TITLE PAGE

Information Type: Clinical Protocol Amendment

Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Ofatumumab Injection for Subcutaneous Use in Subjects with Pemphigus Vulgaris

Clinical Study Identifier: GSK study OPV116910 (also known as Novartis Study COMB157J2301) / NCT01920477

Compound Number: GSK1841157 (also known as OMB157)

Development Phase: III

Effective Date: 05-Sep-2016

Protocol Amendment Number: 8

Description: Ofatumumab is a novel human IgG1k lytic monoclonal antibody that specifically binds to the human CD20 antigen, which is expressed only in B lymphocytes from the pre–B-cell stage to the plasmacytoid immunoblast stage.

This global study will investigate the efficacy, safety, and tolerability of ofatumumab injection for subcutaneous (SC) use in the treatment of subjects with pemphigus vulgaris. The primary objective of the study is to determine the efficacy, based on disease remission, of ofatumumab SC at a dose of 20 mg administered every 4 weeks (with an additional 20-mg 'loading' dose [ie, 40 mg total] at both Week 0 and Week 4) in subjects with pemphigus vulgaris. Other objectives include evaluation of safety, tolerability, B-cell depletion and repletion, anti-desmoglein antibody levels, immunogenicity, pharmacokinetics, and other clinical and quality of life endpoints.

Subject: pemphigus vulgaris, ofatumumab, monoclonal antibody

Authors: [redacted]

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N142611_02	2013-APR-23	Original
2012N142611_03	2013-JUN-21	Amendment No. 1
Improve clarity, adjust timing of some assessments, and address questions/comments from the US FDA.		
2012N142611_04	2013-SEP-26	Amendment No. 2
Improve clarity and address questions/comments from the US FDA. This amendment was superseded by Protocol Amendment 3 before implementation at any study center.		
2012N142611_05	2014-MAR-13	Amendment No. 3
Change dose, dosing regimen, and associated assessment time points.		
2012N142611_06	2014-SEP-18	Amendment No. 4
Addition of cross-reference to Appendix 2 for country-specific requirements.		
2012N142611_07	2015-APR-02	Amendment No. 5
Minor inclusion criteria changes, corrections and clarifications for consistency throughout protocol, and inclusion of country-specific requirements for Japan.		
2012N142611_08	2015-SEP-28	Amendment No. 6
Inclusion and exclusion criteria changes (Inclusion #3, Inclusion #5, Exclusion #4, and Exclusion #8), changes to the Individualized Follow-up Period, addition of an objective and three endpoints for the Individualized Follow-up Period, addition of country-specific requirements for Korea, removal of references to the dilution method of study treatment preparation, corrections and clarifications for consistency throughout the protocol. OPV116910 Protocol Amendment 6 supported a change at the end of the treatment period to allow subjects who completed treatment and were otherwise eligible to roll-over into an open-label extension study (OPV117059). Only sites in the USA had subjects near completion of the treatment period; therefore, Amendment 6 was only submitted to the USA FDA at the time of finalization and the changes in study conduct detailed in Amendment 6 were only implemented in study centers in the USA.		

2012N142611_09	2016-APR-25	Amendment No. 7
Subjects are required to stay in the Individualized Follow-up Period until both their IgG levels AND their CD19+ B-cell counts are ≥LLN or baseline levels (if <LLN) or up to 2 years after the last dose of investigational product (whichever comes first). Subjects are no longer required to stay in Individualized Follow-up for a minimum of 1 year. Due to the fact that Amendment 6 was only submitted in the USA, study conduct transitioned from Amendment 6 to Amendment 7 for study centers in the USA and from Amendment 5 to Amendment 7 for study centers in all other countries.		

Date	**Version**
2016-Sep-01	Amendment No. 8
Sponsor transition from GSK to Novartis, including addition of Novartis study IDs (GSK study OPV116910 now also known as Novartis study COMB157J2301 and GSK study OPV117059 now also known as Novartis study COMB157J2301E1) and changes of Sponsor company name, addresses, and personnel details. Pregnancy reporting period amended to 24 hours. Protocol Amendment 7 incorporated in the full protocol document.	

SPONSOR SIGNATORY:

[redacted], MD, PhD
[redacted]
Novartis Pharma AG

Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier: OPV116910 (also known as COMB157J2301)

Sponsor Legal Registered Address:

Novartis Pharma AG
Lichtstrasse 35, 4056 Basel
Switzerland

Sponsor Contact Address:

Novartis AG
Novartis Campus
Fabrikstrasse 2, 4056 Basel
Switzerland

In some countries, the clinical study Sponsor may be the local Novartis affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical study submission.

Medical Monitor Contact Information:

United States	Medical Monitor	Phone: [redacted] Fax: Email:
Europe	Medical Monitor	Phone: [redacted] Fax: Email: [redacted]
Asia Pacific	Medical Monitor	Phone: [redacted] Fax: Email: [redacted]

Serious Adverse Events (SAEs) Contact Information:

[redacted]: US Telephone [redacted]
US Fax Line

Regulatory Agency Identifying Numbers: US IND 116301; EudraCT 2013-001370-20

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical 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 AND DEFINITIONS

Abbreviations

[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc (or HBcAb)	hepatitis B core antibody
AST	aspartate aminotransferase
[redacted]	[redacted]
CMH	Cochran–Mantel–Haenszel
CRF	case report form
[redacted]	[redacted]
Dsg	desmoglein
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
g	gram(s)
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAHA	human anti-human antibody
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
Ig	immunoglobulin
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat (population)
IV	intravenous
IVR	interactive voice response
JCV	JC virus
LLN	lower limit of normal (reference range)
mg	milligram(s)
mL	milliliter(s)
PCR	polymerase chain reaction
[redacted]	
PGx	pharmacogenetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PML	progressive multifocal leukoencephalopathy
PP	per protocol (population)
PV	pemphigus vulgaris
QTc	corrected QT interval

RAP	reporting and analysis plan
RBC	red blood cell
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous(ly)
SPM	study procedures manual
SR	sustained remission
TB	tuberculosis
[redacted]	[redacted]
ULN	upper limit of normal (reference range)
WBC	white blood cell

Protocol-Specific Definitions

Study Periods:

Core Study Period	The Core Study Period includes the 56-week double-blind Treatment Period and 4-week Follow-up Visit (at Week 60).
Individualized Follow-up Period	If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until both the CD19+ B-cell counts and circulating IgG levels are ≥LLN or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first). Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.
Screening Period	A Screening Period of 2 to 12 weeks will occur prior to randomization to allow subjects to achieve disease control using a stable oral dose of prednisone/prednisolone. Multiple visits to the clinic are permitted during this time to assess disease status and to adjust the oral prednisone/prednisolone dose.

Clinical Definitions:

Did not flare/relapse	Achieved remission on minimal steroid therapy and did not subsequently have a flare/relapse of disease by Week 60
Disease control	No new lesions for ≥2 weeks
Disease flare/relapse	Appearance of ≥3 new lesions within 1 month that do not heal spontaneously within 1 week, or when there is an extension (worsening) of lesions that were present at the randomization visit *(Note: the appearance of 1 or 2 new lesions is not considered a flare/relapse)*
Duration of remission on minimal steroid therapy	Total time (sum) of all periods of remission while on minimal steroid therapy (oral prednisone/prednisolone dose ≤10 mg/day) up to Week 60

Eliminated use of systemic steroids	An oral prednisone/prednisolone dose of 0 mg/day for ≥2 weeks
Minimal steroid therapy	An oral prednisone/prednisolone dose of ≤10 mg/day
Remission	Absence of new or nonhealing (established) lesions for ≥8 weeks *(Note: Subjects with existing, healing lesions may be considered in remission if other criteria are met.)*
Remission on minimal steroid therapy	Absence of new or nonhealing (established) lesions while on an oral prednisone/prednisolone dose of ≤10 mg/day for ≥8 weeks
Sustained remission (SR)	The absence of new or nonhealing (established) lesions for ≥8 weeks that is sustained until Week 60
Time to remission off steroid therapy	Time from randomization to the time the subject initially tapered off all steroids for ≥8 weeks with an absence of new or nonhealing (established) lesions by Week 60
Time to remission on minimal steroid therapy	Time from randomization to the time the subject initially tapered his/her oral prednisone/prednisolone dose to ≤10 mg/day and maintained ≤10 mg/day of oral prednisone/prednisolone with no new or nonhealing (established) lesions for ≥8 weeks by Week 60
Time to initial flare/relapse	Time from randomization to the time of appearance of ≥3 new lesions within 1 month that do not heal spontaneously within 1 week, or to the time when there is an extension of lesions that were present at the randomization visit
Time to sustained remission on minimal steroid therapy	Time from randomization to the time the subject initially tapered his/her oral prednisone/prednisolone dose to ≤10 mg/day and maintained ≤10 mg/day of oral prednisone/prednisolone with no new or nonhealing (established) lesions for ≥8 weeks AND maintained that status until Week 60

PROTOCOL SUMMARY

Rationale

Pemphigus vulgaris (PV) is an acquired, rare, chronic, debilitating, and potentially life-threatening autoimmune vesiculobullous disorder that is characterized by mucocutaneous blisters. Without treatment, such blistering eventually leads to erosions in the skin, resulting in significant mortality.

Systemic glucocorticoids have been the cornerstone of management, reducing mortality from 70% to less than 20% [Carson, 1996; Langan, 2008]. In the United States, various steroid preparations are approved for treatment of pemphigus. In Europe, both steroids and azathioprine are approved for pemphigus or PV. Unfortunately, chronic treatment with high-dose corticosteroids causes significant morbidity. A recent Cochrane report [Martin, 2011] identified only 11 randomized controlled studies assessing pemphigus interventions, and concluded that the optimal therapeutic strategy remains unclear.

Intravenous (IV) rituximab, a chimeric immunoglobulin (Ig) G1 monoclonal antibody targeting the B-cell specific CD20 antigen, has been reported to successfully treat PV in case-series reports in severe or refractory disease [Ahmed, 2006; Cianchini, 2007; Joly, 2007; Eming, 2008; Kim, 2011; Kasperkiewics, 2012; Leshem, 2013; Lunardon, 2012], and in a single case report as a first-line therapy [Craythorne, 2011]. The reduction of pathogenic antibodies via targeted B-cell depletion forms the basis for the use of rituximab in the treatment of PV, and clinical response to rituximab has correlated with B-cell depletion [Mouquet, 2008; Eming, 2008; Colliou, 2013]. Use of rituximab for PV treatment remains limited by the need for infusion suites for drug administration and the lack of any randomized prospective clinical studies evaluating its efficacy and safety. Rituximab is not an approved treatment for PV.

Ofatumumab is a monoclonal antibody that targets the CD20 antigen on B-cells. The actions of ofatumumab on B-cells are similar to rituximab; however, ofatumumab binds to a different epitope on the CD20 molecule and has demonstrated superior *in vitro* Fc effector functions (complement-dependent and antibody-dependent cellular cytotoxicity). B-cell depletion has been documented with IV administration of ofatumumab in subjects with rheumatoid arthritis and multiple sclerosis, and with subcutaneous (SC) administration of ofatumumab in subjects with rheumatoid arthritis (GlaxoSmithKline Study OFA110867). Therefore, ofatumumab injection for SC use (ofatumumab SC) has the potential to reduce disease activity in patients with PV, a potentially life-threatening condition.

Objectives

Primary Objective

To determine the efficacy, based on disease remission, of ofatumumab SC at a dose of 20 mg administered every 4 weeks (with an additional 20-mg loading dose [ie, 40 mg total] at both Week 0 and Week 4) in subjects with PV.

Secondary Objectives

- To evaluate the safety and tolerability of ofatumumab SC.
- To evaluate disease flare/relapse during treatment with ofatumumab SC.
- To evaluate reductions in steroid dose while maintaining disease control.
- To assess population pharmacodynamics and the extent of B-cell depletion and repletion following ofatumumab SC.
- To evaluate the immunogenicity of ofatumumab SC.
- To assess the population pharmacokinetics of ofatumumab SC.

[redacted]

Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety, and tolerability of ofatumumab SC in subjects with PV, who have failed a previous attempt to taper steroid dosing (ie, had a disease flare during the taper attempt). The study includes a Screening Period, a 56-week Treatment Period, and a 4-week Follow-up visit. Subjects will visit the clinic during Screening; at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have structured phone visits between each of the clinic visits from Week 10 through Week 22. It is anticipated that total duration of participation in this study will be approximately 72 weeks.

A Screening Period of 2 to 12 weeks will occur prior to randomization to allow subjects to achieve disease control (no new lesions for ≥2 weeks) using a stable oral dose of prednisone/prednisolone (20 mg/day up to 120 mg/day or 1.5 mg/kg/day [whichever is higher] for ≥2 weeks). Multiple visits to the clinic are permitted during the Screening Period to assess disease status and to adjust the oral steroid dose. Once disease control is achieved, subjects who continue to meet all inclusion and exclusion criteria may be randomized. All screening procedures should be completed within 12 weeks of informed consent being given.

