy: Cytopenias cannot be used to define disease progression
- After treatment: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20g/L (2 g/dL) or to less than 100g/L (10g/dL), or by a decrease of platelet counts by more than 50% or to less than $100 \times 10^9$/L (100.000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

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

### 6.2.2. Bone Marrow Examination

Unilateral bone marrow aspirate smear and a suitable bone marrow biopsy will be performed at baseline (or within 6 weeks prior to entering the study) ONLY as part of the CR evaluation for patients entering or during the study in CR. A pathologist at a central laboratory will evaluate the biopsy and smear. Details regarding collection of bone marrow samples are provided in a separate procedure manual.

Bone marrow examination (aspirate smear and biopsy) to confirm CR, as determined by the clinical and laboratory results listed in Section 6.2.1.1 is required at least 2 months after completion of therapy or at least 2 months of therapy or response while on study. The marrow should be analyzed by flow cytometry to confirm absence of clonal CLL cells. Samples are to be reviewed in conjunction with any prior pathology, as available.

Minimal residual disease assessment will also be performed on bone marrow aspirate obtained after CR (see Section 6.2.3). When possible, the first drop from bone marrow aspirate will be used for MRD measurement.

### 6.2.3. Minimal Residual Disease (MRD)

For subjects enrolling in the study who are in CR, baseline MRD will be assessed at screening, prior to any treatment visit.

For subjects who improve to a CR while on study, a bone marrow examination will be performed after at least 2 months of therapy or response while on study.

The bone marrow sample if available, and/or peripheral blood sample will be examined by flow cytometry with the following B-CLL MRD panel [Rawston, 2007]:

- CD5/CD19 with CD20/CD38
- CD5/CD19 with CD81/CD22
- CD5/CD19 with CD79b/CD43

In addition CD3/CD19 with CD14/CD45 analysis is performed to allow enumeration of CD19+ cells and contamination assessment and CD5/CD19 with Igλ/Igκ analysis is performed to confirm clonality.

Subjects with negative MRD will receive follow-up MRD assessments of the peripheral blood until MRD analysis becomes positive.

The absence of MRD is defined as less than one B-CLL cell per 10,000 leukocytes.

### 6.2.4. CT-Scans

According to the IWCLL updated NCI-WG response criteria for CLL [Hallek, 2008], CT-scans are recommended in clinical trials to assess response. This study will prospectively explore the validity of CT scans for a more sensitive detection of disease progression. CT-Scans are required prior to start of therapy. CT scans will be done approximately yearly while on study including at the end of treatment/observation, and/or upon relapse. If a scheduled CT scan indicates disease progression, and the subject will be withdrawn, it is not necessary to repeat a CT scan for a withdrawal visit. The actual CT scan (not just the radiologist report) should be available and performed to the criteria specified in the SPM.

## 6.3. Laboratory Assessments

All the analyses will be performed by a central laboratory, except for the direct antiglobulin test (Coomb's test) that will be performed locally. A detailed description of the procedures for sampling, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the SPM or by the central laboratory.

The protocol should be followed as closely as possible, but if as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment) of protocol required lab assessments are acceptable, however, it is important that the sample for the central laboratory analysis is taken at the same time. The local laboratory results of absolute neutrophil count (ANC), platelet count, peripheral blood lymphocytes, and hemoglobin must also be entered into the eCRF, if these results are used to manage a treatment decision. Central laboratory

information will also be entered into the eCRF. Safety assessments, such as hematology not specified in the protocol, are allowed between visits, per investigator discretion and local practice.

### 6.3.1. Flow Cytometry for B-CLL Diagnosis/Confirmation of Phenotype and B-cell Monitoring

#### 6.3.1.1. B-CLL Diagnosis/Phenotype Confirmation

The B-CLL immunophenotype will be assessed by analysis of surface expression of: CD5, CD19, CD20, CD23, CD76b, and surface Ig at screening, if possible and at relapse. If the subject is in CR, results prior to latest response may be used, if available.

#### 6.3.1.2. B-Cell Monitoring

B-cell monitoring ($CD5^+CD19^+$ and $CD5^-CD19^+$) will be performed every two months and at every follow-up visit until values return to normal levels on two consecutive determinations.

### 6.3.2. Peripheral Blood Sampling for Hematology and Biochemistry

Blood samples will be drawn for analysis of the following parameters at visits according to the time and events schedule:

- **Hematology:** hemoglobin, hematocrit, reticulocytes, platelets, leukocytes, and white blood cell differential (neutrophils, eosinophils, basophils, lymphocytes and monocytes, prolymphocytes - all expressed in % and in absolute numbers)

- **Biochemistry:** sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic acid dehydrogenase (LDH), albumin, glucose (random). Haptoglobin will be analyzed at screening and 3 months after last treatment.

### 6.3.3. Prognostic Factors

Whole blood will be collected at the baseline visit, if possible, and/or upon relapse for later analysis of the following prognostic factors:

- $IgV_H$ mutational status
- $V_H3$-21 usage
- Cytogenetics (by FISH) including but not limited to; $6q^-$, $11q^-$, +12q, $17p^-$, $13q^-$
- $\beta_2$ microglobulin

Analysis of these factors are performed in batches by a central laboratory. Details for procedures and shipments are provided separately.

### 6.3.4. Peripheral Blood Sampling for Safety and Disease Status

The following laboratory tests will be performed:

- Direct antiglobulin test (Coombs test) at screening and 3 months after last treatment.
- Hepatitis B (HBV) and Hepatitis C (HCV) at screening.

  *For subjects that are HBsAg negative, HBcAb positive and HBV DNA negative (see Section 4.3) blood samples will be collected for HBV DNA testing every 2 months during the treatment/observation and during follow-up at the 3 months and 6 months visit.*
- Screening pregnancy test (HCG) for women of childbearing potential, unless they have had a hysterectomy, have undergone tubal ligation within one year before the screening visit, or have been postmenopausal for at least one year.
- Human Anti-Human Antibody (HAHA) prior to first dose of ofatumumab, every 6 months during ofatumumab treatment, and at 3 and 6 months post treatment (i.e. predose Visit 1, at Months 7, 13, 19, and 25 during treatment and at 3 and 6 months after last ofatumumab dose, regardless of when it occurs). A HAHA sample (and a pharmacokinetic sample) should also be obtained at the last treatment visit if it does not occur at a scheduled sampling time (e.g., if treatment is discontinued early). HAHA samples will only be collected for subjects randomized to ofatumumab.
- Complement: CH50 at baseline and after last treatment visit.
- IgA, IgG and IgM at screening, every 6 months during treatment, and after last treatment visit and/or upon relapse. In case of infection, these immunoglobulins may be tested at the physician's discretion. Additional samples may be collected post last treatment (such as 3 and 6 months f/u), if warranted.

## 6.4. Safety Assessments

### 6.4.1. Liver chemistry stopping and follow-up criteria

According to Novartis policy across all compounds, liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology. (Refer to Appendix 5)

#### 6.4.1.1. Liver Chemistry Stopping Criteria

1. ALT > 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin; bilirubin fractionation required*)
2. ALT > 8xULN
3. ALT ≥ 5xULN for more than 2 weeks

***NOTE**: *serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 xULN, then the following actions must still be performed.*

**When any of the liver chemistry stopping criteria is met, do the following:**

- **Immediately** withdraw investigational product
- Report the event to Novartis **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin), termed 'Hy's Law', **must be reported as an SAE**.

NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2 and 3:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 3 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Can continue ofatumumab
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above

- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

#### 6.4.1.2. Liver Chemistry Follow-up Assessments

Make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody (if subject resides outside the US or Canada, or has travelled outside US or Canada in past 3 months);
- Blood sample for PK analysis of ofatumumab, obtained within as soon as possible but no later than 5 months of last dose (approximately 5 half-lives of the drug). Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

### 6.4.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

### 6.4.3. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

All infections must be reported as an AE regardless of causality.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessment that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

### 6.4.4. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

   An overnight hospital stay due to slow infusion rates will not be considered a Serious Adverse Event.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may

interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 6.4.5. Toxicity Assessment of AEs and SAEs

The investigator is required to make an assessment of the toxicity grade of each AE or SAE reported. In this protocol, the maximum toxicity grade of each non-hematologic AE/SAEs will be evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 (please refer to the SPM for details).

It is important to consider low blood counts at the initiation of therapy when evaluating hematologic toxicity of CLL subjects. Due to this, standard solid tumor toxicity criteria cannot be used or subjects would exhibit grade II to IV toxicity at study onset. For this reason, hematologic toxicity (platelets, hemoglobin and neutrophils) of each AE/SAE will be evaluated according to an adaptation of the IWCLL Grading Scale for Hematological Toxicity in CLL Studies [Hallek, 2008].

**Table 4 Grading scale for Hematological Toxicity**

| Grade[1] | Decrease in Platelets[2] or Hb[3] (nadir) from pretreatment value (%) | Absolute Neutrophil Count/µL[4] (nadir) |
|---|---|---|
| 1 | 11%-24% | ≥1500 and <2000 |
| 2 | 25%-49% | ≥1000 and <1500 |
| 3 | 50%-74% | ≥500 and <1000 |
| 4 | ≥75% | <500 |

1. Grades: 1-mild; 2-moderate; 3-severe; 4-life-threatening; 5-fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.
2. Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20,000/µL, this will be considered grade 4 toxicity, unless a severe or life threatening decrease in the initial platelet count (e.g., 20,000/µL) was present pretreatment, in which case the subject is not evaluable for toxicity referable to platelet counts.
3. Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the absolute neutrophil count (ANC) reaches less than 1,000/µL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was less than 1,000/µL prior to therapy, the subject is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented.

### 6.4.6. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.

Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

Specific attention will be paid to monitor events of special interest such as infusion reactions, tumor lysis syndrome, infections and progressive multifocal leukoencephalopathy (PML). Please refer to the SPM and/or the following text*.

***Handling Infusion Reactions:***

Infusion reactions are commonly associated with anti-CD20 antibody therapy. Ofatumumab can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions.

The site staff must be prepared to intervene if an infusion reaction occurs. Special caution should be taken during the first infusion for each subject and during the infusion for any subject who did not tolerate a previous infusion well. It is recommended that a crash cart is readily accessible in the event of an emergency. Infusion reactions should be treated according to the investigators judgment and best clinical practice.

Interruption, restart and increasing the rate of the infusion depending on the severity of the AE must be according to the description below and at the investigator's discretion. An increase of the infusion rate after an interruption must not exceed the scheduled amount as described in Table 2 and Table 3 (i.e. not more than doubled rate and no earlier than every 30 minutes). See Section 5.1.1.3 for details on management related to intensity of adverse events.

***Handling Tumor Lysis Syndrome:***

Monitoring and treatment of potential Tumor Lysis Syndrome (TLS) should be performed as per oncology standard of care.

Symptoms of TLS include:

- Hyperkalemia, potentially leading to cardiac conduction abnormalities, muscle weakness or paralysis
- Hyperphosphatemia, potentially leading to renal failure
- Hypocalcemia. Symptoms include (but are not limited to): tetany, seizures, mental retardation / dementia, parkinsonian (extrapyramidal) movement disorders, papilledema, emotional instability / agitation / anxiety, myopathy
- Hyperuricemia, potentially leading to renal failure

Risk factors for TLS include a high tumor burden, high concentrations of circulating cells (≥ 25,000/mm3), hypovolemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Thus TLS should be suspected in subjects with large tumor burden who develop acute renal failure along with hyperuricemia (> 15 mg/dL) or hyperphosphatemia (> 8 mg/dL). Acute uric acid nephropathy is associated with little or no urine output. The urinalysis may show uric acid crystals or amorphous urates. The hypersecretion of uric acid can be detected with a high urine uric acid:creatinine ratio > 1.0, compared to a value of 0.6-0.7 for most other causes of acute renal failure.

In those patients considered to be at risk for TLS, management includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance (consider aggressive hydration i.e. ~3,000 ml/$m^2$/day fluid administered parenterally) and supportive care. If signs of TLS occur, the investigator can administer rasburicase or allopurinol (e.g. Zyloprim, Allohexal, Allosig, Progout, Zyloric) or other drugs used to treat hyperuricemia, per prescribing information, if deemed appropriate.

***Handling Progressive multifocal leukoencephalopathy (PML):***

PML is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual and has been reported with ofatumumab. JC virus (JCV) infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus, an indication for which rituximab has not been approved. Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list, and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

If a subject develops neurological signs or symptoms consistent with PML, treatment should be halted and the subject referred to a neurologist for evaluation. At a minimum, blood JCV PCR and/or MRI should be performed; if either test is positive, Cerebrospinal Fluid (CSF) JCV PCR should be performed. If blood JCV PCR and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should be withdrawn from treatment, proceed to the Follow-Up Period, and be followed until resolution. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

The investigator will do the following when reporting a serious infection (including PML) or sign/symptom consistent with PML.

- Refer to Section 6.4.10 of this document for further information and detailed guidance for completing and transmitting these and other SAE reports for subjects who experience a serious infection, malignancy, death, or sign or symptom of PML.
- Provide key source documentation for the Sponsor to assist with the safety evaluation process.

Examples of key source documents include but are not limited to: hospitalization records, discharge summaries, laboratory evaluations, biopsy results, culture/sensitivity results, death certificates, and autopsy reports.

If the subject has not otherwise been withdrawn from the study, then the investigator should contact the Sponsor to discuss the appropriate course of action regarding study continuation.