At the Baseline Visit (Day 0), approximately 136 eligible subjects will be centrally randomized 1:1 across 2 strata (disease duration [≤1 year, >1 year] and baseline prednisone dose [<60 mg/day, ≥60 mg/day]) to receive SC administration of ofatumumab 20 mg or placebo once every 4 weeks (with an additional 20-mg 'loading' dose at both Week 0 and Week 4) for a total of 56 weeks (total of 17 injections across 15 monthly dosing visits). Two weeks after the first dose of ofatumumab SC or placebo (ie, Week 2), the oral steroid dose will be gradually reduced according to a fixed dose-taper schedule

with a goal of reducing (ie, to ≤10 mg/day) or eliminating the dose of prednisone/prednisolone.

After the last dose of ofatumumab SC or placebo at Week 56, subjects will be followed-up for a minimum of 4 weeks, with a visit scheduled at Week 60. As the ofatumumab development program in the indication PV has been terminated, subjects completing the study will no longer be eligible to participate in the extension study (OPV117059 [also known as COMB157J2301E1]). Subjects who were enrolled in the extension study prior to program termination may remain in the extension study until exit criteria are met. Subjects who do not participate in the planned extension study will not receive any additional treatment after completion of this study.

If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until both the CD19+ B-cell counts and circulating IgG levels are ≥ lower limit of normal (LLN) or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first). Individualized Follow-up visits will be scheduled every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.

Study Population

Approximately 136 subjects will be randomized into the study.

Study Endpoints/Assessments

Co-Primary Endpoints*:

- Time to sustained remission on minimal steroid therapy.
- Duration of remission on minimal steroid therapy.

Secondary Endpoints*:

- Proportion of subjects achieving remission on minimal steroid therapy at Week 60.
- Time to remission while on minimal steroid therapy by Week 60.
- Time to initial flare/relapse by Week 60.
- Proportion of subjects who did not flare/relapse by Week 60.
- Time to remission off steroid therapy by Week 60.
- Proportion of subjects achieving remission while off steroid therapy by Week 60.
- Number of days a subject maintained minimal steroid therapy by Week 60.
- Cumulative dose of corticosteroids.

**Note: definitions are provided with the list of abbreviations and in Section 6.2.*

Safety:

- Adverse events (AEs).
- Adverse event frequency, severity, and relationship to investigational product.
- Frequency and severity of infections.
- Frequency of serious AEs.
- Frequency of withdrawals due to treatment-related AEs.
- Frequency of AEs leading to permanent discontinuation of investigational product.
- Frequency of AEs of special interest, postinjection systemic reactions, and injection site reactions.
- Change from baseline in vital signs.
- Frequency of vital signs of clinical concern.
- Change from baseline in laboratory (hematology, chemistry, and urinalysis) parameters.
- Frequency of laboratory (hematology, chemistry, and urinalysis) results of potential clinical concern.
- Immunogenicity as measured by the incidence, titer, and type of human anti-human antibody immune response.

Pharmacokinetic Endpoints:

- Plasma (trough) concentrations of ofatumumab.
- Exposure-response relationship.
- *For subjects in the pharmacokinetic-pharmacodynamic substudy*: Maximum ofatumumab concentration; time of maximum concentration; and area under the time concentration curve.
- Effect of demographic factors, including baseline covariates, on pharmacokinetic endpoints.

Pharmacodynamic Endpoints:

- Change from baseline in B-lymphocyte counts in peripheral blood.
- Time to repletion of CD19+ B-cells to either ≥ the baseline level or ≥LLN range, whichever is lower.
- B-cell depletion and repletion as measured by CD19+ peripheral blood B-lymphocyte count via routine fluorescent activated cell sorting analysis.
- *For subjects in the pharmacokinetic-pharmacodynamic substudy*: CD19+ peripheral blood B-lymphocyte count via routine fluorescent activated cell sorting analysis with subsets including, but not restricted to, naïve and memory phenotypes.

1. INTRODUCTION

1.1. Disease Background

Pemphigus vulgaris (PV) is an acquired, rare, chronic, debilitating, and potentially life-threatening autoimmune vesiculobullous disorder that is characterized by mucocutaneous erosions or blisters. The term "pemphigus" includes PV, pemphigus foliaceus, and paraneoplastic pemphigus, with PV being the most widely diagnosed form of pemphigus.

Pemphigus vulgaris presents with peak frequency generally occurring at 30 to 60 years of age and older, with an incidence of approximately 7 per million worldwide and a mortality rate of <20%. The disease is caused by pathogenic antibodies directed against desmoglein (Dsg) 1 and 3, which are members of the desmosomal cadherin family. The *in vivo* binding of these anti-Dsg autoantibodies (mainly immunoglobulin [Ig] G4 and IgG1) causes a loss of adhesion between keratinocytes, and the resultant formation of intra-epidermal blisters [Amagai, 1995]. These blisters eventually lead to erosions in the skin which, prior to the corticosteroid era, frequently resulted in mortality.

1.2. Current Treatments

Systemic glucocorticoids have been the cornerstone of management for PV, reducing mortality from 70% to less than 20% [Carson, 1996; Langan, 2008]. In the United States, steroids are indicated for the treatment of pemphigus; in some European countries, steroids and azathioprine are labeled for use in patients with pemphigus or PV. Chronic high-dose steroid treatment, however, causes significant morbidity, resulting in patients being additionally treated with various adjuvant medications with the intention of minimizing steroidal side effects (eg, increased blood pressure, hyperglycemia, neuropsychiatric changes, and bone demineralization). An optimal steroid–sparing agent has not yet been identified, due in part to the paucity of randomized controlled studies conducted to date. A recent Cochrane report [Martin, 2011] identified only 11 randomized, controlled studies assessing pemphigus interventions, and concluded that the optimal therapeutic strategy remains unclear.

Intravenous (IV) rituximab, a chimeric IgG1 monoclonal antibody that depletes B-cells by targeting the B-cell-specific CD20 antigen, was identified in case-series reports as a successful treatment for severe or refractory PV [Ahmed, 2006; Cianchini, 2007; Joly, 2007; Eming, 2008; Kim, 2011; Kasperkiewics, 2012; Leshem, 2013; Lunardon, 2012], and in a single case report as a first-line therapy [Craythorne, 2011]. The reduction of pathogenic antibodies via targeted B-cell depletion forms the basis for the use of rituximab in the treatment of PV, and clinical response to rituximab has correlated with B-cell depletion [Mouquet, 2008; Eming, 2008; Colliou, 2013]. Rituximab, which is not approved for use in PV, has not been evaluated for the treatment of PV in randomized prospective clinical studies, and its use remains limited given the need for infusion suites for drug administration.

1.3. Ofatumumab

Ofatumumab is a monoclonal antibody that targets the CD20 antigen on B-cells. It is currently approved and marketed (ARZERRA™) for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. Administration of ARZERRA is via IV infusion, with 12 doses over 30 weeks (300 mg initial dose, followed by 2000 mg weekly for 7 doses, then 2000 mg every 4 weeks for 4 doses). In addition, ofatumumab has been investigated as an IV infusion for other oncology indications, and as an IV infusion and as a subcutaneous (SC) injection for autoimmune disorders (ie, relapsing-remitting multiple sclerosis [RRMS] and rheumatoid arthritis).

The actions of ofatumumab on B-cells are similar to rituximab; however, ofatumumab binds to a different epitope on the CD20 molecule and has demonstrated superior *in vitro* Fc effector functions (complement-dependent and antibody-dependent cellular cytotoxicity). Robust B-cell depletion has been documented following IV administration of ofatumumab to subjects with autoimmune conditions (rheumatoid arthritis and RRMS). B-cell depletion with ofatumumab SC has also been documented following single-dose administration to subjects with rheumatoid arthritis (GlaxoSmithKline [GSK] Study OFA110867) and repeat-dose administration to subjects with RRMS (GSK Study OMS112831).

Additional information is provided in the Investigator's Brochure [Ofatumumab/OMB157/GSK1841157 Investigator's Brochure, 2016].

1.4. Rationale

Although no cure is currently available for PV, the efficacy of systemic corticosteroids (often administered at high doses and concomitantly with other immunosuppressive treatment) in managing PV has been well demonstrated [Harman, 2003]. Systemic corticosteroids are currently the most commonly utilized therapy for the management of PV. Multiple side-effects associated with high-dose corticosteroids, however, increase morbidity and may necessitate the use of adjuvant steroid-sparing therapies.

For subjects failing PV treatment due to adverse events (AEs) associated with high-dose steroid treatment or other immunosuppressants, or due to dosing inconvenience (as in the case of rituximab with the attendant need for an infusion suite), additional therapeutic approaches are needed to appropriately treat PV.

The objective of this study is to evaluate the efficacy, tolerability, and safety of ofatumumab injection for SC use (ofatumumab SC) at a dose of 20 mg administered every 4 weeks (with an additional 20-mg loading dose [ie, 40 mg total] at both Week 0 and Week 4) in subjects with PV. It is anticipated that with sustained B-cell depletion in the presence of ofatumumab SC, and the resultant reduction of pathogenic anti-Dsg autoantibodies in PV, that clinical remission of the disease will result.

2. OBJECTIVE(S)

2.1. Primary Objective

To determine the efficacy, based on disease remission, of ofatumumab SC at a dose of 20 mg administered every 4 weeks (with an additional 20-mg loading dose [ie, 40 mg total] at both Week 0 and Week 4) in subjects with PV.

2.2. Secondary Objectives

- To evaluate the safety and tolerability of ofatumumab SC.
- To evaluate disease flare/relapse during treatment with ofatumumab SC.
- To evaluate reductions in steroid dose while maintaining disease control.
- To determine the extent of B-cell depletion and repletion following ofatumumab SC.
- To evaluate the immunogenicity of ofatumumab SC.
- To assess the population pharmacokinetics of ofatumumab SC.

3. INVESTIGATIONAL PLAN

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Table 6-1), are essential and required for study conduct.

Refer to Appendix 2 for any additional applicable country-specific requirements.

3.1. Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety, and tolerability of ofatumumab SC in subjects with PV, who have failed a previous attempt to taper steroid dosing (ie, had a disease flare during the taper attempt). The study includes a Screening Period, a Core Study Period (consisting of the 56-week Treatment Period and 4-week Follow-up visit), and an Individualized Follow-up Period (as applicable).

Subjects will visit the clinic during Screening; at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have

structured phone visits between each of the clinic visits from Week 10 through Week 22 (see Appendix 14). It is anticipated that total duration of participation in the Core Study Period will be approximately 72 weeks.

A Screening Period of 2 to 12 weeks will occur prior to randomization to allow subjects to achieve disease control (no new lesions for ≥2 weeks) [Murrell, 2008]) using a stable oral dose of prednisone/prednisolone (20 mg/day up to 120 mg/day or 1.5 mg/kg/day [whichever is higher] for ≥2 weeks). Multiple visits to the clinic are permitted during this Screening Period to assess disease status and to adjust the oral prednisone/prednisolone dose. Once disease control is achieved, subjects who continue to satisfy the eligibility criteria may be randomized. All screening procedures should be completed within 12 weeks of informed consent being given.

At the Baseline Visit (Day 0), approximately 136 eligible subjects will be centrally randomized 1:1 across 2 strata (disease duration [≤1 year, >1 year] and baseline prednisone dose [<60 mg/day, ≥60 mg/day]) to receive SC administration of ofatumumab 20 mg or placebo once every 4 weeks (with an additional 20-mg 'loading' dose at both Week 0 and Week 4) for a total of 56 weeks (total of 17 injections across 15 monthly dosing visits).