***Monitoring of Hepatitis in patients:***

For subjects who are HBsAg negative, HBcAb positive and HBV DNA negative, blood samples will be collected for HBV DNA testing every 2 months during the treatment/observation period and during follow-up at the 3 months and 6 months post last dose visits.

For subjects who require hepatitis monitoring, extra visits outside those defined in the protocol may be required.

### 6.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

### 6.4.8. Time Period and Frequency of Detecting AEs and SAEs

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 of time (i.e. Visit 1 until 60 days after last visit, up 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.

Subject who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBC positive. Anti-viral therapy should be initiated, if required. If a subject's HBV DNA becomes positive during the study, the Novartis medical lead should be notified. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab should be discussed with the medical lead before appropriate treatment decisions are made for that individual subject.

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be reported promptly to Novartis.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to Novartis.

### 6.4.9. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

### 6.4.10. Prompt Reporting of Serious Adverse Events and Other Events to Novartis

SAEs and pregnancies meeting the pre-defined criteria will be reported promptly to Novartis as described in the following table once the investigator determines that the event meets the protocol definition for that event.

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE" data collection tool | 24 hours | Updated "SAE" data collection tool |
| Pregnancy | 24 hours | Pregnancy Form | 2 Weeks | Updated Pregnancy Form |

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to Novartis are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

## 6.5. Patient Reported Outcome (PRO) Measures

Subjects will be asked to complete the following PRO measures at baseline, selected treatment and follow-up visits throughout the trial to document changes in symptoms and functioning that are important for patients with B-CLL. All PRO questionnaires are included in Appendix 3: Patient Reported Outcome Measures.

### 6.5.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

The EORTC QLQ-C30 was developed for use in a wide range of oncology clinical trial populations and is intended to be supplemented by tumor specific modules [Aaronson, 1993; Osoba, 1994]. 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, Diarrhoea, and Dyspnoea), a single item asking about Financial Difficulties and a global health status/quality of life domain consisting of two items. Thus the EORTC-QLQ-C30 provides a measure of symptom and Health Related Quality of Life (HRQL) domains from the perspective of the subject.

Subjects respond to the items on a four point Likert scale ranging from 1 'Not at all' to 4 'Very much' and it takes approximately 11 minutes to complete. Subjects are asked to think back over the past week when responding to the items. The EORTC QLQ-C30 is self-administered and has been widely used in various oncology populations. It is available in over 50 languages and higher scores indicate better HRQL. The EORTC QLQ-C30 is widely used and has been well validated in a number of different cancer indications. The QLQ-C30 has been used in several recent studies with B-CLL patients [Catovsky, 2007; Doorduijn, 2005; Holzner, 2004].

### 6.5.2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukaemia 16 item module (EORTC QLQ-CLL 16)

The EORTC QLQ-CLL16 EORTC QLQ-CLL 16] has been developed to the high standards of rigour required by the EORTC group, but its psychometric properties are as yet untested. The first three phases of the EORTC development process have been completed for the CLL16 module including generation of items based on literature review and semi-structured interviews with specialists and patients; review of the draft items by professionals and 3-5 patients; and pre-testing of the module for acceptability and relevance through cognitive debriefing in a sample of patients. Subjects respond to the items on a four point Likert scale ranging from 1 'Not at all' to 4 'Very much' and it is estimated to take less than ten minutes to complete. Subjects 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, again, psychometric validation of these domains will be described in the detailed psychometric validation statistical analysis plan.

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

The EQ-5D is a self-administered, generic, indirect utility measure [EuroQoL Group, 1990]. The EQ-5D consists of a 0-100 Visual Analogue Scale (VAS) on which subjects are asked to rate their current overall health status and five single-item dimensions which ask subjects to rate their health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The five single items can be summed and expressed as a single global index of health-related quality of life. For each of the five items patients must choose between three levels of difficulty in accomplishing tasks in that dimension. The VAS is then used in combination with the dimension scores to generate a patient profile.

One response exists per dimension, such that:

- Level 1 (no problem) is coded as "1"
- Level 2 (some or moderate problems) is coded as "2"
- Level 3 (unable, or extreme problems) is coded as "3"

The health states are described in terms of five-digit numbers based on the answers to each of the five questions. The states can then be converted to a single score using a table that contains health utility values for the 243 different possible health states. Thus a health utility score is created that can be incorporated into analyses of cost effectiveness. Additionally, a three-digit number between 0 and 100 is read off the VAS, from the exact point where the subject has marked the scale. The EQ-5D takes less than five minutes to complete. The EQ-5D was recently used in a study of B-CLL patients [Doorduijn, 2005].

### 6.5.4. Patient Reported Constitutional Symptoms ('B-Symptoms') score

The EORTC QLQ-C30 and QLQ-CLL16 module include items asking about symptoms due to B-CLL and other problems commonly associated with B-CLL or its treatment, such as increased risk of infections. To provide a clear indication of the change in constitutional or 'B'-symptoms, an additional scoring approach will be evaluated based on items that reflect 'B-symptoms' from the QLQ-C30 and the QLQ-CLL16 module, 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) and skin problems such as itching (CLL item 37) lethargic (CLL item 39), slowed down (CLL item 40). This score is proposed to provide patient reported data that might be supportive of the 'B-symptoms' clinician rating. The validity and reliability of this 'B-symptoms' score will be assessed through psychometric validation using blinded data from this trial, as summarised in the psychometric validation RAP.

### 6.5.5. Health Change Questionnaire

The Health Change Questionnaire consists of a single question in which the subject is asked if he/she has experienced any change in his/her health overall since beginning the study. The Health Change Questionnaire should be administered at all post-baseline visits at which PRO measures are administered. It is included for the purpose of validating the PRO measures (in particular the QLQ-CLL16 measure which has not been previously validated).

### 6.5.6. Administration of PRO Measures

The EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D should be administered at baseline and at each treatment clinic visits; beginning with Visit 3, and at each follow-up visit 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.

## 6.6. Pharmacokinetics

Blood samples will be collected from subjects receiving ofatumumab predose and 0.5 h after the end of the infusion (EOI) at treatment on Month 1 Week1 (Day 1), Month 1 Week 2 (Day 8), Months 3, 7, 13, 19 and 25. In addition, predose samples will be collected prior to ofatumumab administration on Months 5 and 9. A pharmacokinetic sample (and a HAHA sample) should also be obtained at the last treatment visit if it does not occur at a scheduled sampling time (e.g., if treatment is discontinued early). Samples will also be collected at any time of day during clinic visits at 3 and 6 months post-last ofatumumab dose. Table 5 provides the pharmacokinetic sample collection schedule.

Predose samples may be collected at any time prior to dosing, and 0.5 h post-EOI samples may be collected within a ± 15 minute window around the scheduled time. The actual date and time of each sample collection will be recorded in the eCRF.

**Table 5 Ofatumumab pharmacokinetic sample collection schedule**

| Month | Week | Visit | Sampling time |
|---|---|---|---|
| 1 | 1 | 1 | Predose, 0.5 h post-EOI |
| 1 | 2 | 2 | Predose, 0.5 h post-EOI |
| 3 | 9 | 3 | Predose, 0.5 h post-EOI |
| 5 | | 4 | Predose |
| 7 | | 5 | Predose, 0.5 h post-EOI |
| 9 | | 6 | Predose |
| 13 | | 8 | Predose, 0.5 h post-EOI |
| 19 | | 11 | Predose, 0.5 h post-EOI |
| 25 | | 14 | Predose, 0.5 h post-EOI |
| 28 | | 15 | 3 months after last dose[1,2] |
| 31 | | 16 | 6 months after last dose[1,2] |

1. Collect sample at any convenient time on study day.
2. Collect sample relative to last dose of ofatumumab regardless of when it occurs

Sample collection, processing, and shipping instructions are provided in the study procedures manual.

## 6.7. Biomarkers

Biomarker analysis is integral part of disease status confirmation and monitoring, as well as identification of prognostic markers. See Section 6.3 for more detail.

# 7. DATA MANAGEMENT

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets that support the protocol objectives.

For this study subject data will be entered into the electronic case report forms (eCRFs), transmitted electronically to Novartis and its authorized agents and be combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the MedDRA and a custom drug dictionary. eCRFs (including queries and audit trails) will be retained by Novartis, and copies will be sent to the investigator to maintain as the investigator copy.

# 8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 8.1. 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:

$H_0$: 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)

$H_1$: 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)

## 8.2. Study Design Considerations

### 8.2.1. 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:

- 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
- Median PFS for the ofatumumab maintenance treatment group is 39.2 months
- 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 drop out 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

### 8.2.2. 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 6 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.

**Table 6 Estimated Power for Differing Median Values of PFS**

| 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 |

### 8.2.3. Sample Size Re-estimation

Sample size re-estimation will not be performed for this study.

## 8.3. Data Analysis Considerations

### 8.3.1. Analysis Populations

#### 8.3.1.1. Populations defined for the analyses

1) **Intent-to-Treat (ITT) Population**: This population will include subjects who are randomized in this 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.

2) **Safety Population:** This 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.

3) **Per Protocol (PP) Population**: This population 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 result when using the ITT population. However, if the number of subjects in the PP population is 10% or smaller than the ITT population, then the analysis will not be performed.

4) **Pharmacokinetic Population**: This population will consist of all subjects in the ITT population for whom a pharmacokinetic sample is obtained and analyzed.

## 8.3.2. Analysis Data Sets

The primary data set for efficacy will be based on the response assessments. The primary data sets for safety will 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].

## 8.3.3. Treatment Comparisons

### 8.3.3.1. Primary Comparisons of Interest

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.

### 8.3.3.2. Secondary and Other Comparisons of Interest

The primary efficacy endpoint will serve as a 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 (see Section 8.3.4) or at the 0.0498 significance level at the final 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 [redacted] 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 only if the primary endpoint, PFS, is significant.

1. Time to next CLL therapy
2. Overall survival

The control for multiplicity across the 'inferential secondary endpoints', 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 will between the ofatumumab maintenance treatment and no further treatment arms for other secondary endpoints will be done at an alpha equals 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

### 8.3.4. Interim Analysis

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. Details of the interim analysis for safety will be given in the IDMC Charter.

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 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. Enrollment was expected to be completed at the time of this analysis.

However, when the required number of events occurred prior to fully enrolling the study, but with the full number of evaluable subjects available, and before the results were known, it was decided that if the primary endpoint met the predefined significance level of $p<0.001$, demonstrating clinical benefit for the ofatumumab arm, further enrollment would be discontinued.

The study conduct will continue regardless of the outcome of the interim analysis of the primary endpoint. This interim analysis will also evaluate safety. The interim analysis of the primary endpoint, PFS, will be conducted as described in Section 8.3.5.1, and further details of the interim analysis will be provided in the IDMC Charter. The final analysis will be conducted at a significance level of 0.0498.

### 8.3.5. Key Elements of Analysis Plan

The final analysis will take place when the total number of events 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.

**Withdrawal**

Subjects will be treated until disease progression or withdrawal from study treatment due to unacceptable adverse event(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 analysis, will be included in the analysis, regardless of treatment duration.

**Missing Data**

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, with the exception of objective response. Treated subjects who do not have any response data will be assumed to be non-responders. Further details will be given in the Reporting and Analysis Plan (RAP).

**Derived and Transformed Data**

The evaluation of progression-free-survival will be determined by investigator assessment of response according to the IWCLL updated NCI-WG CLL criteria [Hallek, 2008].

**Other Issues**

Data from all participating centers will be pooled for the analyses. It is anticipated that subject accrual will be spread thinly across centers. Therefore, summaries of data by center would probably not be informative and will not be provided.

#### 8.3.5.1. Efficacy Analyses

**Primary Analysis**

The primary endpoint is progression-free-survival which is defined as the time from randomization to the date of disease progression or death due to any cause. The investigator assessment of response will be assessed according to the IWCLL updated NCI-WG CLL criteria [Hallek, 2008].

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, and further details of the interim analysis will be provided in the IDMC Charter.

The final analysis of PFS will be tested 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.

In addition to the stratified log-rank test based on the Kaplan-Meier procedure, a Cox regression model will be used and will include covariates for treatment, stratification factors, and other baseline data deemed appropriate. 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' vs 'no further treatment'.

**Table 7 PFS Assignment**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline tumour | Randomization | Censored |
| Progression documented between scheduled visits | - Date of assessment of new lymph node (if progression is based on new lymph node)<br>- Date of last assessment (if progression is based on increase in sum of measured lymph nodes) | Progressed |
| No progression (at end of trial) | Date of last assessment of measured lymph nodes | Censored |
| Treatment discontinuation for undocumented progression | Date of last assessment of measured lymph nodes | Censored |
| New anticancer treatment started | Date of last assessment of measured lymph nodes | Censored |
| Death before first assessment | Date of death | Progressed |
| Death between adequate assessment visits | Date of death | Progressed |
| Death or progression after more than one missed visit | Date of last assessment of measured lymph nodes | Censored |

Subgroup analyses will be conducted for PFS for the stratification factors.

**Secondary 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 positive minimal residual disease (MRD). These rates will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response, number of prior treatments and type of prior treatment).

- Overall survival

Overall survival is defined as time from randomization to date of death. The same analysis will be conducted as described for the primary endpoint, PFS.

- Time to next therapy

Time to next therapy is defined as the time from randomization to date of receiving the next CLL treatment. The same analysis will be conducted as described for the primary endpoint.

- Progression-free survival after next-line therapy

This endpoint will be defined as time from randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy. [redacted]

- Time to progression after next-line therapy

This endpoint will be defined as time from progression following randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy. [redacted]

- Frequency of transfusions

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

- Evaluation of myelosuppression (anemia, neutropenia, thrombocytopenia)

The number and percentage of patients with myelosuppression will be provided.

- IgG, IgA, IgM

Summaries of IgG, IgA, and IgM will be provided at scheduled visits.

**Disease Markers:**

- Minimal Residual Disease (MRD)

The number and percentage of subjects with positive MRD will be provided. The proportion of subjects wills positive MRD will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors (response, number of prior treatments and type of prior treatment).

- B-cell monitoring

CD5/CD19 change from baseline will be summarized to assess the treatment effect. The number and percentage of subjects with complete B-cell depletion will be summarized.

- 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.

#### 8.3.5.2. Safety Analyses

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. Details of the interim analysis for safety will be given in the IDMC Charter.

The safety population will be used for the safety analyses. For continuous variables, the mean, median, standard deviation (std), minimum, and maximum will be provided in the summary tables. For categorical variables, the frequency and percentage will be provided in the summary tables.

**Extent of Exposure**

Extent of exposure will be provided by summarizing the number of doses received by each subject and the duration of each infusion.

**Adverse Events**

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by system organ class.

Events will be summarized by frequency and proportion of subjects by system organ class and preferred terms.

If the AE is listed in the IWCLL Grading Scale for Hematological Toxicity in CLL Studies [Hallek, 2008] or NCI CTCAE (version 4.0) tables, the maximum grade will be summarized.

The incidence of AEs, severity of AE, deaths and the primary cause of death will also be provided.

The incidence of subjects with grade 3, 4, and 5 infections will also be provided at each visit.

The number and percentage of subjects with Autoimmune Hemolytic Anemia (AIHA) will be calculated.

**Clinical Laboratory Evaluations**

Hematology and clinical chemistry data will be summarized at each scheduled visit according to IWCLL Grading Scale for Hematological Toxicity in CLL Studies

[Hallek, 2008] and NCI CTCAE version 4.0. The proportion of subjects with values outside the reference range will also be presented.

The change in HAHA titers from predose to post-baseline visits and the number and the proportion of positive and negative results at each visit will be provided in the ofatumumab arm only. A listing of HAHA results and associated ofatumumab plasma concentration at each timepoint will be generated.

#### 8.3.5.3. PRO Analyses

The EORTC QLQ-C30 and the EQ-5D will be scored as per the developers instructions, with scores created for each pre-specified domain. For the EORTC QLQ-CLL16, the developers have proposed a scoring, but it has not been validated yet. Therefore this scoring will be validated using the blinded data from the present trial.

In addition to the developer's hypothesized domains for both EORTC instruments it is also proposed that a 'B-symptoms' score will be created including the following items from the two instruments: 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), and skin problems such as itching (CLL item 37), lethargic (CLL item 39), slowed down (CLL item 40). This score is proposed to provide patient reported data that might be supportive of the constitutional symptoms assessment by the clinician.

Details of the scoring methods of all PRO measures will be provided in the RAP. Each PRO domain will be summarized for each treatment group and the total PRO sample at each time point will be presented in tabular format as mean, standard deviation, median, minimum, and maximum. Methods for imputation of missing data will be detailed in the RAP.

At each post-baseline timepoint, changes in PRO scores will be calculated by subtracting the baseline score from the score at the subsequent timepoint. Appropriate statistical tests will be proposed in the RAP to evaluate the significance of the change in scores over time, and to compare the scores between treatment arms.

Standard psychometric validation analyses will be performed for all PRO measures (EORTC QLQ C30, EORTC QLQ CLL16, 'B-Symptoms score', and EQ-5D). For the EORTC QLQ-CLL16 and B-Symptoms score, estimation of minimal clinically important differences will also be explored. Details of the methods for all of these psychometric validation analyses will be provided in the psychometric validation RAP.

#### 8.3.5.4. Pharmacokinetic Analyses

The plasma concentrations for individual subjects will be determined using validated analytical methods for ofatumumab. Plasma ofatumumab concentration-time data will be summarized and displayed in tabular and graphical form. Individual plasma concentrations of ofatumumab will be listed.

Population pharmacokinetic modeling, using non-linear mixed effects modeling will be performed using validated software such as the computer program NONMEM, if data

permit. Data from this study may be combined with data from other studies for analysis. The aims of this modeling approach are to:

a.) Define the structural pharmacokinetic model that characterizes the population time course of plasma levels of ofatumumab in this patient population

b.) Describe between-subject variability for pharmacokinetic parameter estimates

c.) Estimate intra-subject variability on predicted concentrations.

If possible, the effects of patient characteristics (such as gender, weight, height, disease status, etc.) will be investigated in order to account for potential sources of inter-individual variability in systemic exposure. If there are sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a reporting and analysis plan.

[redacted]

# 9. STUDY CONDUCT CONSIDERATIONS

## 9.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Novartis will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US IND.

The study will be conducted in accordance with all applicable regulatory requirements, including IND Number 11,719.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2000, as amended in 2002 and 2004 including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Novartis will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

## 9.2. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Novartis procedures, Novartis monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

Novartis will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

## 9.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

## 9.4. Study and Site Closure

Upon completion or termination of the study, the Novartis monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and Novartis Standard Operating Procedures.

Novartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If Novartis determine that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Novartis will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where

required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

## 9.5. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

## 9.6. Provision of Study Results and Information to Investigators

The database results will be provided to [redacted] for the purposes of independent analysis for publication purposes in a peer reviewed journal. Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Upon completion of the clinical study report, Novartis will ensure public disclosure of the clinical trial research results via the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) according to the Novartis SOP and will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

## 9.7. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

# 10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.

Abbott BL. Chronic Lymphocytic Leukemia: Recent Advances in Diagnosis and Treatment. *Oncologist* 2006;11:21-30.

Binet JB, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 1981;48:198-206.

Binet JB, Caligaris-Cappio FC, Catovsky DC, Cheson BC, Davis TD, Dighiero GD, et al. Perspectives on the Use of New Diagnostic Tools in the Treatment of Chronic Lymphocytic Leukemia. *Blood* 2006;107:859-861.

Bleeker WB, Munk ME, Mackus WJM, van den Brakel JHN, Pluyter, et al. Estimation of Dose Requirements for Sustained In Vivo Activity of a Therapeutic Human Anti-CD20 Antibody. *Br J Haematology*. 2008;140:303-312.

Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, Pearson M, Waselenko JK, Ling G, Grever MR, Grillo-Lopez AJ, Rosenberg J, Kunckel L, Flinn IW. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin* Oncol 2001; 19:2153-64.

Byrd JB, Stilgenbauer S, Flinn IW. Chronic Lymphocytic Leukemia. *Hematology* 2004;163-183.

Catovsky DC, Richards SR, Matutes EM, Oscier DO, Dyer MD, et al. Assessment of Fludarabine plus Cyclophosphamide for patients with Chronic Lymphocytic Leukemia (the LRF CLL4 Trial): a Randomized Controlled Trial. *Lancet* 2007;370:230-239.

Chiorazz NC, Rai KR, Ferrarini MF. Mechanisms of Disease Chronic Lymphocytic Leukemia. *N Engl J Med.* 2005;352:804-815.

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

Collins-Burow B. and Santos ES. Rituximab and its role as maintenance therapy in non-Hodgkin lymphoma. *Expert Rev of Anticancer Ther.* 2007;7:257-273.

Del Poeta G, Del Principe MI, Buccisano F, Maurillo L, Capelli G, Luciano F, Pio Perrotti A, Degan M, Venditti A, de Fabritis P, Gattei V, Amadori S. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. *Cancer* 2008; 112:119-128.

Dohner H, Fischer K, Bentz M, Hansen K, Benner A, et al. p53 Gene Deletions Predicts for Poor Survival and Non-Response to Therapy with Purine Analogs in Chronic B-Cell Leukemias. *Blood* 1995;85:1580-1589.

Doorduijn J, Buijt I, Holt B, Steijaert M, Uyl-de Groot C, Sonnevold P. Self-reported quality of life in elderly patients with aggressive non-Hodkin's lymphoma treated with CHOP chemotherapy. *Eur J Haematol* 2005; 75:116-23.

EuroQoL Group. EuroQoL a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

Forstpointner R, Unterhalt M, Dreyling M, Bock H-P, et al. Maintenance theray with rituximab leads to significant prolongation of response duration after salvage treatment with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphoma: results of a prospective randomized study of the German low grand lymphoma study group (GLSG). *Blood* 2006; 108:4003-4008.

Hainsworth JD, Litchy S, Barton JH, Houston GA, Hermann RC, Bradof JE, Greco FA. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minne Pearl Cancer Research Network. *JCO* 2003; 21: 1746-1751

Hallek MH, Cheson BC, Catovsky DC, Caligaris-Cappio FC, Dighiero GD, Dohner HD, Hillmen PH, Keating MK, Montserrat EM, Rai KR, Kipps TK. Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 Guidelines. *Blood* 2008; 11: 5446-5456.

Hallek MH, Schmitt BS, Wilhelm MW, Busch RB, Krober AK, Fostitsch HPF, Sezer OS, Herold MH, et al. Fludarabine plus cyclophosphamide is an efficient treatment for advanced chronic lymphocytic leukemia (CLL): results of a phase II study of the German CLL Study Group. *Br J Haematol.* 2001;114:342-348.

Hochster H, Weeler E, Gascoyne RD, Habermann TM, Gordon LI, Ryan T, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG1496 study. *JCO* 2009; 27: 1607-1614.

Holzner, BH, Kemmler GK, Kopp MK, Nguyen VN, Sperner US, Greil RG. Quality of life of patients with chronic lymphocytic leukemia: Results of a longitudinal investigation over 1 yr. *Eur J Haematol.* 2004;72;381-389.

Huhn DH, von Schilling CvS, Wilhelm MW, Ho AH, Hallek MH, Kuse RK, et al. Rituximab Therapy of Patients with B-Cell Chronic Lymphocytic Leukemia. *Blood* 2001;98:1326-1331.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun M. Cancer Statistics, 2008. *CA: A Cancer Journal for Clinicians* 2008;58:71-96

Keating MK, O'Brien SO, Albitar MA, Lerner SL, Plunket WP, Giles FG, et al. Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2005;23:4079-4088.

Keating MK, Flinn IF, Jain VJ, Binet JB, Hillmen PH, Byrd JB, Albitar MA, Brettman LB, Santabarbara PS, Wacker BW, Rai KR. Therapeutic Role of Alemtuzumab (Campath-1H) in Patients Who Have Failed Fludarabine: Results of a Large International Study. *Blood* 2002;99:3554-3561.

Miller MM, et al. Rating Chronic Medical Illness Burden in Geropsychiatric Practice and Research: Application of the Cumulative Illness Rating Scale. *Psychiatry Res.* 1992;41:237-248.

Montoto S, Lopez-Guillermo A, Ferrer A, et al. Survival after progresión in patients with follicular lymphoma: analysis of prognostic factors. *Ann Oncol* 2002; 13:523-530.

Nabhan C, Gartenhaus RB, Tallman MS. Purine nucleoside analogues and combination therapies in B-cell chronic lymphocytic leukemia: dawn of a new era. *Leuk Res.* 2004; 28:429-442.

O'Brien SO, Moore JM, Boyd TB, Larratt LL, Skotnicki AS, Koziner BK, Chanan-Kahn CK, Seymour JS, Bociek RB, Pavletic SP, Rai KR. Randomized Phase III Trial of Fludarabine Plus Cyclophosphamide With or Without Oblimersen Sodium (Bcl-2 antisense) in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2007;25:1114-1120.

O'Brien SO, Kantarjian HK, Cortes JC, Beran MB, Koller CK, Giles FG, Lerner SL, Keating MK. Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2001(a);19:1414-1420.

O'Brien SO, Kantarjian HK, Thomas DT, Giles FG, Freireich EF, et al. Rituximab Dose Escalation Trial in Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2001(b);19:2165-2170.

Ofatumumab Investigator's Brochure, GSK Version 1. February 2009.

Oscier DO, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol.* 2004;125:294-317.

Osoba D, Zee B, Pater J, Warr D, Kaizer L, Latreille J. Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Qual Life Res*. 1994;3:353-364

Rai, KR, et al. Clinical Staging of Chronic Lymphocytic Leukemia. *Blood* 1975;46:219-234.

Rawston AC, Villamor N, Ritgen M, Bottcher S, Ghia P, et al. (2007). International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 21(5): 956-964

Redaelli, A., et al. The Clinical and Epidemiological Burden of Chronic Lymphocytic Leukaemia. *Eur J Cancer Care.* 2004;13:279-287.

Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlander N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK. *SEER Cancer Statistics Review, 1975-2005.* National Cancer Institute. Bethesda, MD USA; 2008.

Robak T et al. Rituximab, Fludarabine, and Cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone : Final results from the international randomized phase III REACH trial. *Blood* 2008;112 ASH Abstract 1ba-1.

Robak TR. Recent progress in the management of chronic lymphocytic leukemia. *Cancer Treatment Reviews* 2007;33:710-728.

Shanafelt TS, Kay NK, Morrison VM, Goldin LG. Comprehensive Management of the CLL Patient: A Holistic Approach. *Hematology* 2007;1:324-331.

Schlulz HS, Klein S, Rehwald U, Reiser M, et al. Phase 2 Study of a Combined Immunochemotherapy using Rituximab and Fludarabine in Patients with Chronic Lymphocytic Leukemia. *Blood* 2002;100:3115-3120.