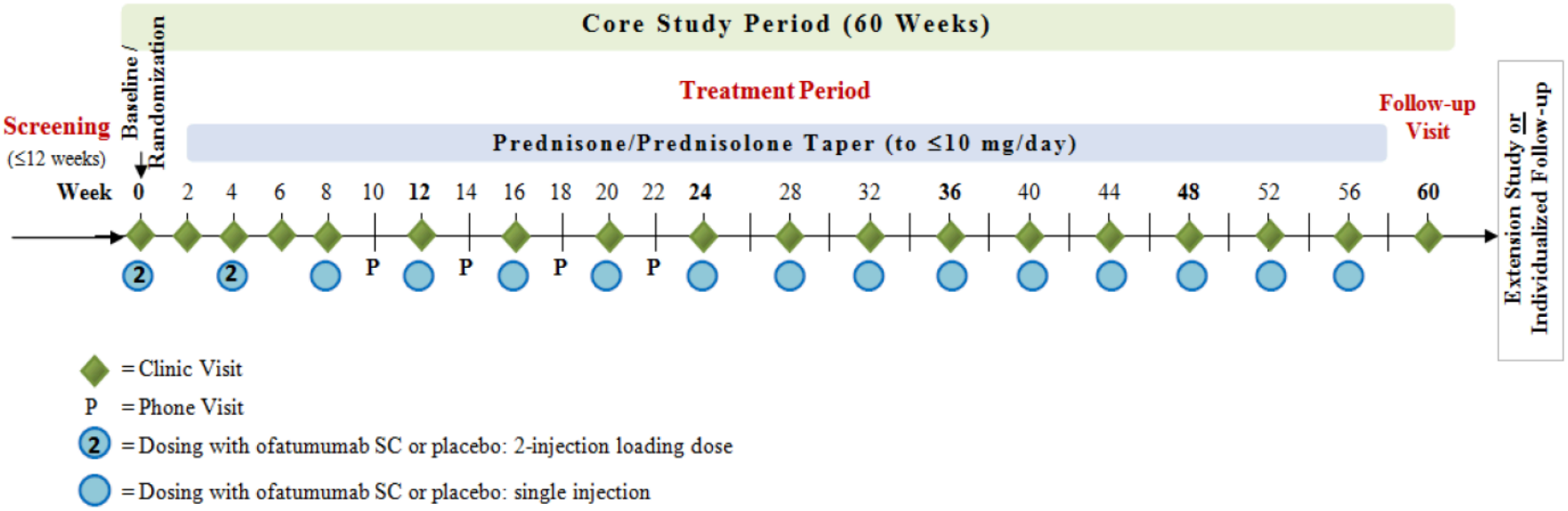
Two weeks after the first dose of ofatumumab SC or placebo (ie, Week 2), the oral steroid dose will be gradually reduced according to a fixed dose-taper schedule with a goal of reducing (ie, to ≤10 mg/day) or eliminating the dose of prednisone/prednisolone (see Table 3-2).

After the last dose of ofatumumab SC or placebo at Week 56, subjects will be followed-up for a minimum of 4 weeks, with a visit scheduled at Week 60. As the ofatumumab development program in the indication PV has been terminated, subjects completing the study will no longer be eligible to participate in the extension study (OPV117059 [also known as COMB157J2301E1]). Subjects who were enrolled in the extension study prior to program termination may remain in the extension study until exit criteria are met. Subjects who do not participate in the planned extension study will not receive any additional treatment after completion of this study.

If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until both the CD19+ B-cell counts and circulating IgG levels are ≥ lower limit of normal (LLN) or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first) (see Figure 3-2). Individualized Follow-up visits will be scheduled every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period (as applicable; guidance will be provided within the [redacted] visit report, laboratory values will remain blinded).

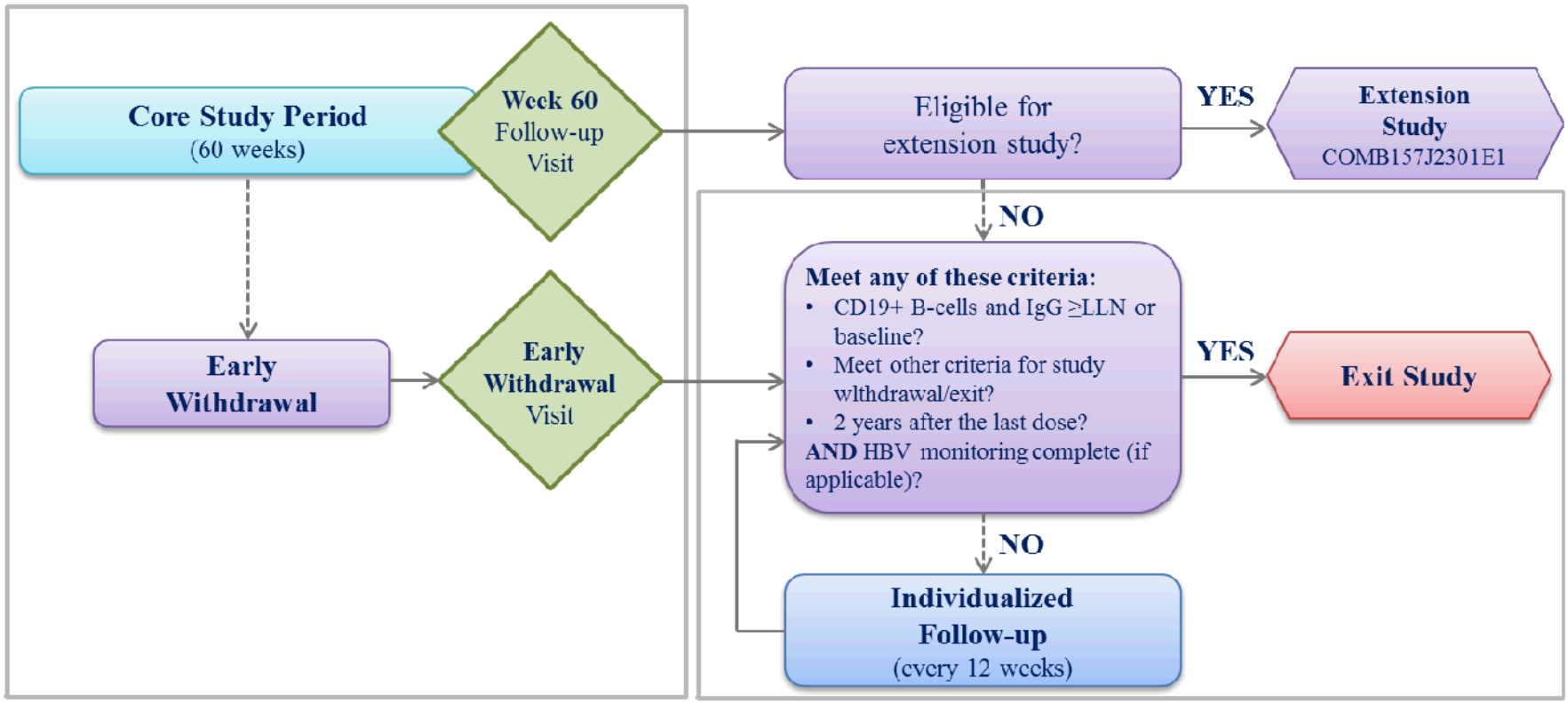
An independent data monitoring committee (IDMC) will evaluate risks relative to benefits through review of safety and efficacy data on an ongoing basis during the study. Any case of suspected or confirmed progressive multifocal leukoencephalopathy (PML) will go through independent PML adjudication and an opinion will be provided to the Sponsor.

Figure 3-1 Study Schema



Abbreviation: SC=subcutaneous.

Figure 3-2 Study Flowchart



Abbreviations: HBV=hepatitis B virus; Ig=immunoglobulin; LLN=lower limit of normal.

Table 3-1 Study Objectives and Endpoints

Primary Objective	**Co-Primary Efficacy Endpoints**
To determine the efficacy, based on disease remission, of ofatumumab SC at a dose of 20 mg administered every 4 weeks (with an additional 20-mg loading dose [ie, 40 mg total] at both Week 0 and Week 4) in subjects with PV	• Time to sustained remission on minimal steroid therapy • Duration of remission on minimal steroid therapy
	Secondary Efficacy Endpoints – supporting primary objective
	• Proportion of subjects achieving remission on minimal steroid therapy at Week 60 • Time to remission while on minimal steroid therapy • Time to remission off steroid therapy by Week 60 • Proportion of subjects achieving remission while off steroid therapy by Week 60
Secondary Objectives – *Efficacy and Pharmacodynamic*	**Secondary Endpoints**
To evaluate disease flare/relapse during treatment with ofatumumab SC	• Time to initial flare/relapse by Week 60 • Proportion of subjects who did not flare/relapse by Week 60
To evaluate reductions in steroid dose while maintaining disease control	• Number of days a subject maintained minimal steroid therapy to Week 60 • Cumulative dose of corticosteroids
To determine population pharmacodynamics and the extent of B-cell depletion and repletion following ofatumumab SC	• Change from baseline in B-lymphocyte counts in peripheral blood • Time to repletion of CD19+ B-cells to either ≥baseline level or ≥LLN, whichever is lower • B-cell depletion and repletion as measured by CD19+ peripheral blood B lymphocyte count via routine fluorescent activated cell sorting analysis • *For subjects in the pharmacokinetic-pharmacodynamic substudy:* CD19+ peripheral blood B-lymphocyte count via routine fluorescent activated cell sorting analysis with subsets including, but not restricted to, naïve and memory phenotypes
Secondary Objectives – *Pharmacokinetic*	
To assess the population pharmacokinetics of ofatumumab SC	• Plasma (trough) concentrations of ofatumumab • Exposure-response relationship • *For subjects in the pharmacokinetic-pharmacodynamic substudy:* Maximum ofatumumab concentration; time of maximum concentration; and area under the time-concentration curve • Effect of demographic factors, including baseline covariates, on pharmacokinetic endpoints

Secondary Objectives – *Safety*	Safety Endpoints
To evaluate the immunogenicity of ofatumumab SC in subjects with PV	• Immunogenicity as measured by the incidence, titer, and type of human anti-human antibody immune response
To evaluate the safety and tolerability of ofatumumab SC	• AEs: – Frequency, severity, and relationship to investigational product – Frequency and severity of infections – Frequency of serious AEs – Frequency of withdrawals due to treatment-related AEs – Frequency of AEs leading to permanent discontinuation of investigational product – Frequency of AEs of special interest, postinjection systemic reactions, and injection site reactions • Change from baseline in vital signs and frequency of vital signs of clinical concern • Change from baseline in laboratory (hematology, chemistry, and urinalysis) parameters and frequency of laboratory results of potential clinical concern
[redacted]	[redacted]

Abbreviations: AE=adverse event; [redacted]; [redacted]; LLN=lower limit of normal; PV=pemphigus vulgaris; SC=subcutaneous.

3.1.1. Screening Period

Before any study-specific procedures are performed, the appropriate written informed consent must be obtained (see Section 9.2). To assess subject eligibility, all screening assessments, as listed in the Time and Events Table (Table 6-1), should be completed. A Screening Period of up to 12 weeks will allow subjects to achieve disease control (ie, no new lesions for ≥2 weeks) using a stable dose of 20 mg/day up to 120 mg/day (or 1.5 mg/kg/day, whichever is higher) of oral prednisone/prednisolone for ≥2 weeks. Once disease control has been attained, subjects may be randomized to treatment, provided they continue to fully satisfy the eligibility criteria. Refer to the study procedures manual (SPM) for retesting and/or rescreening procedures.

3.1.2. Treatment Period

Subjects who meet all eligibility criteria will be randomized 1:1 to receive either ofatumumab SC or placebo; all doses of investigational product will be administered at the study center once every 4 weeks under the observation of the investigator, with the first dose (Week 0) signifying the start of the 56-week Treatment Period.

During the 56-week Treatment Period, site personnel will administer all doses of investigational product in the clinic. Subjects must be treated with acetaminophen/paracetamol and an antihistamine (cetirizine or equivalent) 1 to 2 hours prior to each administration of investigational product to lessen the likelihood of localized reactions.

Subjects will remain on the stable daily oral steroid dose achieved during the Screening Period until Week 2, when they will begin tapering their steroid dose with the goal of reducing or eliminating the daily use of steroids. Subjects' daily oral steroid dose will be reduced by 1 dose level every 2 weeks (as illustrated in Table 3-2) until the onset of disease flare/relapse. For a subject who experiences disease flare/relapse, the prednisone/prednisolone dose will be increased by 1 to 4 levels per week until disease control is achieved (ie, no new lesions for ≥2 weeks); the prednisone/prednisolone taper will then be reinitiated after a 2-week period of disease control.

Table 3-2 Oral Prednisone/Prednisolone Dose-taper Schedule

Current Dose	Next Taper Dose [a] (every 2 weeks)	Increase Dose for Flare/Relapse [b] (increase by 1 to 4 levels per week)				Dose for Post-Flare Taper
		1 level	2 levels	3 levels	4 levels	
160	140	180	200	220	240	Decrease dose by 1 level after 2 weeks of disease control, then return to standard taper schedule.
140	120	160	180	200	220	
120	100	140	160	180	200	
100	80	120	140	160	180	
80	60	100	120	140	160	
60	50	80	100	120	140	
50	40	60	80	100	120	
40	30	50	60	80	100	
30	25	40	50	60	80	
25	20	30	40	50	60	
20	17.5	25	30	40	50	
17.5	15	20	25	30	40	
15	12.5	17.5	20	25	30	
12.5	10	15	17.5	20	25	
10 [c]	7.5	12.5	15	17.5	20	
7.5	5	10	12.5	15	17.5	
5	2.5	7.5	10	12.5	15	
2.5	0	5	7.5	10	12.5	
0	0	2.5	5	7.5	10	

a. Prednisone/prednisolone is reduced by 1 dose level every 2 weeks, with the goal being elimination of prednisone/prednisolone. For subjects at a starting dose >160 mg, taper dose by 20 mg every 2 weeks until the dose is 160 mg, at which point the decrements shown on the table above should be used.

b. Subjects will remain on the standardized oral prednisone/prednisolone taper schedule until disease flare/relapse. In the event of disease flare/relapse, oral prednisone/prednisolone will be increased by a rate of 1 to 4 levels per week until disease control is re-established. The oral prednisone/prednisolone taper will then be reinitiated after disease control is maintained for 2 weeks.

c. Once the dose is reduced to 10 mg, an attempt at reducing the steroid dose further need only be attempted until the first flare/relapse occurs. In the event of a flare/relapse at a prednisone/prednisolone dose of ≤10 mg/day, the dose will be temporally increased in order to re-establish disease control (no new lesions for >2 weeks); after disease control is maintained, further steroid tapering attempts to <10 mg will be at the investigator's discretion.