Tam CT, Keating MK. Chemoimmunotherapy of Chronic Lymphocytic Leukemia. *Best Pract & Res Clin Haematol.* 2007;20:479-498.

Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA, Thomas DA, Cortes J, Lerner S, Keating MJ. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008 Aug 15;112(4):975-80

Teeling, J. L., et al. The Biological Activity of Human CD20 Monoclonal Antibodies Is Linked to Unique Epitopes on CD20. *J Immunol*. 2006;177:362-371.

van Oers MH. Rituximab maintenance in indolent lymphoma: indications and controversies. Curr Oncol Re 2007; 9: 378-83.

van Oers MHJ, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, Jack A, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results on a prospective randomized phase 3 intergroup trial. *Blood* 2006; 108: 3295-3301.

Wierda WW, O'Brien SO, Wen SW, Faderl SF, Garcia-Manero GG, Thomas DT, et al. Chemoimmunotherapy with Fludarabine, Cyclophoshamide, and Rituximab for Relapsed and Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2005;23:4070-4078.

Zenz TZ, Dohner HD, Stilgenbauer SS. Genetics and Risk-Stratified Approach to Therapy in Chronic Lymphocytic Leukemia. *Best Pract Res Clin Haematol.* 2007;20:439-453.

# 11. APPENDICES

## 11.1. Appendix 1: Time and Events

| Phase | SCREEN | Treatment or Observation (~ every 8 wks after 1st visit) | | | Follow-up (every 3 months for 5 years) | WD |
|---|---|---|---|---|---|---|
| Visit | Screening | 1 | 2 | 3-14 | 15-34 | |
| Week | (-6 to -1) | 1 | 2 | 9-97 | 109-337 | |
| Month | 0 | 1 | 1 | 3-25 | 28-85 | |
| Visit Window | | ± 7d | ± 3d | ± 7d | ± 14d | |
| Administration of Ofatumumab (if assigned to treatment group) | | X | X | X | | |
| Informed Consent | X | | | | | |
| Eligibility Criteria | X | | | | | |
| Demographics | X | | | | | |
| Medical History[1] | X | | | | | |
| Height | X | | | | | |
| Body weight | X | | X | X | X | X |
| Physical Exam | X | | X | X | X | X |
| Lymph node evaluation | X | | X | X | X | X |
| Organ Evaluation | X | | X | X | X | X |
| ECOG | X | | X | X | X | X |
| ECG | X | | | | | |
| Adverse Event Assessments | | X | X | X | X[12] | X |
| Concomitant Medications | | X | X | X | X[12] | X |
| CT Scan | X | | | X[2] | X[2] | X |
| Bone marrow biopsy | X[3] | | | X[3] | | |
| Flow cytometry (MRD) | X[3] | | | X[3] | X[3] | X[3] |
| Flow cytometry(CD5/CD19) | X | | | X | X[4] | X |
| Prognostic Factors[5] | X | | | | | X |
| Response Evaluation | | X | X | X | X | X |
| PRO | X | | | X | X | X |
| Hematology[6] | X | X | X | X | X | X |
| Biochemistry[6] | X | X | X | X | X | X |
| Hepatitis[7] and Pregnancy Test | X | | | | | |
| Igs | X | | | X[8,9] | | |
| HAHA [10] | | X | | X[8,9] | X[9] | X |
| Coombs and CH50 | X | | | | X | |
| PK Sampling[11] | | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | |

1. Medical history to include disease characteristics as defined in Section 6.1.
2. Sreening, yearly while on study, at the subject's last treatment visit and upon relapse
3. For subjects in CR ONLY- may be confirmed with bone marrow biopsy/flow cytometry
4. Until B-cell value is within normal levels (See Section 6.3.1.2.)
5. Prognostic Factors as defined in Section 6.3.3
6. See Section 6.3.2
7. Subjects that are HBsAg negative, HBcAb positive and HBV DNA negative may be included but must undergo HBV DNA monitoring as listed in Section 6.3.4
8. At the subject's last treatment visit
9. Every six months. Igs may be assessed during infection per PI. (See Section 6.3.4)
10. HAHA for ofatumumab treatment only-predose, every six months, at last treatment, and 3& 6 months post last ofatumumab dose, regardless of when it occurs.
    (See Section 6.3.4)
11. For pharmacokinetic sampling, see Table 5, Section 6.6; + 15 min window for 0.5h post EOI samples is allowed
12. Only SAEs and associated concomitant medications are to be reported from 60 days after the last dose/observation time. (See Section 6.4.8.)

## 11.2. Appendix 2: Response Definition Summary

This table is based on the parameters described in Section 6.2.1.

| | Parameter | CR | PR | PD |
|---|---|---|---|---|
| | **Response definition:** | **All criteria to be met** | **At least 2 of criteria 1, 2, 3 plus one criteria of 5a-c to be met** (minimum duration of 2 months) | **At least one criteria to be met** |
| **1** | Blood lymphocytes | <4000/µL | ≥50% decrease from BL | ≥50% increase over BL (and ≥5000/µL B-cells) |
| **2** | Lymphadenopathy[1] | absent (none >1.5cm) | ≥50% decrease from BL, no increase or new | ≥50% increase or new (>1.5cm) |
| **3** | Hepato/spleno megaly | absent | ≥50% decrease from BL | Increase ≥50%, or new |
| **4** | Constitutional symptoms | absent | n/a | n/a |
| **5a** | Neutrophils | >1500/µL | >1500/µL or ≥50% increase over BL | n/a |
| **5b** | Platelet count | >100,000/uL | >100,000/uL or ≥50% increase over BL | ≥50% decrease from B, or to >100,000/uL second. to CLL[2] |
| **5c** | Hemoglobin | >11 g/dL | >11 g/dL or increase ≥50% over BL | Decrease of >2 g/dL from BL or to <10 g/dL second. to CLL[2] |
| **6** | Marrow | Normocellular, no B-lymphoid nodules, <30% lymphocytes | n/a | n/a |
| **7** | other | n/a | n/a | CLL- transformation, cytopenia after treatment |

1. Sum of the products of multiple lymph nodes
2. Occurrence of cytopenia attributable to CLL at least 3 months after treatment defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells

BL=baseline,
Note: SD is defined as absence of progressive disease (PD) and failure to achieve at least a PR.

Modified from Table 4 IWCLL guidelines [Hallek, 2008]. For complete description and guidance, please refer to Hallek, 2008.

## 11.3. Appendix 3: Patient Reported Outcome Measures

### EORTC QLQ-C30

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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## EORTC QLQ-CLL 16

**EORTC QLQ – CLL16**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 31. Have you lost weight? | 1 | 2 | 3 | 4 |
| 32. Have you had a dry mouth? | 1 | 2 | 3 | 4 |
| 33. Did you bruise? | 1 | 2 | 3 | 4 |
| 34. Did you have abdominal discomfort? | 1 | 2 | 3 | 4 |
| 35. Has your temperature been going up and down? | 1 | 2 | 3 | 4 |
| 36. Did you have night sweats? | 1 | 2 | 3 | 4 |
| 37. Have you had skin problems (e.g. itchy, dry)? | 1 | 2 | 3 | 4 |
| 38. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 39. Did you feel lethargic? | 1 | 2 | 3 | 4 |
| 40. Have you felt "slowed down"? | 1 | 2 | 3 | 4 |
| 41. Were you limited in planning activities, for example meeting friends, in advance? | 1 | 2 | 3 | 4 |
| 42. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |

| During the past four weeks: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 43. Have you had trouble with chest infections? | 1 | 2 | 3 | 4 |
| 44. Have you had trouble with other infections? | 1 | 2 | 3 | 4 |
| 45. Have you needed repeated courses of antibiotics? | 1 | 2 | 3 | 4 |
| 46. Have you worried about picking up an infection? | 1 | 2 | 3 | 4 |

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Specimen

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

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

**Self-Care**

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

**Usual Activities (e.g., work, study, housework, family, or leisure activities)**

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

**Pain/Discomfort**

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

**Anxiety/Depression**

I am not anxious or depressed ☐

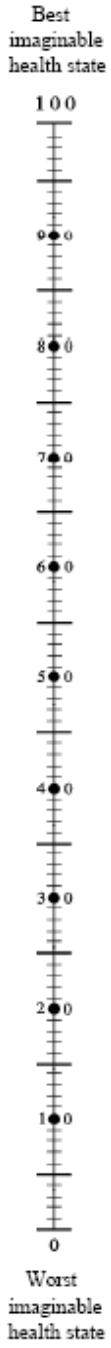
I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own health state today**



## Health change Questionnaire

Since you began the study, has there been any change in your health overall (please mark only one box)?

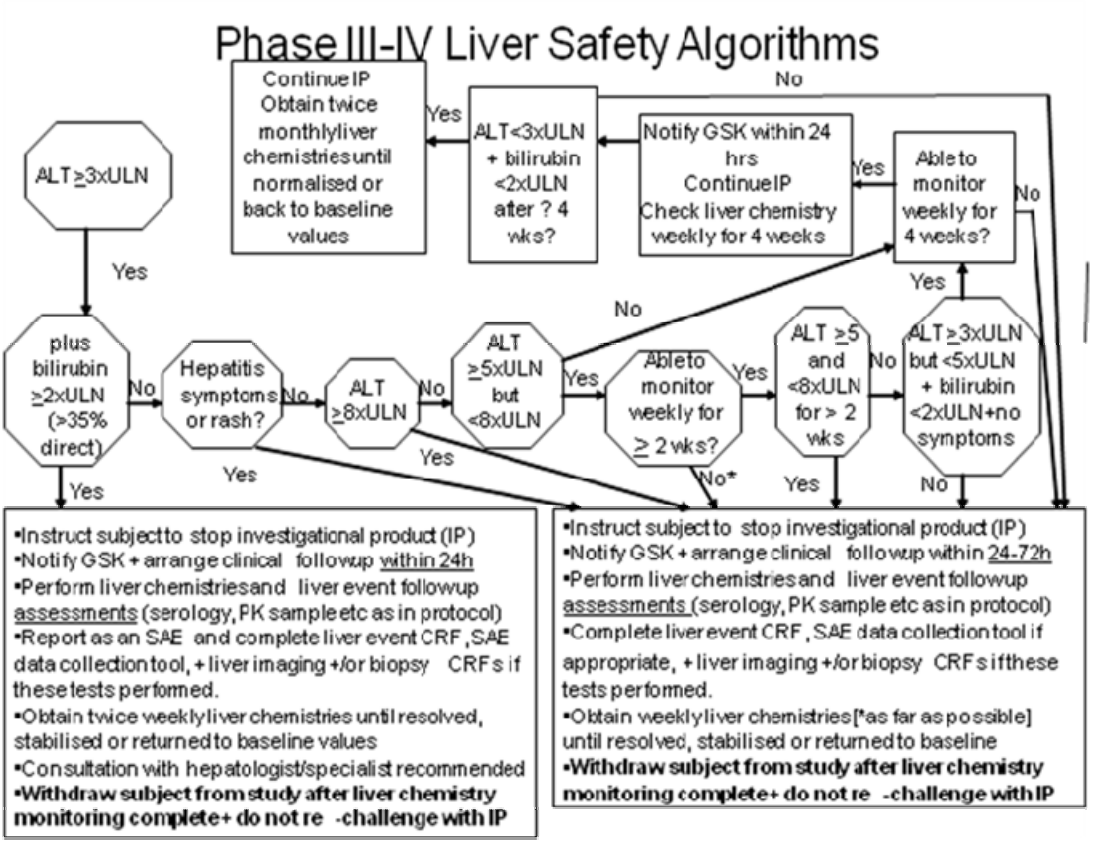
My Health is:

- ❒ A great deal better
- ❒ Moderately better
- ❒ A little better
- ❒ Almost the same, hardly any better at all
- ❒ Unchanged
- ❒ Almost the same, hardly any worse at all
- ❒ A little worse
- ❒ Moderately worse
- ❒ A great deal worse

## 11.4. Appendix 4: Country Specific Requirements

The French regulatory agency required that information from the Study Procedures Manual be included in Section 6.4.8 of the protocol. Therefore, Amendment 3 was required for France.

## 11.5. Appendix 5: Liver Chemistry Stopping and Follow-up Criteria†




† In order to align with the change of sponsorship from GSK to Novartis, all references to 'GSK' in this Appendix 5 should refer to 'Novartis.'

## 11.6. Appendix 6: Protocol Changes

Note: deleted language is printed as ~~strikethrough~~ and added language is printed in **bold.**

### Protocol Changes for Amendment 1

The main purpose for this amendment is to specify baseline MRD assessment, to add post-PD PRO questionnaires, [redacted] Other clarifications have also been included in amendment 1.

Note: deleted language is printed as ~~strikethrough~~ and added language is printed in **bold.**

Sponsor Information Page:

~~GlaxoSmithKline~~
[redacted]
~~Telephone:~~ [redacted]

[redacted] ~~MD, PhD~~
[redacted]
~~Tel:~~ [redacted]
~~Mob:~~ [redacted]
~~Fax:~~ [redacted]
~~Email:~~ [redacted]

**[redacted], MD**
[redacted]
**Telephone Number:** [redacted]
**Mob:** [redacted]
**Fax:** [redacted]
**Email:** [redacted]

List of Abbreviations:
~~CIRS Cumulative Illness Rating Scale~~
**Ig Immunoglobulins**

PROTOCOL SUMMARY

Study Design

CT Scans are required for confirmation of CR and partial remission (PR) **and yearly while on study.**
Study Endpoints/Assessments
Secondary Endpoints:

- **Progression-free survival after next-line therapy**
- **Time to progression after next-line therapy**

Section 2 Objectives
Secondary Objectives

- To evaluate the **improvement in response,** improvement in response time to next CLL treatment and overall survival in subjects receiving ofatumumab maintenance compared to no further treatment
- **To evaluate the PFS after next-line therapy and the time to progression after next-line therapy**

Section 3.1.3 Treatment Phase

300mg IV ~~Day 1~~ **Week 1** followed by 1000mg IV on ~~Day 8~~ **Week 2**

Section 3.14 Follow-up Phase:
Follow-up assessment after disease progression on treatment will ~~include a 1 month post-treatment safety assessment and subsequent follow-up visits to~~ assess survival status, date of next CLL therapy, type of therapy and response to therapy.