3.1.3. Follow-up Period

Subjects will be followed-up for a minimum of 4 weeks after the last dose of investigational product at the Week 56 visit. The follow-up visit will include B-cell counts and other safety, efficacy, and quality of life assessments.

If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study (OPV117059) will remain in Individualized Follow-up until:

- CD19+ B-cell counts and circulating IgG levels are ≥LLN or baseline levels (if <LLN)
- Other criteria for study withdrawal/exit are met (see Section 4.4.3)
- Two years after the last dose of investigational product (whichever comes first).

The Individualized Follow-up assessments should be scheduled approximately every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.

Note: Subjects who are hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (anti-HBc) positive, and hepatitis B virus (HBV) DNA negative (or if in Japan and HBsAg negative, anti-HBc (HBcAb) negative, but hepatitis B surface antibody [HBsAb] positive) must continue HBV DNA polymerase chain reaction (PCR) monitoring at a minimum of every 12 weeks for 6 months after the last dose of study treatment.

For subjects who participate in the extension study, OPV116910 (also known as COMB157J2301) Week 60 study assessments will be completed before any study-related assessments are performed for the extension study.

3.1.4. Pharmacokinetic-Pharmacodynamic Substudy

This protocol includes a substudy to determine the pharmacokinetics and pharmacodynamics of ofatumumab SC in subjects with PV. The substudy will be conducted at selected study centers and will enroll approximately 25 subjects. Subject participation in the substudy is optional and requires informed consent. A subject may be enrolled in the primary study whether or not he/she chooses to participate in the substudy.

The Time and Events Table for the substudy-specific visits and sampling time points is provided in Table 6-3. An attempt should be made to draw pharmacokinetic samples at the same time of day as administration of the first dose of investigational product.

3.2. Discussion of Design

The design of the study has taken into account the low incidence and chronic relapsing nature of PV, and the fact that therapy with corticosteroids—albeit associated with significant side effects—represents the standard of care for management of PV. The study is designed to evaluate the efficacy of ofatumumab SC in an environment where a subject requiring corticosteroids is undergoing a taper towards minimal treatment or, ideally, no treatment with systemic steroids. For this reason, the study has been designed to add the randomized study treatment (1 group receiving ofatumumab SC and the other group receiving placebo) over a background of tapering steroids in all subjects.

The dosing duration of 1 year will allow adequate time to assess time to remission in both study groups. Historical data indicate that remission can be expected in approximately

54% of subjects in the placebo group (with steroid dose adjustment), and in about 80% of subjects in the ofatumumab SC group [Beissert, 2010].

When administered via IV infusion, ofatumumab has been associated with infusion reactions that have occasionally led to temporary interruption or withdrawal of treatment. To reduce such reactions, premedication with acetaminophen/paracetamol, oral or IV antihistamine, and oral and/or IV glucocorticoids has been used in clinical studies involving oncology and rheumatoid arthritis populations. In the current study, to lessen the likelihood of localized reactions with administration of ofatumumab SC, oral doses of acetaminophen/paracetamol and antihistamine will be administered 1 to 2 hours prior to the administration of investigational product. All subjects (ofatumumab SC and placebo groups) will be premedicated in order to maintain blinding and to minimize confounding variables on dosing days.

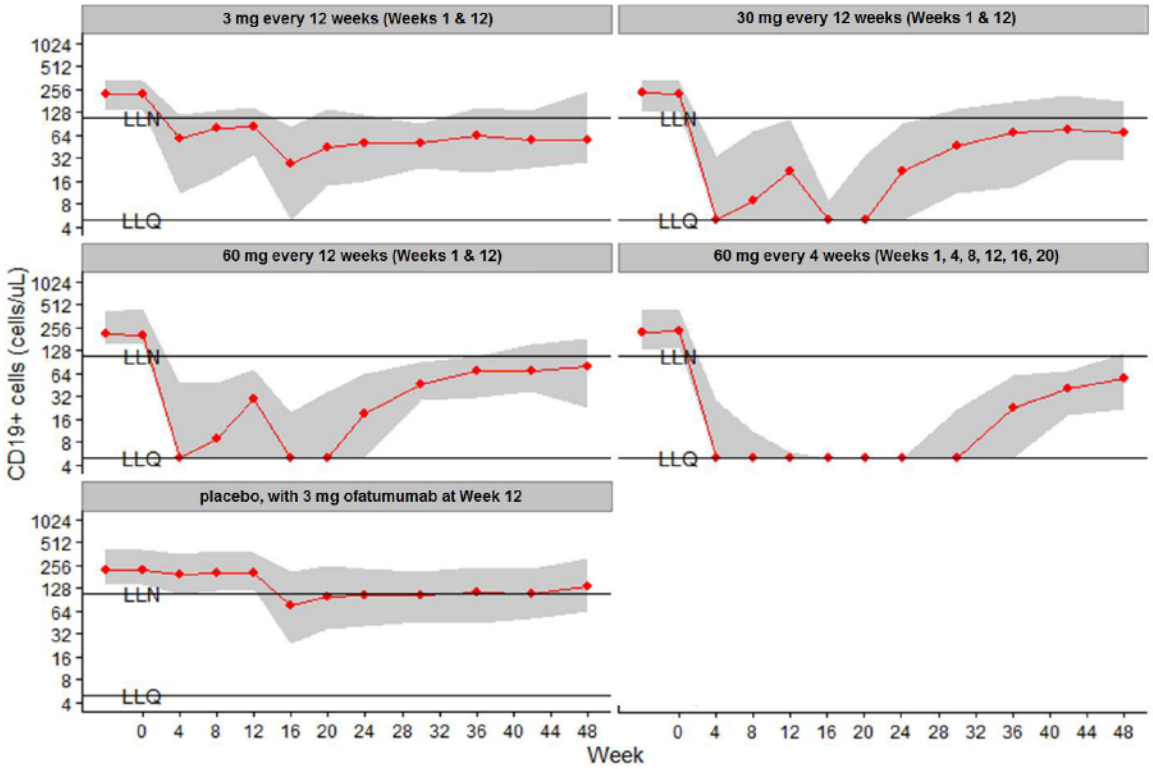
Within the protocol, reference to Novartis is inclusive of tasks and responsibilities that will be performed by a contract research organization (eg, [redacted]).

3.3. Dose Rationale

For Study OPV116910, an ofatumumab SC dose of 20 mg will be administered every 4 weeks through Week 56 (with an additional 20-mg 'loading' dose [ie, 40 mg total] at both Week 0 and Week 4). This dose was selected on the basis of the following factors: safety and tolerability from studies conducted in other autoimmune indications (rheumatoid arthritis and RRMS), B-cell depletion/repletion data from a single SC dose study (GSK Study OFA110867; N=6/arm) in subjects with rheumatoid arthritis, newly-available data from a large Phase II repeat-dose (up to 20 weeks) study in subjects with RRMS (GSK Study OMS112831; N=232), and pharmacometric modeling.

The original dose rationale proposed an ofatumumab SC dose of 60 mg every 12 weeks; however, in the ongoing Phase II RRMS study (GSK Study OMS112831), ofatumumab SC doses of 3 to 60 mg every 12 weeks were not found to completely suppress B cells during the inter-dosing interval (Figure 3-3). However, when dosed every 4 weeks, ofatumumab suppressed B cells to below the limit of quantification during the inter-dosing interval in more than 90% of subjects.

Figure 3-3 Observed Median and Inter-decile Range B-cell Depletion for Ofatumumab SC in GSK Study OMS112831



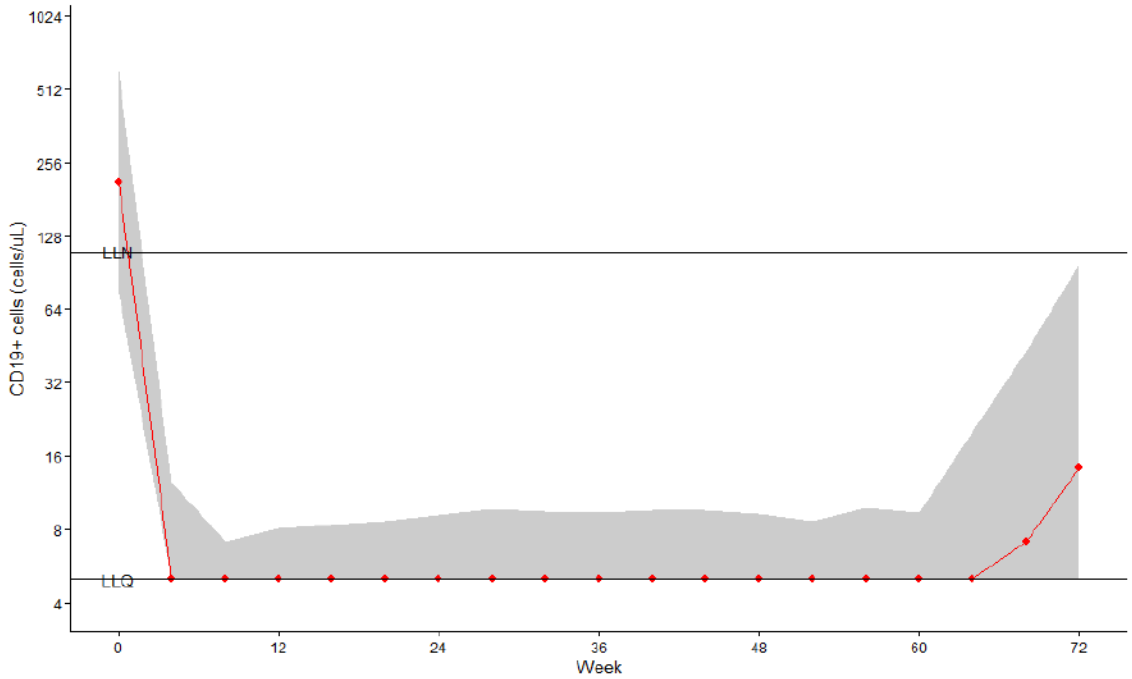
Abbreviations: LLN=lower limit of normal; LLQ=lower limit of quantitation; SC=subcutaneous.

Achieving adequate B cell depletion is viewed as essential for maintenance of efficacy in PV [Eming, 2008; Mouquet, 2008], although no threshold for B cell depletion has been demonstrated. This fact notwithstanding, suppression of B cells to levels seen with off-label rituximab is desirable to ensure comparable efficacy, particularly during a period of steroid withdrawal. On the basis of observed B-cell suppression with doses of 3, 30, and 60 mg and pharmacometric modeling, dividing the dose to administer ofatumumab SC 20 mg every 4 weeks, rather than 60 mg every 12 weeks, is anticipated to achieve that goal.

The predicted median B cell depletion and the predicted median percentage B cell inhibition, complete with inter-decile ranges, are shown in Figure 3-4 and Figure 3-5 (n=1000 per simulation), respectively. At steady-state (Week 12), the predicted median inhibition is 99%, with 90% of subjects achieving B cell inhibition greater than 97.5%, as indicated by the shaded region. To help achieve a rapid onset of clinical effect, loading doses of 40 mg (as two 20-mg SC injections) will be administered at Weeks 0 and 4.

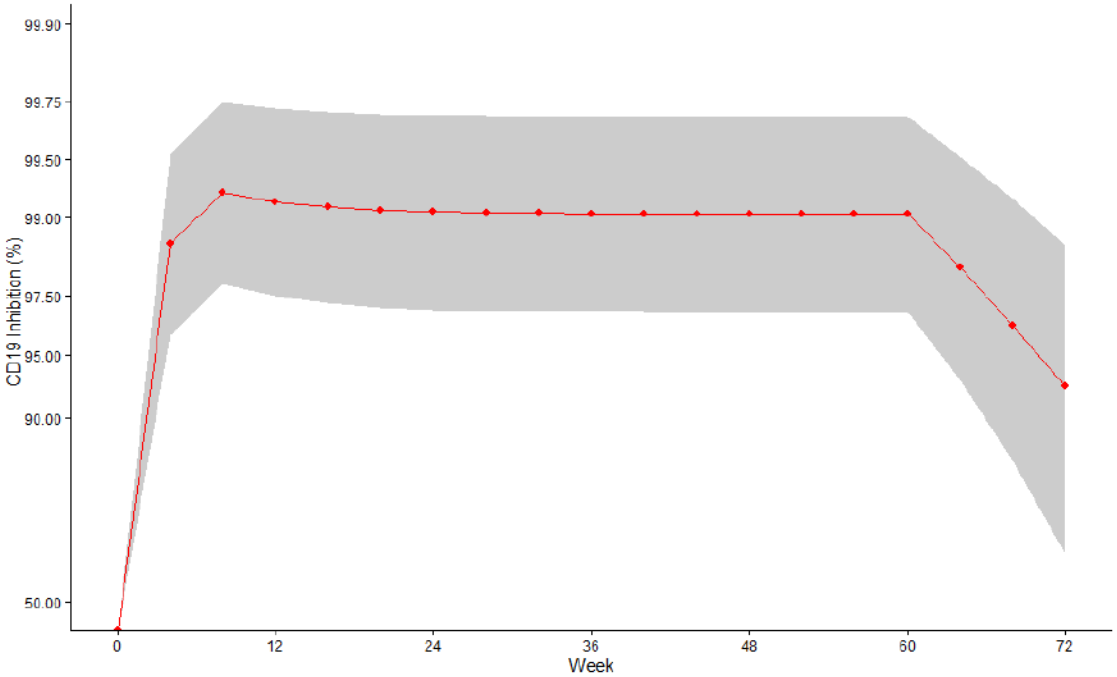
The current dosing regimen is expected to rapidly deplete B-cells and maintain the desired level of suppression during the inter-dosing intervals in the majority of subjects in order to maintain disease remission once achieved. After dosing ceases, the predicted median time to replete to the LLN (110 cells/uL) in subjects with PV is approximately 28 weeks.

Figure 3-4 Predicted Median and Inter-decile Range B-cell Depletion with Ofatumumab SC 40 mg Administered at Weeks 0 and 4, then 20 mg Administered Every 4 Weeks Through Week 56



Abbreviations: LLN=lower limit of normal; LLQ=lower limit of quantitation; SC=subcutaneous.

Figure 3-5 Predicted Median and Inter-decile Range B-cell Percent Inhibition with Ofatumumab SC 40 mg Administered at Weeks 0 and 4, then 20 mg Administered Every 4 Weeks Through Week 56



Abbreviation: SC=subcutaneous.

With respect to safety and tolerability, all doses in GSK Study OMS112831 were well tolerated and there were no new or unexpected safety findings during the Treatment Period (follow-up was ongoing as of January 2014). Administration of ofatumumab SC in subjects with PV is also anticipated to be well-tolerated.

In summary, on the basis of results of the repeat-dose study in subjects with RRMS and subsequent dose modeling, administration of ofatumumab SC 20 mg every 4 weeks (with an additional dose at Weeks 0 and 4 in order to reach steady-state more quickly during initial steroid-tapering) should provide more consistent B-cell suppression in subjects with PV than the previously-proposed dose regimen of 60 mg administered every 12 weeks.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Before subjects may be entered into the study, Novartis requires a copy of the site's written institutional review board (IRB)/independent ethics committee (IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 9.2). All subjects must personally sign and date the consent form before any subsequent screening procedures may be performed.

A subject will be considered enrolled once a randomization number is assigned. A subject may only be randomized once, and each randomization number may only be assigned to 1 subject.

4.1. Number of Subjects

Approximately 136 subjects (68 subjects per treatment group) will be enrolled into the study, which accounts for a drop-out rate of ≤13% (see Section 8.2.1). Approximately 48 sites in approximately 15 countries are expected to participate in this study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the Novartis investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure [Ofatumumab/OMB157/GSK1841157 Investigator's Brochure, 2016].

Deviations from inclusion criteria are not allowed, as they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

It is the investigator's responsibility to confirm that potential subjects are willing and able to provide written informed consent, participate in the study as an outpatient, make frequent visits to the study center during the Treatment and Follow-up Periods, and comply with all study requirements including restrictions on usage of concomitant medications and other treatments.

To be eligible for enrollment in the study, subjects must meet all of the following criteria:

All Subjects

1. Adults (18 through 70 years of age) with clinically-documented diagnosis of PV for >2 months and <10 years.
2. History of biopsy consistent with PV (H and E staining and direct immunofluorescence). If no history, a biopsy may be performed during the Screening Period.
3. At least 1 previous episode of a failed steroid taper (ie, disease flare/relapse) at a prednisone/prednisolone dose >10 mg/day, with a Pemphigus Severity of Clinical Disease score of moderate (2) or severe (3) (may be historical/retrospective assessment [see Appendix 6 and SPM for guidance]), where severity of disease at flare/relapse necessitated an increase of >20 mg/day. *Note: prednisone/prednisolone dose should not be increased for the sole purpose of entry into this study.*

Additional Criteria Prior to Randomization

4. Screening anti-Dsg antibodies consistent with a diagnosis of PV (ie, elevated anti-Dsg3 antibodies).
5. Has initiated and received a stable dose of prednisone/prednisolone from a minimum of 20 mg/day (eg, 0.25 mg/kg/day for an 80-kg person) up to a maximum of 120 mg/day or 1.5 mg/kg/day (whichever is higher) for ≥2 weeks prior to randomization. (*Note: subjects who are on every-other-day dosing regimens need to change to a daily dosing regimen for ≥2 weeks during the Screening Period in order to qualify.*)
6. Has exhibited PV disease control, defined as no new lesions for ≥2 weeks.

Additional Criteria for Female Subjects

7. A female subject is eligible to enter the study if she:
   a. Is of nonchildbearing potential, who is documented as either surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or post-hysterectomy) or is postmenopausal without menses for >2 years. Women who are <2 years postmenopausal are required to have menopausal status confirmed by follicle-stimulating hormone (FSH) and estradiol levels at the screening evaluation. If FSH and estradiol levels do not provide confirmation of menopause, subject will be considered to be of childbearing potential.
   b. Is of childbearing potential, defined as a woman who has functional ovaries, ducts, and a uterus with no documented impairment that would cause sterility. This includes women with oligomenorrhea (even severe), women who are perimenopausal, and women who have just begun to menstruate. Subject must:
      - Have a negative serum pregnancy test at screening
      - Agree to the consistent and correct use of acceptable methods of contraception during heterosexual intercourse, beginning when the subject provides

informed consent and lasting until 12 months after last dose of investigational product. Acceptable methods of contraception are limited to the following:

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Levonorgestrel implants
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device or intrauterine system with a documented failure rate of <1% per year
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study; this male must be the subject's sole partner
- Double-barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)
- Complete abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject
- ** In **Japan**, refer to Appendix 2 for applicable country-specific clarifications regarding acceptable methods of contraception for subject inclusion in this study.**

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

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria will not be enrolled:

1. Diagnosis of pemphigus foliaceus, paraneoplastic pemphigus, or other autoimmune blistering disease (other than PV).
2. Past or current history of hypersensitivity to components of the investigational product or medically significant adverse effects (including allergic reactions) from cetirizine (or antihistamine equivalent) or paracetamol/acetaminophen.
3. Prior treatment with rituximab without achieving disease control within 6 months of initiating rituximab dosing.

4. Prior treatment with any of the following within the specified periods:

Medication and Other Treatment Restrictions Prior to Randomization

Any time	6 weeks	8 weeks[a]	6 months	18 months
Ofatumumab, total body irradiation, bone marrow transplantation, anti-CD4	Live vaccine	Immunosuppressive or immunomodulatory agents, including: – azathioprine – cyclosporine – dapsone – mycophenolate – methotrexate – tacrolimus	– cyclophosphamide – cladribine – plasmapheresis – immunoabsorption or immunoglobulin therapy – alemtuzumab – mitoxantrone	Rituximab or other anti-CD20 treatments

5. Confirmed PML, or neurological findings potentially consistent with PML (see Appendix 4 and Appendix 5).
6. Evidence or history of clinically significant infection including:
   - Chronic or ongoing active infectious disease requiring long-term systemic treatment, including, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, or active hepatitis C.
   - Positive test for HBsAg. For HBsAg negative, but anti-HBc/HBcAb positive (regardless of HBsAb status), an HBV DNA test will be performed and the subject will be excluded if results are positive. Consult with a physician experienced in the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.
   - History of positive serology for human immunodeficiency virus.
   - Previous serious opportunistic or atypical infections.
   - Prior history, or suspicion, of tuberculosis (TB).
   - ** In **Japan**, refer to Appendix 2 for additional country-specific screening procedures and exclusion criteria for TB, Pneumocystis pneumonia, and hepatitis B.**
7. Past or current malignancy, except for:
   - Cervical carcinoma Stage 1B or less.
   - Noninvasive basal cell and squamous cell skin carcinoma.
   - Cancer diagnoses with a duration of complete response (remission) >5 years. *Note*: A history of hematologic malignancy excludes a subject from participation, regardless of response.
8. Significant concurrent, uncontrolled medical condition that could affect the subject's safety, impair the subject's reliable participation in the study, impair the evaluation of endpoints, or necessitate the use of medication not allowed by the protocol.

9. Any of the following screening laboratory values:
    - White blood cells <3.8 GI/L (<3800/mm^3).
    - Neutrophils <2 GI/L (<2000/mm^3).
    - Platelets <130 GI/L (<130,000/mm^3).
    - Circulating IgG, IgA, or IgM levels <10% of the LLN and requiring treatment in the opinion of the investigator.
    - Alanine aminotransferase (ALT) >2.0 times the upper limit of normal (ULN).
    - Aspartate aminotransferase >2.0 × ULN.
    - Alkaline phosphatase >1.5 × ULN.
    - Bilirubin >1.5 × ULN (except in cases of isolated predominantly indirect hyperbilirubinemia due to Gilbert's syndrome).
10. Use of an investigational drug or other experimental therapy within 4 weeks, 5 pharmacokinetic half-lives, or the duration of biological effect (whichever is longer) prior to Screening.
11. Electrocardiogram (ECG) showing a clinically significant abnormality or showing a corrected QT interval (QTc) ≥450 msec (≥480 msec for subjects with a bundle branch block) (ECG to be obtained during Screening/prior to receiving the first dose of study drug).
12. Woman who is breastfeeding.

4.4. Withdrawal Criteria

4.4.1. Dose-holding Criteria

Investigational product dosing will be held in the following situations:

- Neutropenia with an absolute neutrophil count <1 GI/L (<1000/mm^3; <1.0 x10^9/L) (ie, Grade 3 and higher [CTCAE, 2013]).
- Suspected serious systemic infection.
- Positive symptoms on neurological symptoms questionnaire (see Appendix 4 and Appendix 5).

If the condition resolves within 1 week, administer the held dose and then return to the regular dosing schedule. If the condition does not resolve within 1 week after a held dose, skip that dose; after the condition resolves, return to the regular dosing schedule. Consult with the medical monitor if a subject misses 2 or more consecutive doses.

4.4.2. Discontinuation of Investigational Product

Subjects must discontinue investigational product for any of the following reasons:

- Sponsor request, for reasons such as significant protocol deviation (and after discussion with the investigator).
- Study is terminated by the Sponsor.
- Subject meets PML discontinuation criteria (see Appendix 4).
- Subject develops any other serious opportunistic or atypical infection.
- Subject meets liver chemistry stopping criteria (see Appendix 3).
- Subject initiates treatment with a prohibited PV disease-modifying drug.
- Subject becomes pregnant.
- Subject experiences a serious or life-threatening cardiac arrhythmia.

Any subject who discontinues from the Treatment Period should complete an Early Withdrawal Visit and transition into the Individualized Follow-up Period for important safety monitoring (as applicable; see Section 3.1.3), unless he/she meets a criterion for mandatory withdrawal from the study (see Section 4.4.3).

4.4.3. Withdrawal from the Study

Subjects must discontinue investigational product and be withdrawn from the study for the following reasons:

- Subject withdraws consent.
- Subject initiates treatment with a prohibited PV disease-modifying drug that depletes B-cells (eg, rituximab).
- Sponsor request (after discussion with the investigator).
  ** In **Japan**, refer to Appendix 2 for applicable country-specific details.**

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

5.1.1. Investigational Product

Ofatumumab SC (GSK1841157; human mAb ofatumumab injection for SC use) will be supplied by Novartis as a liquid concentrate in a prefilled glass syringe with staked needle, stopper, and plunger, with a needle safety device. Initially, syringes containing 0.6 mL (60 mg) of concentration 100 mg/mL drug product will be provided.

Placebo in prefilled glass syringes to match the ofatumumab syringes, will be made and supplied by Novartis, using normal saline (sterile, pyrogen-free 0.9% NaCl) and filled to

0.6 mL in a prefilled glass syringe with staked needle, stopper, and plunger, with a needle safety device.

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

For study centers initiated using the dilution method for study treatment preparation, an unblinded pharmacist (or appropriately-qualified designee) at the study center will prepare each dose via a dilution process according to the detailed instructions in the pharmacy manual. Briefly, the contents of 2 prefilled (0.6 mL) syringes (either 1 ofatumumab 60-mg syringe plus 1 placebo syringe or 2 placebo syringes) will be injected into a sterile vial and 0.4 mL of the resulting solution will be drawn into a new syringe to achieve the 20-mg ofatumumab (concentration 50 mg/mL) or placebo dose. Solutions obtained from the dilution method will be filtered through Kendall 5 micron filter needles prior to injection. The in-use time after the drug product is drawn into the syringe for administration should not exceed 2 hours; however, it is recommended that the drug product be administered immediately.