Section 3.2 Discussion of Design and Dose Rationale

**With the current treatment options, patients receiving chemoimmunotherapy (i.e. FCR) have the longest PFS. For patients not naïve to rituximab, this PFS represents a median of 28 months [Wierda, 2005] and a 40% increase of this PFS would be 39.2 months.**

Section 4.3 Exclusion Criteria
Criteria 3, 4, 5 combined into one criteria (#3). Criteria following #3 re-numbered.
Criteria #6 regarding heptatic DNA monitoring modified. Criteria #10 added.
Criteria #17 deleted.

~~3. Known transformation of CLL (e.g. Richter's transformation)~~

~~4. Known prolymphocytic leukemia (PLL)~~

5. ~~Known CNS involvement of CLL~~

3. **Known transformation of CLL (e.g. Richter's transformation), prolymphocytic leukemia (PLL), or CNS involvement of CLL**
4. Active Autoimmune Hemolytic Anemia (AIHA) requiring treatment except if in the opinion of the investigator and medical monitor it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data
5. Previous autologous or allogeneic stem cell transplantation

**6.** Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis B or C ~~(Hepatitis B**:** Positive serology for hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg **but** HBcAb positive **and** HBsAb negative, a HB DNA test will be performed and if positive the subject will be excluded. Note: If HBcAb positive **and** HBsAb positive, which is indicative of a past infection, the subject can be included.)~~

**(Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded*.)**

**7.** Other past or current malignancy (with the exception of basal cell carcinoma of the skin or in situ carcinoma of the cervix or breast) unless the tumor was successfully treated with curative intent at least 2 years prior to trial entry except if in the opinion of the investigator and medical monitor it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data

**8.** Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to screening ~~(Visit 1)~~, congestive heart failure, and arrhythmia requiring therapy, with the exception of extra systoles or minor conduction abnormalities except if in the opinion of the investigator and medical monitor it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data

**9.** History of significant cerebrovasculaor disease or event with symptoms or sequelae

**10. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator or GSK medical monitor contraindicates participation in this study**

**11.** Glucocorticoid unless given in doses ≤ 100 mg/day hydrocortisone (or equivalent dose of other glucocorticoid) if for exacerbations other than CLL (e.g. asthma)

**12.** Known HIV positive

**13.** Screening laboratory values:

- Platelets<50 x $10^9$/L
- Neutrophils<1.0 x $10^9$/L
- Creatinine > 1.5 times upper normal limit (unless normal creatinine clearance)
- Total bilirubin > 1.5 times upper normal limit (unless due to liver involvement of CLL)

- Alanine Aminotransferase (ALT) > 2.5 times upper normal limit (unless due to liver involvement of CLL)
- Alkaline phosphatase > 2.5 times upper normal limit

**14.** Known or suspected hypersensitivity to ofatumumab that in the opinion of the investigator or medical monitor contraindicates study participation

**15.** Subjects who have received treatment with any non-marketed drug substance or experimental therapy within 5-terminal half-lives or 4 weeks whichever is longer prior to first dose of study medication or currently participating in any other interventional clinical study
*Note: Participation in any other interventional clinical study after disease progression during post PD follow-up is permitted OR participation in any other interventional clinical study where the subject received **ONLY** standard approved CLL therapy is permitted.*

**16.** Lactating women, women with a positive pregnancy test at Visit 1 or women (of childbearing potential) as well as men with partners of childbearing potential, who are not willing to use adequate contraception from study start through one year following last ofatumumab dose. Adequate contraception is defined as abstinence, oral hormonal birth control, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device, and male partner sterilization if male partner is sole partner for that subject. For females in the USA, the use of a double barrier method is also considered adequate (condom or occlusive cap plus spermicidal agent).

~~**17.** Subjects known or suspected of not being able to comply with a study protocol (e.g. due to alcoholism, drug dependency or psychological disorder)~~

**** If HBV DNA is negative, subject may be included but must undergo HBV DNA monitoring (see Section 6.3.4). Prophylactic antiviral therapy may be initiated at the discretion of the investigator.***

Section 6.1.3 Cumulative Illness Rating Scale (CIRS):
This section was deleted as the CIRS is not applicable to this relapsed patient population entering the study in remission.

Section 6.1.6 Electrocardiogram

**Additional ECGs may be obtained as clinically warranted at the discretion of the PI or delegate.**

~~**Cumulative Illness Rating Scale (CIRS)**~~

~~The CIRS will be assessed at screening. The CIRS is a tool to measure multi-morbidity. This index measures the chronic medical illness burden and severity of co-existing chronic diseases [Miller, 1992]. See Appendix 4.~~

Section 6.2.3 Minimal Residual Disease (MRD):

**For subjects enrolling in the study who are in CR, baseline MRD will be assessed at screening, prior to any treatment visit.**

Section 6.3.4 Peripheral Blood Sampling for Safety and Disease Status:

- Direct antiglobulin test (Coombs test) at screening and ~~1month post last dose~~ **3 months after last treatment.**
- Human Anti-Human Antibody (HAHA) at screening, every 6 months during treatment, 3 and 6 months post treatment visit, or at last treatment visit.
  A HAHA sample (and a pharmacokinetic sample) should also be obtained at the last treatment visit if it does not occur at a scheduled sampling time (e.g., if treatment is discontinued early).

Section 6.3.4. Peripheral Blood Sampling for Safety and Disease Status

**For subjects that are HBsAg negative, HBcAb positive and HBV DNA negative (see Section 4.3) blood samples will be collected for HBV DNA testing every 2 months during the treatment/observation and during follow-up at the 3 months and 6 months visit.**

Section 6.4.8 Time Period and Frequency of Detecting AEs and SAEs:

**All SAEs and AEs for subjects not receiving treatment (observation) will be collected for the same duration of time (i.e. Visit 1 until 60 days after last visit, 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.

Section 6.5.6 Administration of PRO Measures:

**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.**

Section 6.6 Pharmacokinetics:

**A pharmacokinetic sample (and a HAHA sample) should also be obtained at the last treatment visit if it does not occur at a scheduled sampling time (e.g., if treatment is discontinued early).**

Table 5: Added "**Week**" column to clarify that Visit 1 Month 1 will be at **Week 1**; Visit 2 Month 1 will be at **Week 2** and Visit 3 Month 3 will be at **Week 9**.
To footnote 2 "**regardless of when it occurs**" added.

Section 8.1 Hypotheses

$H_0$: Distribution of the progression-free survival ~~curves~~ **events** for the ofatumumab maintenance treatment and for the no further treatment groups are the same (Hazard ratio is equal to 1)

$H_1$: Distribution of the progression-free survival ~~curves~~ **events** for the ofatumumab maintenance treatment and for the no further treatment groups are not the same (Hazard ratio is not equal to 1)

Section 8.3.3.2 Secondary and Other Comparisons of Interest:

~~The following secondary endpoints will also be assessed and compared between the ofatumumab maintenance treatment and the no further treatment groups:~~

- ~~Overall survival~~
- ~~Time to next CLL therapy~~
- ~~Improvement in response~~

**The primary efficacy endpoint will serve as a 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 (see Section 8.3.4) or at the 0.0498 significance level at the final 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 [redacted] 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 only if the primary endpoint, PFS, is significant.**

**1. Time to next CLL therapy**
**2. Overall survival**

**The control for multiplicity across the 'inferential secondary endpoints', 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 will between the ofatumumab maintenance treatment and no further treatment arms for other secondary endpoints will be done at an alpha equals 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**

Section 8.3.5.1 Efficacy Analyses:

- **Progression-free survival after next-line therapy**

**This endpoint will be defined as time from randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy.** [redacted]

- **Time to progression after next-line therapy**

**This endpoint will be defined as time from progression following randomization until progression or death following next-line therapy and counting as events deaths prior to next-line therapy.** [redacted]

Section 11.1 Appendix 1:

Time and Events Table updated to reflect changes as above. Visit numbers and weeks corrected. HAHA and Igs assessment rows combined. Hepatitis, Coombs and complement (CH50) testing added.

| Phase | SCREEN | Treatment or Observation (~ every 8 wks after 1st visit) | | | Follow-up (every 3 months for 5 years) | WD |
|---|---|---|---|---|---|---|
| Visit | Screening | 1 | 2 | 3-**14** | **15-34** | |
| Week | (-6 to -1) | 1 | 2 | 9-**97** | **109-329** | |
| Month | 0 | 1 | 1 | 3-25 | 28-85 | |
| Visit Window | | ± 7d | ± 3d | ± 7d | ± 14d | |
| Administration of Ofatumumab (if assigned to treatment group) | | X | X | X | | |
| Informed Consent | X | | | | | |
| Eligibility Criteria | X | | | | | |
| Demographics | X | | | | | |
| Medical History[1] | X | | | | | |

| Phase | SCREEN | Treatment or Observation (~ every 8 wks after 1st visit) | | | Follow-up (every 3 months for 5 years) | WD |
|---|---|---|---|---|---|---|
| Height ~~and Body weight~~ | X | | | | | |
| **Body weight** ~~Physical Exam~~ | X | | X | X | X | X |
| **Physical Exam** ~~Review of Systems~~ | X | | X | X | X | X |
| Lymph node evaluation | X | | X | X | X | X |
| Organ Evaluation | X | | X | X | X | X |
| ECOG | X | | X | X | X | X |
| ECG | X | | | | | |
| Adverse Event Assessments | | X | X | X | X | X |
| Concomitant Medications | | X | X | X | X | X |
| CT Scan | X | | | X[2] | **X[2]** | **X** |
| Bone marrow biopsy | X | | | X[3] | | |
| Flow cytometry (MRD) | **X[3]** | | | X[3] | X[3] | X[3] |
| Flow cytometry(CD5/CD19) | **X** | | | X | | **X** |
| Prognostic Factors[4] | X | | | | | X |
| Response Evaluation | | X | X | X | X | X |
| PRO | X | | | X | **X** | X |
| Hematology | X | X | X | X | X | X |
| Biochemistry | X | X | X | X | X | X |
| Urinalysis | X | | | | | |
| **Hepatitis[7]** and Pregnancy Test | X | | | | | |
| **Igs and HAHA** | X | | | X[5,6] | **X[6]** | |
| **Coombs and CH50** | **X** | | | | **X** | |
| PK Sampling[8] | | X | X | X | X | |
| Vital Signs | X | X | X | X | X | **X** |

1. Medical history to include disease characteristics ~~and CIRS~~ as defined in Section 6.1.
2. Sreening, yearly while on study, at the subject's last treatment visit and upon relapse
3. For subjects in CR ONLY- may be confirmed with bone marrow biopsy/flow cytometry
4. Prognostic Factors as defined in Section 6.3.3
5. At the subject's last treatment visit
6. Every six months. Ig~~G~~s may be assessed during infection per PI. **HAHA also at last treatment and 3& 6 months post last ofatumumab dose, regardless of when it occurs.**
7. **Subjects that are HBsAg negative, HBcAb positive and HBV DNA negative may be included but must undergo HBV DNA monitoring as listed in Section 6.3.4**.
8. For pharmacokinetic sampling, see Table 5, Section 6.6

Appendix 4: ~~Cumulative Illness Rating Scale~~ *deleted* as noted in Section 6.1.3

**Rating Strategy**
0 - No problem
1 - Current mild problem or past significant problem
2 - Moderate disability or morbidity/requires "first line" therapy
3 - Severe/constant significant disability/"uncontrollable" chronic problems
4 - Extremely severe/immediate treatment required/end organ failure/severe impairment function

| | Score |
|---|---|
| Heart | |
| Vascular | |
| Hematopoietic | |
| Respiratory | |
| Eyes, ears, nose, throat, and larynx | |
| Upper gastrointestinal tract | |
| Lower gastrointestinal tract | |
| Liver | |
| Renal | |
| Genito-urinary | |
| Musculoskeletal/integument | |
| Neurological | |
| Endocrine/metabolic and breast | |
| Psychiatric illness | |
| Total Number Categories Endorsed | |
| Total Score | |
| Severity Index: (total score/total number of categories endorsed) | |
| Number of categories at level-3 severity | |
| Number of categories at level-4 severity | |

Five summary variables are listed at the bottom of the scoring sheet. CIRS(G) = Cumulative Illness Rating Scale, operationalized with a manual of guidelines geared toward the geriatric patient.

~~[Miller, 1992]~~

## Protocol Changes for Amendment 2

The main purpose for this amendment is to clarify specifics in the protocol and changes to the inclusion/exclusion criteria as requested by regulatory agencies and investigators. Other additions such as study name, update to CTCAE version to be used and other clarifications and changes have been included in Amendment 2 as noted below.

The CTCAE throughout the entire document including Section 6.4.5 and Section 8.3.5.2 has been updated to the new version, version 4.0.

This amendment applies to all study sites.