In countries (including Japan) and/or study centers not using the dilution method to prepare study injections, Kendall 5 micron filter needles will not be used and there is no need to designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation.

When available, Novartis will supply ofatumumab SC in prefilled glass syringes containing 0.4 mL (20 mg) of concentration 50 mg/mL drug product and matching placebo prefilled glass syringes containing 0.4 mL of normal saline.

Trained site personnel will administer 0.4 mL of investigational product via SC injection into a vertical fold of abdominal skin approximately 2 to 4 inches lateral of the umbilicus. The injection site may be adjusted at investigator's discretion if there are extensive abdominal lesions present. Subjects should stay at the clinic for a minimum of 4 hours after the first dose of investigational product to be monitored for any injection-related AEs. It is recommended that subjects stay at the clinic for a minimum of 1 hour, at the investigator's discretion, after each subsequent dose.

Sites should adhere to dosing on the specific visit schedule as shown in Table 6-1.

Protect investigational products from light and store in a refrigerator at 2° to 8°C (36° to 46°F); do not freeze. Store the investigational product in a secure area under appropriate physical conditions. Access to and administration of the investigational product is limited to the investigator and authorized site staff. Dispense or administer investigational product only to subjects enrolled in the study and in accordance with the protocol. The study monitor will be responsible for reviewing drug accountability of the investigational product at the site. Detailed instructions related to the destruction of unused materials are provided in the pharmacy manual.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff in the pharmacy manual.

5.1.2. Other Study Treatments

Pre- and Postinjection Medications

Prior to each SC injection of investigational product, all subjects are required to receive premedication with acetaminophen/paracetamol and an antihistamine (see Table 5-1), which will be administered at the clinic. Approximately 4 hours after the first injection, subjects will receive a second dose of acetaminophen/paracetamol.

Approximately 4 to 6 hours after subsequent injections of investigational product, subjects may take acetaminophen/paracetamol if needed (this dose may be self-administered by subjects after leaving the clinic).

Table 5-1 Pre- and Postinjection Medications

Time relative to SC injections	Medication	Dose	Route
1-2 hours before each injection	Antihistamine (cetirizine or equivalent)	10 mg [a]	Oral
1-2 hours before each injection	Acetaminophen/paracetamol	1 g	Oral
4 hours after first injection	Acetaminophen/paracetamol	1 g	Oral
4-6 hours after subsequent injections *(if needed after clinic visit)*	Acetaminophen/paracetamol	1 g	Oral

Abbreviation: SC=subcutaneous.
d. If an equivalent antihistamine is chosen, the dose range should be according to locally-accepted practice.

Prednisone/Prednisolone

See Section 3.1.2.

5.2. Treatment Assignment

Study subjects who provide informed consent and undergo Screening assessments receive a unique subject number. This assignment of subject numbers occurs at the Screening visit and serves to identify subject data in an anonymous fashion.

Subject eligibility will be established at the conclusion of the baseline evaluations (prior to randomization and first dose of investigational product at Week 0); subjects who meet all entry criteria will then be randomized in a 1:1 allocation to receive either ofatumumab SC or placebo according to a central randomization schedule.

Assignment to a treatment will be based on a computer-generated randomization list prepared by Novartis or a Novartis-approved vendor; an interactive voice response (IVR) system serves as a central system to allocate randomization numbers to each subject. The subjects and the investigative staff, except the unblinded pharmacist, will be blinded to the treatment assignment.

Subjects who withdraw from the study following informed consent, but prior to randomization to study treatment, will be classified as screen failures. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of

Reporting Trials publishing requirements, and respond to queries from regulatory authorities, a minimal set of screen failure information will be collected in the electronic case report form (eCRF), including demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

5.3. Blinding

This is a double-blind study. Each site that prepares study injections using the dilution method must designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation. All other study staff (including the investigator, subinvestigators, other site staff, the subject, and Sponsor) will be blinded to the treatment allocated to individual subjects.

In countries (including Japan) and/or study centers not using the dilution method to prepare study injections, there is no need to designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation.

The blinded study treatment assignments for individual subject will be maintained by a central IVR system. Emergency unblinding will be available via the central IVR system (refer to the SPM and IVR system guidelines for appropriate procedures to follow).

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency or in the event of a serious medical condition**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator. Investigators have direct access to the subject's individual study treatment. It is preferred (but not required) that the investigator first contacts the medical monitor or appropriate study personnel to discuss options before unblinding the subject's treatment assignment. If study personnel are not contacted before the unblinding, the investigator must notify the medical monitor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the appropriate data collection tool.

Novartis Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or Novartis policy.

If the treatment blind is broken by the site for a subject in the Treatment Period, the subject in question will be withdrawn from the Treatment Period and moved into the Follow-up Period.

During the study, investigators will not receive central laboratory data that have the potential to unblind a subject's treatment assignment. This includes lymphocytes, B-lymphocyte chemokine, [redacted], and human anti-human antibody (HAHA). Refer to the [redacted] investigator manual for additional information.

After the Week 60 visit and each Individualized Follow-up visit, the central laboratory (or designee) will provide the laboratory values and notify the investigator whether or not

a subject needs to remain in follow-up or if the subject may be discharged from the study (based on B-lymphocyte counts and IgG levels).

Sponsor unblinding for analyses will occur after all subjects have completed the Week 60 visit, been withdrawn from the treatment period, or the study has been terminated (see Section 8.3.4).

5.4. 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 administered to 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.

The designated pharmacist must keep drug inventory and accountability logs. The inventory will include details of ofatumumab SC and placebo received and dispensed (administered) to subjects, batch, and identification numbers. All unused prefilled syringes (supplied by Novartis) must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site may destroy the syringes, unless otherwise instructed. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of ofatumumab SC and placebo received and dispensed must be reconciled.

** In **Japan**, unused investigational products will be collected at the end of the study by the Sponsor or Sponsor's consignor.*

5.5. Treatment Compliance

Investigational product will only be administered in the clinic by trained site personnel. Each dose will be recorded in the eCRF.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

Subjects may take other medications for treatment of the symptoms associated with PV, so long as they do not fall into any of the prohibited medications categories (Section 5.6.2). The appearance of 1 or 2 new lesions, not otherwise meeting the criteria for disease flare/relapse, may be treated with supportive care, such as topical preparations.

If the investigator is in any doubt about whether a concomitant medication is permitted during the study, he/she should discuss it with the medical monitor.

5.6.2. Prohibited Medications and Non-Drug Therapies

The medications and therapies/treatments listed in Table 5-2 will not be allowed during the study (including the Screening, Treatment, and Individualized Follow-up Periods).

Use of prohibited medications and therapies during the study may result in the subject being withdrawn from study treatment and potentially withdrawn from the study.

Table 5-2 Prohibited Medications and Non-Drug Therapies

Medication or Therapy	Washout Before Randomization
Lymphocyte-depleting therapies, such as: • IV ofatumumab (ARZERRA) • anti-CD4, total body irradiation, bone marrow transplantation • cyclophosphamide, cladribine • alemtuzumab (Campath) • mitoxantrone	 • At any time • At any time • 6 months • 6 months • 6 months
Rituximab or other anti-CD20 treatments	18 months
Other monoclonal antibodies	Contact medical monitor
Immunoabsorption, plasma exchange/plasmapheresis, immunoglobulin therapy	6 months
Immunosuppressive or immunomodulatory agents, including azathioprine, cyclosporine, dapsone, mycophenolate, methotrexate, and tacrolimus	8 weeks
Received a live vaccine	6 weeks
Initiation of statin therapy	Applicable *during* the study only

Abbreviation: IV, intravenous.

** In **Japan**, alemtuzumab (Campath) and anti-CD4 treatments are not approved.*

5.6.3. Immunizations

The safety of (and ability to generate a primary or anamnestic response to) immunization with live attenuated or inactivated vaccines during ofatumumab treatment has not been studied. The response to vaccination could be impaired when B-cells are depleted.

It is recommended that the investigator review the subject's immunization history as part of the initial screening procedure for a subject being considered for treatment with ofatumumab SC. Vaccination of the subject, in compliance with local area vaccination guidelines for the patient population being treated, is recommended prior to administration of ofatumumab SC. In particular and per local guidelines, hepatitis B vaccination should be considered for subjects at risk for infection with hepatitis B (or in areas with a high prevalence of hepatitis B). After treatment with ofatumumab SC, avoid administration of live attenuated vaccines until B-cell counts have normalized.

5.7. Treatment after the End of the Study

As the ofatumumab development program in the indication PV has been terminated, subjects completing the study will no longer be eligible to participate in the extension study (OPV117059). Subjects who were enrolled in the extension study prior to program termination may remain in the extension study until exit criteria are met. Subjects who

do not participate in the planned extension study will not receive any additional treatment after completion of this study.

The investigator is responsible for ensuring that consideration has been given to the post study care of the subject's medical condition, whether or not Novartis is providing specific post study treatment.

5.8. Treatment of Investigational Product Overdose

If an overdose does occur, there are no recommended medications or nondrug therapies for treatment. The investigator should use his/her clinical judgment in treating any overdose. If an overdose does occur, individuals should be managed with appropriate supportive therapy, as determined by the investigator in consultation with the medical monitor. If there are signs and symptoms associated with an overdose, these should be reported as an AE/SAE.

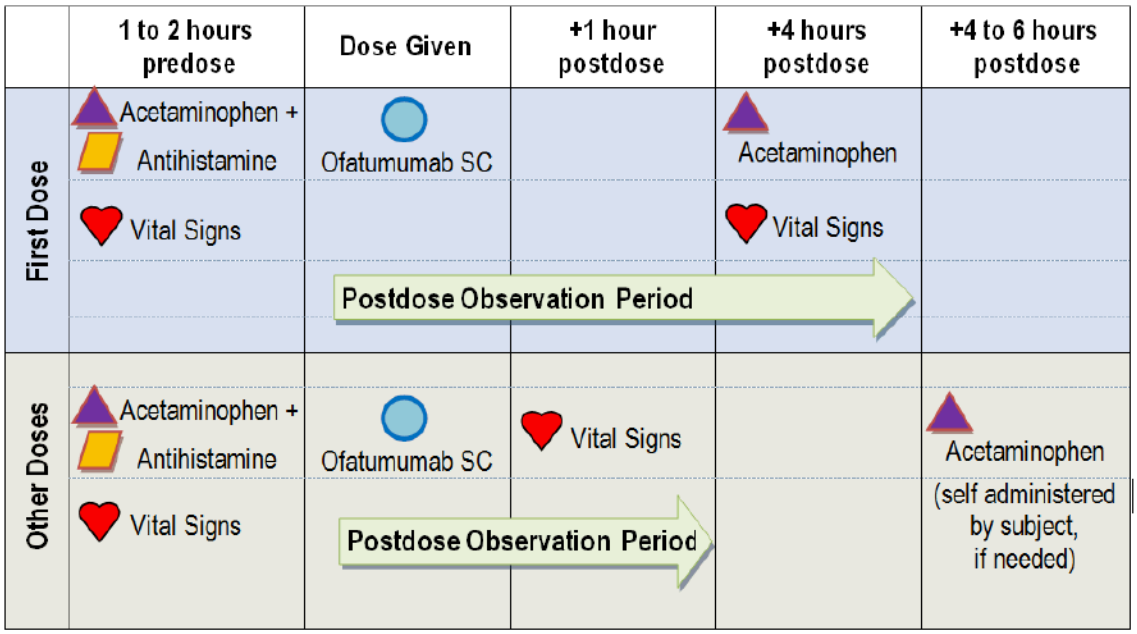
6. STUDY ASSESSMENTS AND PROCEDURES

Table 6-1 presents the schedule of assessments for the study. The investigator, or a medically qualified designee, is to conduct all study assessments. The investigator or designee must obtain written informed consent prior to performing any of the assessments. Record study information in the source documents and, where appropriate, the eCRF.

The Screening Period begins once the subject has provided written informed consent and lasts from 2 to 12 weeks prior to randomization.

If a visit cannot be scheduled on the appropriate date, the visit should be re-scheduled as close as possible to the planned date, ideally within ±3 days.

Figure 6-1 Relative Timing of Key Activities on Ofatumumab SC Dosing Days



Abbreviation: SC=subcutaneous.