### Amendment Summary of Main Changes

| Section(s) | Change | Rationale |
|---|---|---|
| Title | Name of study | Added |
| Sponsor information page | Eudra CT number added | Updated |
| Protocol Summary, Study Design and 3.1.4 Follow-up Phase | If a subject improves to CR during the study, then a bone marrow exam is required to confirm CR at least 2 months after response. CT scan requirements at screening, to confirm new CR, yearly while on study and at disease progression. | Modified bone marrow exam and CT scans for a maintenance study. |
| 4.2 Inclusion criteria | CT scan confirmation removed | Subjects entering the study may not have participated in clinical trial leading to remission- in alignment with IWCLL NCI-WG guidelines (2008) |
| 4.2 Inclusion criteria | Remission within 3 months of response assessment | Added for consistency with study design (Section 3.1) |
| 4.2 Inclusion criteria | Anti-leukemic therapy changed to 3 months/cycles | In alignment with current practices |
| 4.3 Exclusion criteria | Deleted ref to last tx. Rituximab information removed. | Simplied statement for clarity. |
| 4.3 Exclusion criteria | Exemption of Gilbert's syndrome from bilirubin eligibility restriction | No clinical significance of safety concern |
| 4.3 Exclusion criteria | Participation in other interventional studies removed | To avoid confounding study endpoints |

| Section(s) | Change | Rationale |
|---|---|---|
| 4.3 Exclusion criteria & Section 5.4 Prohibited Concomitant Medication or Therapies | Other anti-leukemic medication including glucorticoids | Clarified intent of glucocorticoid restriction and made consistent with Section 5.4 |
| 6.2.1.1 CR | Added timing for bone marrow assessment if CR achieved during maintenance treatment | Modified for a maintenance study |
| 6.2.1.4 SD | Removed | Modified for a maintenance study |
| 6.3 Lab Assessments | Exception of Coomb's test as local lab | Test too sensitive for shipping |
| 6.3.1.2 B-cell monitoring | Change in f/u B-Cell monitoring | Additional labs once values are within normal levels are not needed clinically |
| 6.3.2 Peripheral Blood Sampling | Change in haptoglobin analysis frequency | Bi-monthly monitoring not considered standard of care |
| 6.3.4 and 8.3.5.2 | HAHA sample assessments and analysis | Clarified for subjects receiving ofatumumab (including pre-dose sample following randomization) and analyses |
| 6.4.5 and 8.3.5.2 | CTCAE version from 3.0 to 4.0 | Updated |
| 6.6 PK | Sample window added for 0.5 EOI samples | Site logistics taken into consideration |
| T&E Table | Changes per protocol amendment<br>Urinalysis removed | Updated<br>Urinalysis – no value added and no clinical significance of safety concern |

### Amendment Details

Cover page (p. 1) Name of study added:

# PROLONG:

**P**hase III Trial in **R**elapsed CLL **O**f a Monoc**L**onal Antibody **O**fatumumab mainte**N**ance therapy to delay pro**G**ression vs observation

~~**Ofatumumab Maintenance Treatment versus No Further Treatment in Relapsed CLL Responding to Induction Therapy**~~
~~**OMB112517**~~

p.2 **(PFS)**

p. 4 **Eudra CT number: 2009-012518-39**

List of Abbreviations
**HB(V) Hepatitis B (Virus)**

Protocol Summary, Disease Markers and Section 6.3.3. Prognostic Factors
~~soluble CD20~~
*Rationale:* The soluble CD20 assay has been deleted from the protocol as this assay is currently not available and the development of the assay has been problematic due to limitations in the availability of an assay standard.

Protocol Summary, Study Design and Section 3.1.4 Follow-up Phase

A bone marrow examination is required to confirm Complete Remission (CR) at least 2 months after completion of therapy and when a subject fulfills the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-Sponsored Working Group (NCI-WG) requirements for Complete Remission (CR) [Hallek, 2008]. **Previous results may be used or if not available, a bone marrow exam may be done at screening**. **If a subject's response improves to a CR while on study, then a bone marrow examination is required to confirm CR at least 2 months after response as per the updated IWCLL NCI-WG requirements for CR [Hallek, 2008]. Additionally**, CT Scans are required **at screening**, for confirmation of a **new** CR, ~~and partial remission (PR) and~~ yearly while on study, and **at disease progression.**

*Rationale*: Clarified for a maintenance study.

Section 1.4 Rationale
5) ~~relapased~~ **refractory**

*Rationale: correction*

Section 3.1 Study Design
Reworded entry box from "~~CR or PR within 3 months of max 2 re-induction treatments for relapsed CLL~~" to "**CR or PR within 3 months after relapsed CLL treatment (max 2 prior tx)**"

*Rationale:* To clarify remission after last treatment for relapsed CLL

Section 3.1.3 Treatment Phase

~~and then every 3 months~~

*Rationale*: Redundant information provided in Section 3.1.4 Follow-up Phase

Section 4.2 Inclusion Criteria

2. ~~CR or~~ At least PR according to the revised 2008 NCI-WG CLL criteria~~, confirmed by CT scan,~~ **within 3 months of the response assessment** after **the last dose of** $2^{nd}/3^{rd}$ line treatment

*Rationale:* Confirmation of remission by CT scan is not per current guidelines, and as it is unlikely that a baseline CT scan at induction treatment would have been done, it would not be interpretable. Clarified duration of 3 months to be consistent with Section 3.1.

3. The anti-leukemic treatment before study entry should have been for at least ~~4~~ **3** months ~~of monotherapy with alkylating agents and/~~or ~~at least 4 consecutive~~ **3** cycles ~~of polychemotherapy (e.g. CVP), fludarabine-containing chemotherapy or immunochemotherapy~~

*Rationale: To simplify the wording to take into account all of the variations of treatments and regimens. As most therapy is assessed after 3 months or 3 cycles, this has been modified to reflect practice.*

Section 4.3 Exclusion Criteria

1. **Known** ~~P~~primary or secondary fludarabine-refractory subjects, defined as treatment failure (failure to achieve a CR or PR) or disease progression within 6 months ~~of prior anti-leukemic therapy~~ [Hallek, 2008] ~~NOTE: Subjects refractory to rituximab therapy as last therapy are permitted~~

*Rationale:* Simplifed statement for clarity. Removed rituximab as not relevant to fludarabine-refractory information.

4, 7, 8, 10 ~~medical monitor~~
*Rationale:* Reference to GSK medical monitor's input for clinical assessments removed as per Chief Medical Officer.

6. a HB**V** DNA test will be performed
*Rationale:* To add missing letter "V" in abbreviation.

11. **Other anti-leukemic use of medications including glucocorticoids** ~~Glucocorticoid unless given in doses ≤ 100 mg/day hydrocortisone (or equivalent dose of other glucocorticoid) if for exacerbations other than CLL (e.g. asthma)~~

Rationale: Clarification of the intent of glucocorticoid restrictions and consistency with Section 5.4.

13. Total bilirubin > 1.5 times upper normal limit (unless due to liver involvement of CLL **or Gilbert's syndrome**)
*Rationale:* To clarify that increased bilirubin values would not apply to subjects with Gilbert's syndrome

15. ~~OR participation in any other interventional clinical study where the subject received ONLY standard approved CLL therapy is permitted~~
*Rationale: This was removed to avoid potential confounding of other study endpoints.*

Section 4.4 Withdrawal Criteria

Subjects may be withdrawn from investigational product at any time if it is the wish of the subject (or their legally acceptable representative) for any reason, the investigator judges it necessary due to medical reasons **including disease progression** or the subject becomes pregnant. **(See also Section 8.3.5.)**

*Rationale:* To clarify withdrawal criteria at the request of Korean FDA.

Section 5.1.1.2 Ofatumumab Treatment Schedule

Reference in text to appropriate table corrected.

Table 2 Title: Infusion rate at 1st Ofaumumab**(300 mg)** Infusion
Table 3 Title: Infusion rate at subsequent Ofatumumab **(1000 mg)** Infusion
Footnote: **subsequent infusions= 2nd and 3-14th infusions**

*Rationale:* To clarify the dose of the infusions and which infusions are considered subsequent.

Section 5.4 Prohibited Concomitant Medication or Therapies

- Anti-cancer medication not part of the protocol treatment (e.g. alkylating agents, anti-metabolites, purine analogues, **other** monoclonal antibodies, and other **medications including glucocorticoids**)
- ~~Glucocorticoid unless given in doses equivalent to ≤ 100 mg/day of hydrocortisone, for less than 7 days if for exacerbations other than CLL (e.g. asthma), or unless given as premedication for ofatumumab infusions~~
- Any non-marketed drug substance or experimental therapy

  **Note: Glucocorticoids given for other indications such as exacerbations of asthma or as premedication for ofatumumab infusions are allowed.**

Section 6.2.1.1 Complete Remission (CR)

**or at the earliest 2 months after beginning this maintenance protocol (i.e. ofatumumab treatment/observation)**

*Rationale:* To clarify when during the study an improvement to CR may be noted and additional assessments such as bone marrow aspirate and biopsy be performed.

Section 6.2.1.4 Stable Disease (SD)

~~Subjects who have changed from a CR or a PR, but who have not exhibited PD, may be considered to have SD~~.

*Rationale*: This section was deleted as SD in a maintenance study is not as applicable.

Section 6.2.2. Bone Marrow Examination

**or at least 2 months of therapy or response while on study**

*Rationale:* Provide clarity and consistency with updated sections of protocol.

Section 6.2.3. Minimal Residual Disease (MRD)

For subjects who improve to a CR **while on study**, a bone marrow examination will be performed **after** at least **2** ~~3~~ months of therapy **or response while on study**.

*Rationale*: Provide consistency with other updated sections of the protocol.

Section 6.3 Laboratory Assessments

All the analyses will be performed by a central laboratory**, except for the direct antiglobulin test (Coomb's test) that will be performed locally**.

*Rationale:* This test is very sensitive to disruption, therefore, to ensure accurate results, the assay will be done locally.

Section 6.3.1.2 B-Cell Monitoring
**until values return to normal levels on two consecutive determinations**

*Rationale*: To clarify that if values are within normal levels for two consecutive assessments, no further testing is required.

Section 6.3.2 Peripheral Blood Sampling for Hematology and Biochemistry

~~, and haptoglobulin~~ **Haptoglobin will be analyzed at screening and 3 months after last treatment.**

*Rationale:* Bi-monthly haptoglobin monitoring is not considered standard of care. One pretreatment and one post-treatment assessment will be performed in alignment with the Coombs test analysis schedule for determination of autoimmune hemolytic anemia.

Section 6.3.4 Peripheral Blood Sampling for Safety and Disease Status

Human Anti-Human Antibody (HAHA) ~~at screening~~, prior to first dose of ofatumumab, every 6 months during **ofatumumab** treatment, and at 3 and 6 months post treatment (i.e., ~~screening~~ **predose Visit 1**, at Months 7, 13, 19, and 25 during treatment and at 3 and 6 months after last ofatumumab dose, regardless of when it occurs). A HAHA sample (and a pharmacokinetic sample) should also be obtained at the last treatment visit if it does not occur at a scheduled sampling time (e.g., if treatment is discontinued early). **HAHA samples will only be collected for subjects randomized to ofatumumab**.

*Rationale*: To clarify HAHA sample collection for those subjects receiving ofatumumab.

Immunoglobulins-**Additional samples may be collected post last treatment (such as 3 and 6 months follow-up), as warranted.**

*Rationale*: To allow additional Ig samples to be collected if needed (i.e. clinical concern regarding previous low values.)

Section 6.4.1.1. Liver Chemistry Stopping Criteria

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion ~~5~~ 3subjects should be monitored as frequently as possible.

*Rationale*: Correction of typo (only 3 criteria).

Section 6.6 Pharmacokinetics

**Predose samples may be collected at any time prior to dosing and EOI samples may be collected within a ±15 minute window around the scheduled time.**

*Rationale:* To provide clarification on logistics of pharmacokinetic sample collection.

Section 8.3.2 Analysis Data Sets

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

The ~~tumor~~ 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].

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

~~Response will be assessed by the investigators. Data will be summarized for investigator assessed response, and statistical inference for efficacy claims will be based on the data assessed by the investigators.~~

*Rationale:* Redundant information removed.

Section 8.3.5.2 Safety Analyses/Clinical Laboratory Evaluations

~~The change in Human Anti-Human Antibodies (HAHA) titers from screening to post-baseline visits will also be provided.~~

**The change in HAHA titers from predose to post-baseline visists and the number and the proportion of positive and negative results at each visit will be provided in the ofatumumab arm only. A listing of HAHA results and associated ofatumumab plasma concentration at each timepoint will be generated.**

Rationale: Clarification of context of HAHA information to be provided.

Section 11.1
Appendix 1: Time and Events

| Phase | SCREEN | Treatment or Observation (~ every 8 wks after 1st visit) | | | Follow-up (every 3 months for 5 years) | WD |
|---|---|---|---|---|---|---|
| Visit | Screening | 1 | 2 | 3-14 | 15-34 | |
| Week | (-6 to -1) | 1 | 2 | 9-97 | 109-3**37** | |
| Month | 0 | 1 | 1 | 3-25 | 28-85 | |
| Visit Window | | ± 7d | ± 3d | ± 7d | ± 14d | |
| Administration of Ofatumumab (if assigned to treatment group) | | X | X | X | | |
| Informed Consent | X | | | | | |
| Eligibility Criteria | X | | | | | |
| Demographics | X | | | | | |
| Medical History[1] | X | | | | | |
| Height | X | | | | | |
| Body weight | X | | X | X | X | X |
| Physical Exam | X | | X | X | X | X |
| Lymph node evaluation | X | | X | X | X | X |
| Organ Evaluation | X | | X | X | X | X |
| ECOG | X | | X | X | X | X |
| ECG | X | | | | | |
| Adverse Event Assessments | | X | X | X | X | X |
| Concomitant Medications | | X | X | X | X | X |
| CT Scan | X | | | X[2] | X[2] | X |
| Bone marrow biopsy | X[3] | | | X[3] | | |
| Flow cytometry (MRD) | X[3] | | | X[3] | X[3] | X[3] |
| Flow cytometry(CD5/CD19) | X | | | X | **X**[4] | X |
| Prognostic Factors[4,5] | X | | | | | X |
| Response Evaluation | | X | X | X | X | X |
| PRO | X | | | X | X | X |
| Hematology[6] | X | X | X | X | X | X |
| Biochemistry[6] | X | X | X | X | X | X |
| ~~Urinalysis~~ | ~~X~~ | | | | | |
| Hepatitis[7] and Pregnancy Test | X | | | | | |
| Igs ~~and HAHA~~ | X | | | X[5,6] [8,9] | X[6-9] | |
| **HAHA**[10] | | **X** | | **X** [8,9] | **X**[-9] | X |
| Coombs and CH50 | X | | | | X | |
| PK Sampling[8,11] | | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | |

1. Medical history to include disease characteristics as defined in Section 6.1.
2. Sreening, yearly while on study, at the subject's last treatment visit and upon relapse
3. For subjects in CR ONLY- may be confirmed with bone marrow biopsy/flow cytometry
4. ~~Prognostic Factors as defined in Section 6.3.3~~ **Until B-cell value is within normal levels (See Section 6.3.1.2.)**
5. **Prognostic Factors as defined in Section 6.3.3**~~At the subject's last treatment visit~~
6. ~~Every six months. Igs may be assessed during infection per PI. HAHA also at last treatment and 3& 6 months post last ofatumumab dose, regardless of when it occurs.~~ **See Section 6.3.4**
7. Subjects that are HBsAg negative, HBcAb positive and HBV DNA negative may be included but must undergo HBV DNA monitoring as listed in Section 6.3.4
8. ~~For pharmacokinetic sampling, see Table 5, Section 6.6.~~ **At the subject's last treatment visit.**
9. **Every six months. Igs may be assessed during infection per PI.** ~~**HAHA also at last treatment and 3& 6 months post last ofatumumab dose, regardless of when it occurs.**~~ **(See Section 6.3.4)**
10. **HAHA for ofatumumab treatment only-predose, every six months, at last treatment, and 3& 6 months post last ofatumumab dose, regardless of when it occurs. (See Section 6.3.4)**
11. For pharmacokinetic sampling, see Table 5, Section 6.6;± **15 min window for 0.5h post EOI samples is allowed**

*Rationale*: Urinalysis has been removed at screening as it does not add value to the safety data. Addition of footnote for B-cell values and subsequent footnotes nos. updated. A PK window was added as detailed in Section 6.6. for footnote 9.

## Protocol Changes for Amendment 3

### Where the Amendment Applies

Amendment 3 is applicable to all study sites that are required to include information from the Study Procedures Manual into Section 6.4.8 of the protocol.

### General Protocol Changes for Amendment 3 (07-Feb.-2013) from Amendment 2 (dated 21-MAY-2010)

- Specific details on how to handle the time period and frequency of detecting AEs and SAEs such as infusion reactions, Tumor Lysis Syndrome, Progressive multifocal leukoencephalopathyand Hepatitis described in Section 6.4.8 of the protocol.

### Amendment Details

**Section 6.4.6 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs Specific attention will be paid to monitor events of special interest such as infusion reactions, tumor lysis syndrome, infections and progressive multifocal leukoencephalopathy (PML). Please refer to the SPM and/or the following text*.**

***Handling Infusion Reactions:***

**Infusion reactions are commonly associated with anti-CD20 antibody therapy. Ofatumumab can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions.**

**The site staff must be prepared to intervene if an infusion reaction occurs. Special caution should be taken during the first infusion for each subject and during the infusion for any subject who did not tolerate a previous infusion well. It is recommended that a crash cart is readily accessible in the event of an emergency. Infusion reactions should be treated according to the investigators judgment and best clinical practice.**

**Interruption, restart and increasing the rate of the infusion depending on the severity of the AE must be according to the description below and at the investigator's discretion. An increase of the infusion rate after an interruption must not exceed the scheduled amount as described in Table 2 and Table 3 (i.e. not more than doubled rate and no earlier than every 30 minutes). See Section 5.1.1.3 for details on management related to intensity of adverse events.**

***Handling Tumor Lysis Syndrome:***

**Monitoring and treatment of potential Tumor Lysis Syndrome (TLS) should be performed as per oncology standard of care.**

**Symptoms of TLS include:**

- **Hyperkalemia, potentially leading to cardiac conduction abnormalities, muscle weakness or paralysis**
- **Hyperphosphatemia, potentially leading to renal failure**
- **Hypocalcemia. Symptoms include (but are not limited to): tetany, seizures, mental retardation / dementia, parkinsonian (extrapyramidal) movement disorders, papilledema, emotional instability / agitation / anxiety, myopathy**
- **Hyperuricemia, potentially leading to renal failure**

**Risk factors for TLS include a high tumor burden, high concentrations of circulating cells (≥ 25,000/mm3), hypovolemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Thus TLS should be suspected in subjects with large tumor burden who develop acute renal failure along with hyperuricemia (> 15 mg/dL) or hyperphosphatemia (> 8 mg/dL). Acute uric acid nephropathy is associated with little or no urine output. The urinalysis may show uric acid crystals or amorphous urates. The hypersecretion of uric acid can be detected with a high urine uric acid:creatinine ratio > 1.0, compared to a value of 0.6-0.7 for most other causes of acute renal failure.**

**In those patients considered to be at risk for TLS, management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance (consider aggressive hydration i.e. ~3,000 ml/$m^2$/day fluid administered parenterally) and supportive care. If signs of TLS occur the investigator can administer rasburicase allopurinol (e.g. Zyloprim, Allohexal, Allosig, Progout, Zyloric) or other drugs used to treat hyperuricemia, per prescribing information, if deemed appropriate.**

***Handling Progressive multifocal leukoencephalopathy (PML):***

**PML is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual and has been reported with ofatumumab. JC virus (JCV) infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus, an indication for which rituximab has not been approved. Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list, and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.**

**If a subject develops neurological signs or symptoms consistent with PML, treatment should be halted and the subject referred to a neurologist for evaluation.**

**At a minimum, blood JCV PCR and/or MRI should be performed; if either test is positive, Cerebrospinal Fluid (CSF) JCV PCR should be performed. If blood JCV PCR and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should be withdrawn from treatment, proceed to the Follow-Up Period, and be followed until resolution. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.**

**The investigator will do the following when reporting a serious infection (including PML) or sign/symptom consistent with PML.**

- **Refer to Section 6.4.10 of this document for further information and detailed guidance for completing and transmitting these and other SAE reports for subjects who experience a serious infection, malignancy, death, or sign or symptom of PML.**
- **Provide key source documentation for the Sponsor to assist with the safety evaluation process.**

**Examples of key source documents include but are not limited to: hospitalization records, discharge summaries, laboratory evaluations, biopsy results, culture/sensitivity results, death certificates, and autopsy reports.**

**If the subject has not otherwise been withdrawn from the study, then the investigator should contact the Sponsor to discuss the appropriate course of action regarding study continuation.**

***Monitoring of Hepatitis in patients:***

**For subjects who are HBsAg negative, HBcAb positive and HBV DNA negative, blood samples will be collected for HBV DNA testing every 2 months during the treatment/observation period and during follow-up at the 3 months and 6 months post last dose visits.**

**For subjects who require hepatitis monitoring, extra visits outside those defined in the protocol may be required.**

*Rationale: French regulatory requirement.*

## Protocol Changes for Amendment 4

The main purpose for this amendment is to incorporate the recommendations related to HBV reactivation which are based on the update to internal global safety information for ofatumumab. Recommendations are given on HBV screening, monitoring and management for all subjects who are receiving or may receive ofatumumab in the future and all subjects who have completed treatment with ofatumumab in the past 12 months and are in the follow-up phase of the protocol. This additional guidance for subjects with hepatitis was requested by the FDA for all anti-CD20 monoclonal antibodies. Other additions, clarifications and changes that have been included in Amendment 4 are noted below, and also include the additions for Amendment 3.

This amendment applies to all study sites.

### Amendment Summary of Main Changes

| Section(s) | Change | Rationale |
|---|---|---|
| Sponsor information page | Medical monitor contact Universal Trial Number added | Updated |
| 3.1.1. | Clarification that re-screening is acceptable | Clarification |
| 3.1.4. | Survival f-u remotely | Clarification |
| 4.3 | Further guidance re. HBV reactivation | Addition on HBV per regulatory request |
| 5.1.1.2 | Clarification on dose interruption | Additional guidance |
| 6.2.1 | Clarification on application of CLL guidelines | Additional guidance |
| 6.2.1.3 | Clarification on PD | Additional guidance |
| 6.2.4 | Clarification on CT scans | Clarification |
| 6.3 | Clarification on the use of local labs | Clarification |
| 6.4.8 | Further guidance re. HBV reactivation | Addition on HBV per regulatory request |
| 8.3.5.1 | Deletion of one censoring rule | Correction |
| Appendix 2 | Clarification for response definition summary, to be consistent with Section 6.2.1. | Clarification |

### Amendment Details

Section 3.1.1 Screening Phase
**At the discretion of the physician, rescreening is acceptable**.
*Rationale: clarification*

Section 3.1.4 Follow-up Phase
**It is acceptable for the information for survival follow-up visits to be collected**

**remotely (via telephone, email), as necessary. The frequency of the survival follow-up visits should be per local standard of care, suggested every 3 months for CLL. Minimally, this should be collected at least annually.**
*Rationale: clarification*

Section 4.3 Exclusion Criteria
**Consult with a physician experienced in the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.**
*Rationale: Addition per regulatory request*

Section 5.1.1.2 Ofatumumab Treatment Schedule
**Dose reductions or modifications of ofatumumab are not permitted with the exception of those initiated for patient safety (i.e. due to infusion reactions).**
**If a dose delay is required for ofatumumab, due to but not limited to adverse events, dosing may resume at physician discretion, and if the patient is still considered to be in remission.**
*Rationale: Additional guidance*

Section 6.2.1 Definition of Response
**The IWCLL updated NCI-WG guidelines should be applied in the context of clinical judgment and determination of disease progression is at the physician's discretion.**
*Rationale: Additional guidance*

Section 6.2.1.3 Progressive Disease (PD)
***Note: Physician's discretion should be used to distinguish between potential infection versus progressive disease based on lymphocyte count. It is acceptable to defer definitive judgment of progressive disease until further evidence is available.**
*Rationale: Additional guidance*

Section 6.2.4 CT-Scans
**approximately** yearly
**If a scheduled CT scan indicates disease progression, and the subject will be withdrawn, it is not necessary to repeat a CT scan for a withdrawal visit.**
**The actual CT scan (not just the radiologist report) should be available and performed to the criteria specified in the SPM.**
*Rationale: Clarification*

Section 6.3 Laboratory Assessments
**The protocol should be followed as closely as possible, but if as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis , but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment ) of protocol required lab assessments are acceptable, however, it is important that the sample for the central laboratory analysis is taken at the same time. The local laboratory results of absolute neutrophil count (ANC), platelet count, peripheral blood lymphocytes, and hemoglobin must also be entered into the eCRF, if these results are used to manage a treatment decision. Central laboratory information will also be entered into the**

**eCRF.**

**Safety assessments, such as hematology not specified in the protocol, are allowed between visits, per investigator discretion and local practice.**

*Rationale: Clarification*

Section 6.4.8 Time Period and Frequency of Detecting AEs and SAEs
**Subject who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBC positive. Anti-viral therapy should be initiated, if required. If a subject's HBV DNA becomes positive during the study, the GSK medical monitor should be notified. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab should be discussed with the medical monitor before appropriate treatment decisions are made for that individual subject.**
*Rationale: Addition per regulatory request*

Section 8.3.5.1 Efficacy Analyses
Table 7 PFS Assignment

| | | |
|---|---|---|
| ~~Treatment discontinuation for toxicity or other reason~~ | ~~Date of last assessment of measured lymph nodes~~ | ~~Censored~~ |

*Rationale: Correction, does not apply to subjects already in remission.*

Appendix 2: Response Definition Summary

PD Blood Lymphocytes: (**and** ≥5000/µL B-cells)
PR Neutrophils: >1500/µL **or ≥50% increase over BL**

**Modified fromTable 4 IWCLL guidelines [Hallek, 2008]. For complete description and guidance, please refer to Hallek, 2008.**
*Rationale: Clarification*

## Protocol Changes for Amendment 5

The purpose of this amendment is to stop further enrollment of new subjects in the study because the interim analysis of efficacy met the predefined significance level of $p<0.001$, indicating clinical benefit of the ofatumumab arm. The number of evaluable subjects as defined in the protocol (478) has been met. Minor clarifications have also been included in this amendment.

This amendment applies to all sites.