Table 6-1 Time and Events Table

Period:	Screen	Core Study Period (60 Weeks)																					Early WD[b]
		BL	Treatment Period (56 Weeks)																				F-up[b]
Study Week:	-2 to -12[a]	Day 0	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	52	56	60[b]	
Clinic (C) or Phone (*P*) Visit:	C	C	C	C	C	C	*P*	C	*P*	C	*P*	C	*P*	C	C	C	C	C	C	C	C	C	C	C
Informed consent	X																							
Eligibility criteria	X	X																						
Physical exam, weight, & height	X																							
Demography; PV & medical history	X																							
Smoking status	X	X												X									X	X
Vital signs	X	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X
Electrocardiogram	X																						X	X
Adverse events [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PV lesion mapping	X	X	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X
[redacted]																								
Randomization		X																						
Study treatment administration [e]		XX		XX		X		X		X		X		X	X	X	X	X	X	X	X	X		
Document steroid dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Steroid taper			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory [f]	X	X		H		H		X		H		H		X	H	H	X	H	H	X	H	H	X	X
Serum hCG (women only)	X																						X	X
Urine hCG (women only)		X		X		X		X		X		X		X	X	X	X	X	X	X	X	X		
HAHA; hsCRP [g]		X						X						X			X			X	X	X	X	X
IgG, IgM, IgA	X	X						X						X			X			X	X	X	X	X
[redacted]																								
Pharmacodynamic markers [g]	X	X		X		X		X		X		X		X			X			X	X	X	X	X

Period:	Screen	Core Study Period (60 Weeks)																						Early WD[b]
		BL	Treatment Period (56 Weeks)																				F-up[b]	
Study Week:	-2 to -12[a]	Day 0	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	52	56	60[b]	
Clinic (C) or Phone (*P*) Visit:	C	C	C	C	C	C	*P*	C	*P*	C	*P*	C	*P*	C	C	C	C	C	C	C	C	C	C	C
Pharmacokinetic sample[g]		X		X		X		X		X		X		X			X			X		X	X	X
Pharmacokinetic substudy[g,h,i]		←*See Table 6-3 for PK-PD substudy visits and sample collection time points*→																						
Pharmacogenetics sample[g,h]		X																						
Serum banking for JC virus testing		X																						
Neurological symptom questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																								

Abbreviations: [redacted]; admin=administration; [redacted]; BL=Baseline; BLC=B-lymphocyte chemokine; C=clinic visit; [redacted]; F-up=follow-up visit; HAHA=human anti-human antibody; hCG=human chorionic gonadotropin; hsCRP=high sensitivity C-reactive protein; Ig=immunoglobulin; P=phone visit; PD=pharmacodynamic; PK=pharmacokinetic; PV=pemphigus vulgaris; [redacted]; WD=withdrawal.

a. Screening may be up to 12 weeks for disease consolidation/control and adjustment/stabilization of prednisone/prednisolone dose. Multiple visits (unscheduled) are permitted.
b. If subject is not entering the extension study and CD19+ B cell counts and circulating IgG levels are below the lower limit of normal at Week 60 (or early withdrawal visit), the subject will transition into Individualized Follow-up (see Table 6-2). Subjects requiring additional hepatitis B virus testing will also return for follow-up visits for 6 months after the last dose.
c. Vital signs should be taken before each injection of investigational product, at approximately 4 hours after the first dose, and at approximately 1 hour after subsequent doses.
d. Adverse events (AEs) will be collected from the start of study treatment through the Core Study Period. Serious AEs assessed as related to study participation will be collected from the time a subject consents to participate in the study up to and including any follow-up contact.
e. Premedication: Each dose of study treatment will be preceded by acetaminophen/paracetamol and an antihistamine (see Section 5.1.2).
Postdose observation and medication: After the first dose, subjects should stay at the clinic to be monitored for any injection-related AEs for a minimum of 4 hours, with acetaminophen/paracetamol administered again at 4 hours. After subsequent doses, it is recommended that subjects stay at the clinic for a minimum of 1 hour, with acetaminophen/paracetamol self-administered approximately 4 to 6 hours after dosing if needed.
Note: An additional 20-mg loading dose (total of two 20-mg injections) will be administered at Week 0 and Week 4.
f. Laboratory assessments include hematology, clinical chemistry, and urinalysis. "H" indicates visits with only hematology.
At Screening and Week 60/early withdrawal only—Hepatitis B, Hepatitis C, pneumococcal antibody assay, and toxoid antibody assay.
g. Collect sample predose on dosing days.
h. Informed consent must be obtained before collecting samples for optional testing (ie, pharmacogenetics research and pharmacokinetic-pharmacodynamic substudy analyses).
i. Only sites preidentified to participate in pharmacokinetic-pharmacodynamic substudy. See Table 6-3 for the schedule of visits for sample collection.

Note: Visits from Week 2 through Week 60 to be scheduled within ±3 days of the specified time point. Visits during Individualized Follow-up to be scheduled within ±7 days.

Table 6-2 Time and Events Table: Individualized Follow-up Period

	As applicable[a]								Early WD
Study Week for Core Study Completers:	72	84	96	108	120	132	144	156	
Study Week for Early Withdrawals:	+12	+24	+36	+48	+60	+72	+84	+96	
Adverse events (including SAEs and AEs of special interest)[b]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Document steroid dose	X	X	X	X	X	X	X	X	X
Neurological symptoms questionnaire (PML monitoring)	X	X	X	X	X	X	X	X	X
PV lesion mapping	X	X	X	X	X	X	X	X	X
Pregnancy testing (urine) (women) – test monthly for 12 months after the last dose of ofatumumab SC; subjects may test at home during months without a clinic visit	X	X	X	X					X
Hematology	X	X	X	X	X	X	X	X	X
Clinical chemistry	X	X	X	X	X	X	X	X	X
IgG, IgM, IgA	X	X	X	X	X	X	X	X	X
[redacted]									
Human anti-human antibody	X								X
Pharmacodynamic markers (flow cytometry)	X	X	X	X	X	X	X	X	X
HBV DNA – if applicable, test every 12 weeks for 6 months after the last dose of ofatumumab SC	*PRN*	*PRN*							*PRN*

Abbreviations: AE=adverse event; [redacted]; HBV=hepatitis B virus; Ig=immunoglobulin; PML=progressive multifocal leukoencephalopathy; PRN=as needed/as indicated; PV=pemphigus vulgaris; SAE=serious adverse event; SC=subcutaneous; WD=withdrawal.

a. Subjects entering the Individualized Follow-up Period will continue to be monitored every 12 weeks, until CD19+ B-lymphocyte counts and IgG recover to ≥ lower limit of normal (LLN) or to the subject's Baseline value (if <LLN) or if criteria for study withdrawal are met or for a maximum of 2 years after the last dose of ofatumumab SC.

b. AEs (including AEs of special interest) and SAEs will be collected during the first year of the Individualized Follow-up Period. Only SAEs and AEs of special interest will be collected during the second year of the Individualized Follow-up Period. Any SAEs assessed as related to study participation will be collected from the time a subject consents to participate in the study up to and including any follow-up contact.

Note: Visits during Individualized Follow-up to be scheduled within ±7 days.

Table 6-3 Time and Events Table: Pharmacokinetic-Pharmacodynamic Substudy

Period:	Baseline		Treatment Period (56 Weeks)																F-up	Early WD
Visit Window:			±2 hours					±3 days												
Time Point:	Day 0 predose	Day 0 postdose	Day 1	Day 2	Day 3	Day 4	Day 7/ Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48	Week 52	Week 56	Week 60	
Pharmacokinetic sample [a] – regularly scheduled visits	X[a,b]							X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sample – additional visits		X[b]	X	X	X	X	X													
Pharmacodynamic sample [a] – B-lymphocyte subset analyses	X								X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: F-up=follow-up visit; WD=withdrawal

a. Collect sample predose on dosing days.

b. Day 0 blood draws will occur predose and 4 hours postdose.

Note: from Day 1 through Day 7, pharmacokinetic samples should be collected at the same time of day (±2 hours) that the initial dose of investigational product was administered; Week 2 through Week 60 visits should be scheduled within ±3 days of the specified time point.

****Refer to the full Time and Events table (Table 6-1) for the complete list of assessments to be performed at the regularly scheduled visits****

6.1. Critical Baseline Assessments

Information collected during the Screening Period assessments described below represents key data that identifies and defines subject baseline status. This information is critical for the evaluation and comparison of subsequent measurements and determinations.

Cardiovascular medical history/risk factors will be assessed at Screening/Baseline.

** In **Japan**, refer to Appendix 2 for additional screening assessments for TB, Pneumocystis pneumonia, and interstitial pneumonia.**

6.1.1. Medical History

A complete medical history will be taken at the Screening Visit. Information from the medical history is important to establish the baseline condition of the subject, and will impact the safety monitoring assessments during the study. Any significant medical conditions affecting the subject in the past 5 years should be recorded on the Medical Conditions page of the eCRF. The history should include the following:

- A thorough review of systems, including any past or current conditions
- Prior surgical procedures
- Pharmacotherapy and chronic or recent use of any medication
- Prior immunosuppressive therapies, including type, number, and duration
- Allergies and significant allergic reactions
- Significant infections, or history of recurrent infection, including urinary and respiratory tract infections
- Smoking history (current or previous smoker, number of packs a day smoked)

6.1.2. Pemphigus Vulgaris History

Details of the subject's PV history will be collected (eg, dates of symptom onset, diagnosis, and flares/relapses) in the eCRF. These data are critical for establishing subject eligibility, as well as establishing a baseline for subsequent clinical assessments.

The date of each subject's most recent failed steroid taper that resulted in a disease flare/relapse at a prednisone/prednisolone dose >10 mg/day will be collected in the eCRF. Additionally, a historical assessment of pemphigus clinical severity at the time of the failed steroid taper will be collected using the scale described in Appendix 6.

6.2. Efficacy

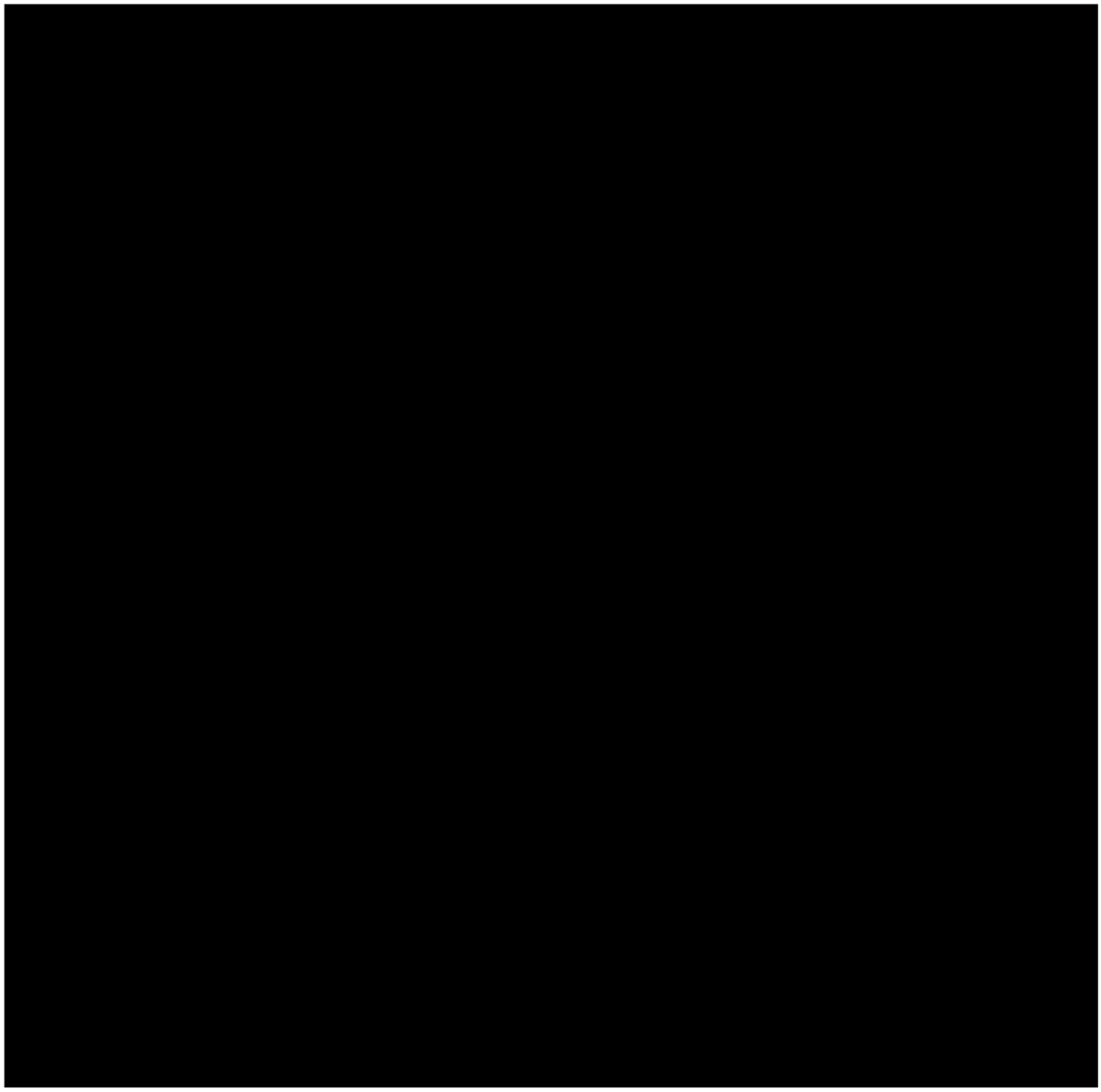
6.2.1. Primary Efficacy Endpoints

Two co-primary efficacy endpoints will be evaluated:

- Time to sustained remission (SR) on minimal steroid therapy (defined as time from randomization to the time the subject initially tapered his/her oral prednisone/prednisolone dose to ≤10 mg/day and maintained ≤10 mg/day of oral prednisone/prednisolone with no new or nonhealing lesions for ≥8 weeks AND maintained that status until Week 60).
- Duration of remission on minimal steroid therapy (defined as total time [sum] of all periods of remission while on minimal steroid therapy [oral prednisone/prednisolone dose of ≤10 mg/day] up to Week 60).