### Amendment Summary of Main Changes

| Section(s) | Change | Rationale |
|---|---|---|
| Protocol Summary-study design | Deletion<br><br><br>Addition | Number of subjects to be randomized deleted, as study will close to enrollment<br>Addition on closing enrollment |
| 1.5 | New section | Added to explain rationale for closing enrollment |
| 3.1.1. | Addition | Clarification |
| 3.1.3. | Change | Correction |
| 3.1.4 | Change | Clarification of CT scans during F/U |
| 4.1 | Update | Clarify study numbers |
| 6.5.6 | Change | Clarification of PRO administration |
| 8.3.4 | Change | New information and update to close enrollment |
| T& E | Addition | Footnote added to clarify SAE and concomitant collection in F/U. |

### Amendment Details

Protocol Summary, study design
~~Approximately 532~~

*Rationale: deletion, as enrolment will stop and evaluable number of subjects reached.*

**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**.

*Rationale: Addition to explain stopping enrolment and emphasis that study design will remain the same.*

Section 1.5 Rationale for Closing Enrollment

**At the start of the study, it was expected that the study would fully enroll prior to the IDMC review at 2/3 of the events. When the required number of events occurred prior to fully enrolling the study, but with the full number of evaluable**

**subjects available, and before the results were known, it was decided that if the primary endpoint met the predefined significance level of p<0.001, demonstrating clinical benefit for the ofatumumab arm, further enrollment would be discontinued. The independent data monitoring committee (IDMC) communicated that the significance level of p<0.001 for the primary endpoint at the interim analysis had been met. Additionally, the study had obtained the number of evaluable subjects required (the number of evaluable subjects at the time of the interim analysis was 479, with 478 evaluable required).**

**The conduct of the study will continue without modification, with continuation of the assessments of the efficacy and safety endpoints and no change in study design, in accordance with the IDMC recommendation. Currently, the standard of care is still observation, so that those subjects on the observation arm are receiving the standard of care and are not being jeopardized by continuation of observation. The recommendation of the IDMC was that subjects should continue in their assigned study arms without change in treatment. Additionally, the IDMC did not identify any safety concerns associated with long-term ofatumumab treatment.**

*Rationale: Addition- due to new information.*

Section 3.1.1. Screening Phase
Blood samples, physical examination, CT scan and bone marrow examination will be performed to determine **the study** baseline ~~disease status and study eligibility.~~

*Rationale: Clarification, not all procedures required for study eligibility per se.*

Section 3.1.3 Treatment Phase

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~~, **at each** treatment visit **beginning with Visit 3,** ~~and end of treatment~~ **at last visit, and at** follow-up visits.

*Rationale: Correction and clarification of study times for PRO administration.*

Section 3.1.4 Follow-up Phase

Additionally, CT Scans are required at screening, ~~for confirmation of a new CR,~~ yearly while on study, **including during follow-up,** and at disease progression**, whenever that may occur.**

*Rationale: Clarification of CT scan requirements for follow-up phase only.*

Section 4.1 Number of Subjects

**The original plan was for** approximately 583 subjects ~~will~~ to be screened (with 532 randomized) to obtain 478 evaluable subjects (assuming 10% screen failure and 10% drop out rates). **All evaluable subjects were obtained, and as the significance level was met at the interim efficacy of analysis, further enrollment will be stopped.**

*Rationale: Update due to new information*.

Section 6.5.6 Administration of PRO Measures

The EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D should be administered at baseline and at **each** treatment clinic visits; ~~Days 1 and 85~~ **beginning with Visit 3**, and **at each** follow-up visit~~s~~ post treatment; every 3 months through Month 60.

Section 8.3.4 Interim Analysis
Enrollment **was** ~~is~~ expected to be completed at the time of this analysis.

**However, when the required number of events occurred prior to fully enrolling the study, but with the full number of evaluable subjects available, and before the results were known, it was decided that if the primary endpoint met the predefined significance level of p<0.001, demonstrating clinical benefit for the ofatumumab arm, further enrollment would be discontinued.**

The study **conduct** will continue regardless of the outcome of the interim analysis of the primary endpoint.

*Rationale: Change- due to new information.*

Section: Time and Events Table

**[12]Only SAEs and associated concomitant medications are to be reported from 60 days after the last dose/observation time. (See Section 6.4.8.)**

*Rationale: Addition to clarify collection of AEs and concomitant medication during follow-up.*

## Protocol Changes for Amendment 6

The purpose of this amendment is to delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents and to make administrative changes to align with Novartis processes and procedures.

This amendment applies to all sites.

## Amendment Summary of Main Changes

| Section(s) | Change | Rationale |
|---|---|---|
| Sponsor signatory | Change of sponsor signatory | Change in study sponsor from GSK to Novartis |
| Multiple | Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents | To align with the change of sponsorship from GSK to Novartis. |
| Multiple | Make administrative changes | To align with the change of sponsorship from GSK to Novartis. |

### Amendment Details

### Section: Title Page:

The title page replaced as per Novartis requirements.

*Rationale: Change in study sponsorship.*

### Section: Sponsor Information Page

The GSK contact information has been replaced with Novartis details.

The term medical monitor has been replaced by medical lead and the email for medical lead provided.

*Rationale: Change in study sponsorship.*

### Section 4.3 Exclusion Criteria

14. Known or suspected hypersensitivity to ofatumumab that in the opinion of the investigator or ~~medical monitor~~ **medical lead** contraindicates study participation

*Rationale: To align with Novartis processes and procedures.*

### Section 5.1 Investigational Product and Reference Therapy

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS)

describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from ~~GSK~~**Novartis** upon request. Adequate precautions must be taken to avoid direct contact with the investigational product.

## Section 5.3 Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of ~~GSK~~ investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to ~~GSK~~**Novartis**, when applicable. Product accountability records must be maintained throughout the course of the study.

*Rationale: Change in study sponsorship.*

## Section 6.4.1 Liver chemistry stopping and follow-up criteria

According to ~~GSK~~**Novartis** policy across all compounds, liver chemistry stopping and follow- up criteria have been designed to assure subject safety and evaluate liver event etiology. (Refer to Appendix 5)

## Section 6.4.1.1 Liver Chemistry Stopping Criteria

- Report the event to ~~GSK~~**Novartis** within 24 hours of learning its occurrence

## 6.4.8 Time Period and Frequency of Detecting AEs and SAEs

Subject who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBC positive. Anti-viral therapy should be initiated, if required. If a subject's HBV DNA becomes positive during the study, the ~~GSK medical monitor~~**Novartis medical lead** should be notified. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab should be discussed with the ~~medical monitor~~**medical lead** before appropriate treatment decisions are made for that individual subject.

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol- mandated procedures, invasive tests, or change in existing therapy) ~~or related to GSK concomitant medication,~~ will be reported promptly to ~~GSK~~**Novartis**.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to ~~GSK~~**Novartis**.

## Section 6.4.9 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to ~~GSK~~**Novartis** within ~~2 weeks~~**24 hours** of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to ~~GSK~~**Novartis**.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to ~~GSK~~**Novartis** as described above.

## Section 6.4.10 Prompt Reporting of Serious Adverse Events and Other Events to ~~GSK~~Novartis

SAEs and pregnancies meeting the pre-defined criteria will be reported promptly to ~~GSK~~**Novartis** as described in the following table once the investigator determines that the event meets the protocol definition for that event.

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE" data collection tool | 24 hours | Updated "SAE" data collection tool |
| Pregnancy | ~~2 weeks~~**24 hours** | Pregnancy Form | 2 Weeks | Updated Pregnancy Form |

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to ~~GSK~~**Novartis** are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

*Rationale: Change in study sponsorship and to align with Novartis processes and procedures.*

## Section 7 Data Management

For this study subject data will be entered into ~~GSK defined~~**the** electronic case report forms (eCRFs), transmitted electronically to ~~GSK~~**Novartis** and **its authorized agents and be** combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable ~~GSK~~ standards and data cleaning procedures to ensure the integrity of the data, e.g., ~~removing~~**resolving** errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using **the** MedDRA and ~~an internal validated medication~~**a custom drug** dictionary~~, GSKDrug~~. eCRFs (including queries and audit trails) will be retained by ~~GSK~~**Novartis**, and copies will be sent to the investigator to maintain as the investigator copy. ~~In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.~~

*Rationale: Change in study sponsorship and to align with Novartis processes and procedures.*

### Section 8.3.5.2 Safety Analyses

Adverse events (AEs) will be coded using the ~~standard GlaxoSmithKline~~ Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and grouped by system organ class.

*Rationale: To align with Novartis processes and procedures.*

### Section 9.1 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, ~~GSK~~**Novartis** will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US IND.

The study will be conducted in accordance with all applicable regulatory requirements, including IND Number 11,719.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2000, as amended in 2002 and 2004 including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

~~GSK~~**Novartis** will provide full details of the above procedures, either verbally, in writing, or both.

### Section 9.2 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and ~~GSK~~**Novartis** procedures, ~~GSK~~**Novartis** monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ~~GSK~~**Novartis** requirements. When reviewing data collection

procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

~~GSK~~**Novartis** will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

## Section 9.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, ~~GSK~~**Novartis** may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

## Section 9.4. Study and Site Closure

Upon completion or termination of the study, the ~~GSK~~**Novartis** monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and ~~GSK~~**Novartis** Standard Operating Procedures.

~~GSK~~**Novartis** reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If ~~GSK determines~~**Novartis determine** that such action is required, ~~GSK~~**Novartis** will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, ~~GSK~~**Novartis** will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, ~~GSK~~**Novartis** will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. ~~GSK~~**Novartis** will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

## Section 9.5 Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local

regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a ~~GSK~~**Novartis** audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

~~GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.~~

**Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.**

The investigator must notify ~~GSK~~**Novartis** of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

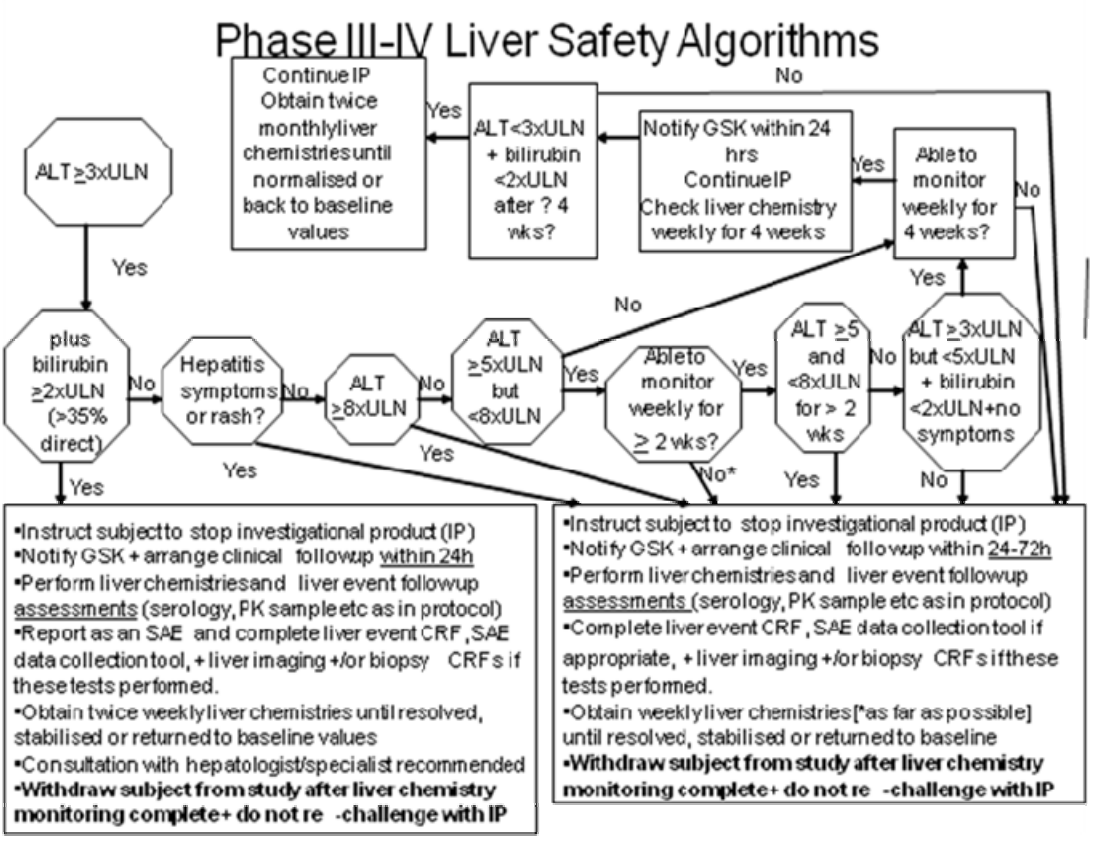
## Section 9.6 Provision of Study Results and Information to Investigators

The database results will be provided to [redacted] for the purposes of independent analysis for publication purposes in a peer reviewed journal. Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ~~GSK~~**Novartis** site or other mutually-agreeable location.

Upon completion of the clinical study report, ~~GSK~~**Novartis** will ensure public disclosure of the clinical trial research results via the ~~GSK~~**Novartis** Clinical ~~Trials~~ ~~**Register**~~**Trial Results website (www.novartisclinicaltrials.com)** according to the ~~GSK~~**Novartis** SOP and **will** provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

*Rationale: Change in study sponsorship and to align with Novartis processes and procedures.*

## Appendix 5: Liver Chemistry Stopping and Follow-up Criteria†




† **In order to align with the change of sponsorship from GSK to Novartis, all references to 'GSK' in this Appendix 5 should refer to 'Novartis.'**

*Rationale: Change in study sponsorship.*