6.2.2. Secondary Efficacy Endpoints

- Proportion of subjects achieving remission on minimal steroid therapy (defined as subjects who had an absence of new or nonhealing lesions while on an oral prednisone/prednisolone dose of ≤10 mg/day for ≥8 weeks) at Week 60.
- Time to remission while on minimal steroid therapy (defined as time from randomization to the time the subject initially tapered his/her oral prednisone/prednisolone dose to ≤10 mg/day and maintained ≤10 mg/day of oral prednisone/prednisolone with no new or nonhealing lesions for ≥8 weeks) by Week 60.
- Time to initial flare/relapse (defined as the time from randomization to the time that ≥3 new lesions within 1 month appear and do not heal spontaneously within 1 week, or to the time when there is an extension of lesions that were present at the randomization visit) by Week 60.
- Proportion of subjects who did not flare/relapse (defined as subjects who achieved remission on minimal steroid therapy and did not subsequently have a flare of disease) by Week 60. A flare/relapse is defined as new lesions that do not heal spontaneously within 1 week, or when there is an extension of lesions that were present at the randomization visit.
- Time to remission off steroid therapy by Week 60 (defined as the time from randomization to the time the subject initially tapered off all steroids for ≥8 weeks with an absence of new or nonhealing lesions).
- Proportion of subjects achieving remission while off steroid therapy by Week 60.
- Number of days a subject maintained minimal steroid therapy (an oral prednisone/prednisolone dose of ≤10 mg/day in the absence of new or nonhealing lesions) by Week 60.
- Cumulative dose of corticosteroids.



6.3. Safety

The following safety endpoints will be assessed:

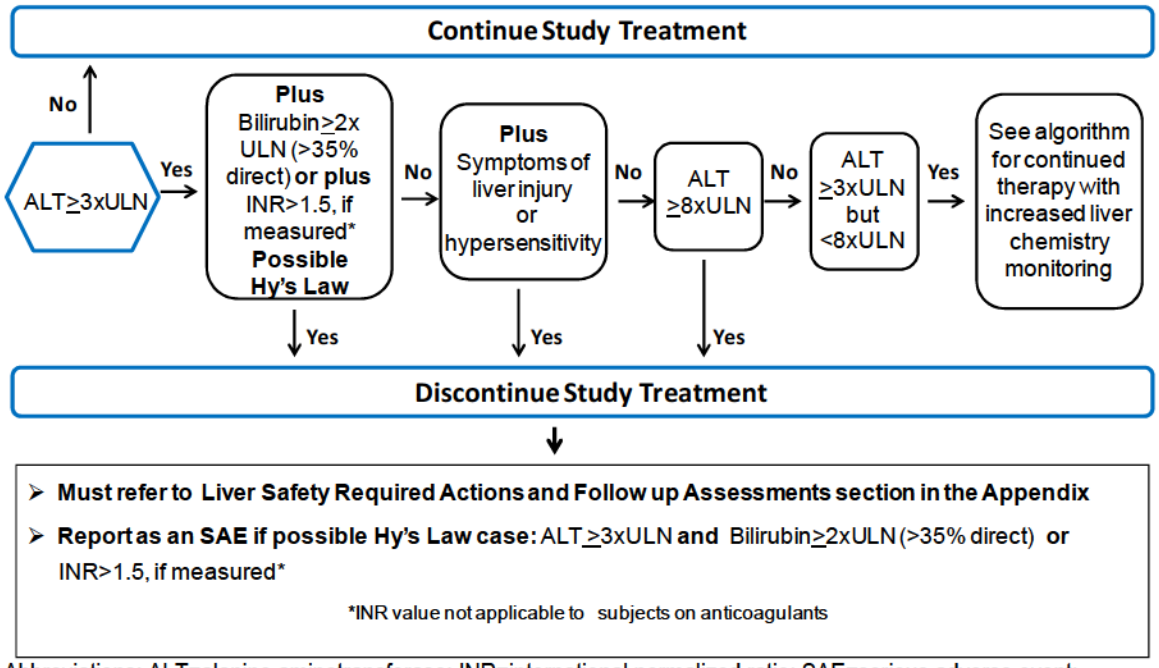
- Adverse events
- Adverse event frequency, severity, and relationship to investigational product
- Frequency and severity of infections
- Frequency of SAEs
- Frequency of withdrawals due to treatment-related AEs.
- Frequency of AEs leading to permanent discontinuation of investigational product.
- Frequency of AEs of special interest, postinjection systemic reactions, and injection site reactions.
- Change from baseline in vital signs.

- Frequency of vital signs of clinical concern.
- Change from baseline in laboratory (hematology, chemistry, and urinalysis) parameters.
- Frequency of laboratory (hematology, chemistry, and urinalysis) results of potential clinical concern.
- Immunogenicity as measured by the incidence, titer, and type of HAHA immune response.

6.3.1. Liver Chemistry Stopping and Follow-up Criteria

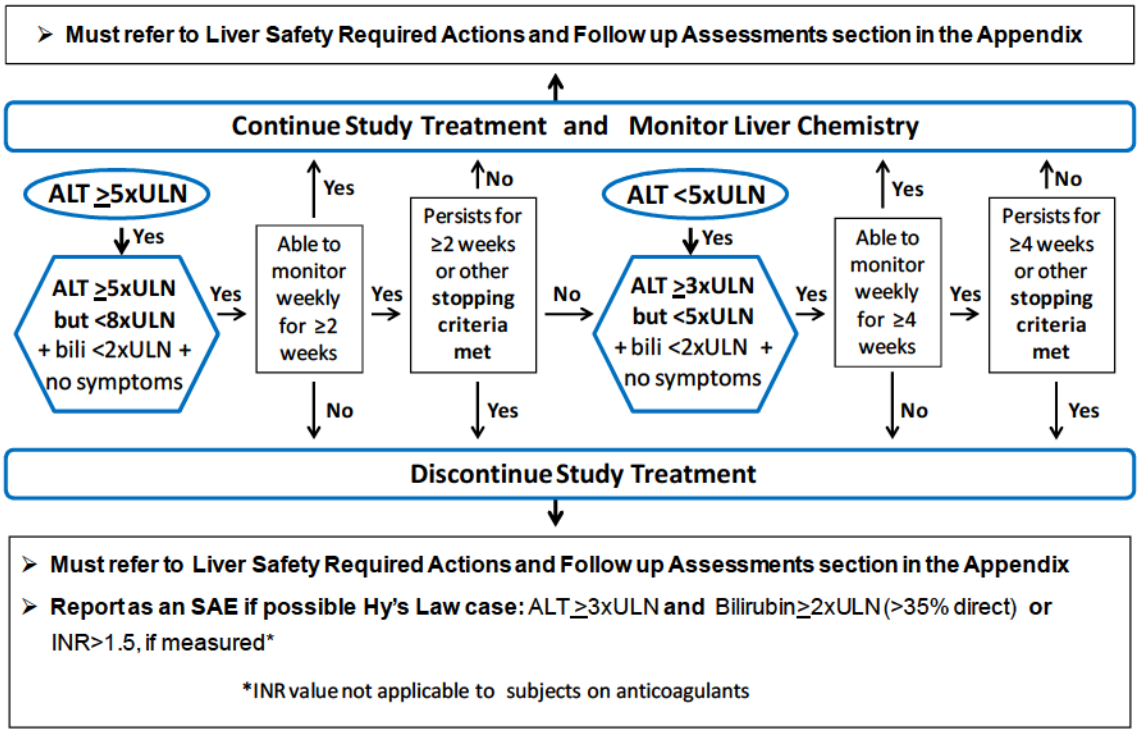
Liver chemistry stopping and follow-up criteria have been designed to ensure subject safety and evaluate liver event etiology (in alignment with the Food and Drug Administration premarketing clinical liver safety guidance). Liver safety required actions and follow-up assessments can be found in Appendix 3.

Figure 6-2 Liver Chemistry Stopping and Increased Monitoring Algorithm



Abbreviations: ALT=alanine aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

Figure 6-3 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥ 3xULN but <8xULN



Abbreviations: ALT=alanine aminotransferase; bili=bilirubin; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

6.3.2. 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.

6.3.2.1. Definition of an AE

Any untoward medical occurrence in a subject 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 (ie, lack of efficacy), abuse, or misuse.

Events meeting the definition of an AE include:

- 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 study treatment 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 study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"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:

- Medical or surgical procedure (eg, 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
- 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

6.3.2.2. Definition of an SAE

An SAE 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 outpatient 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.

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 (eg, 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 1 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.

g. All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥3×ULN **and** bilirubin ≥2×ULN (>35% direct) (or ALT ≥3×ULN and international normalized ratio [INR]>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: bilirubin fractionation is 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. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2×ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.3.2.3. Adverse Events of Special Interest

The medical monitor should be notified of the occurrence of the following AEs of special interest:

- Any opportunistic infections, such as infections caused by organisms that do not cause disease in a person with a healthy immune system, or types of infections that do not commonly occur in someone with a healthy immune system (eg, Pneumocystis pneumonia, cryptococcal meningitis, mycobacterium infections, cytomegalovirus retinitis, systemic candidiasis).
- Serious postinjection systemic reactions: subjects may be withdrawn from investigational product administration at the discretion of the investigator.
- PML: follow any cases of suspected PML as per the algorithm in Appendix 4. Confirmed PML is to be reported as an SAE.
- HBV reactivation (see Section 6.3.10.2).
- Severe mucocutaneous reactions (eg, toxic epidermal necrolysis and Stevens-Johnson syndrome).

- Cytopenias.
- Cardiovascular events (see Section 6.3.4).

All infections and serious postinjection systemic reactions should be monitored closely throughout the study and recorded on the AE/SAE forms as soon as possible. As applicable, the investigator must also complete the respective 'Severe Infections' or 'Postinjection Systemic Reaction' eCRF page.

Refer to Section 4.4.2 and Section 4.4.3 for discontinuation and withdrawal criteria.

6.3.3. 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 (eg, 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 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.

6.3.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep venous thrombosis
- Revascularization

This information should be recorded within 1 week of when the AE/SAE(s) are first reported.

6.3.5. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded within 1 week of when the death is first reported.

6.3.6. Pregnancy

Pregnancy information will be collected from the start of study treatment through the follow-up contact. 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 that is brought to the investigator's attention after the subject has completed the study and is considered by the investigator as possibly related to the study treatment 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.

6.3.7. Time Period and Frequency of Detecting AEs and SAEs

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

All AEs will be collected from the start of study treatment through the end of the Core Study Period. SAEs and AEs of special interest will continue to be collected during the Individualized Follow-up Period.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (eg, study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a Novartis concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to Novartis within 24 hours, as indicated in Section 6.3.9.

6.3.8. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include the following:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

6.3.9. Prompt Reporting of Serious Adverse Events and Other Events to Novartis

Investigators must report all events meeting the protocol-defined criteria for SAEs, pregnancies, and liver function abnormalities to Novartis promptly, as described in Table 6-4, once the investigator determines that the event meets the definition.

Table 6-4 Reporting of Serious Adverse Events and Other Events to Novartis

	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
Cardiovascular or Death events: *Additional information*	1 week	"CV events" and/or "Death" data collection tool(s)	1 week	Updated "CV events" and/or "Death" data collection tool(s)
Pregnancy	24 hours	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Nonserious adverse events related to study treatment	5 days (calendar)	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
ALT≥3×ULN **and** bilirubin ≥2×ULN (>35% direct) (or ALT≥3×ULN **and** INR >1.5, if INR measured)[a]	24 hours[b]	"SAE" data collection tool. "Liver Event" Documents (ie, "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable)[c]	24 hours	Updated "SAE" data collection tool. Updated "Liver Event" Documents[c]
ALT≥8×ULN; ALT≥3×ULN with hepatitis or rash or ≥3×ULN and <5×ULN that persists ≥4 weeks	24 hours[b]	"Liver Event" Documents[c]	24 hours	Updated "Liver Event" Documents[c]
ALT≥5×ULN plus bilirubin <2×ULN	24 hours[b]	"Liver Event" Documents do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[c]	24 hours	Updated "Liver Event" Documents, if applicable[c]
ALT≥5×ULN and bilirubin <2×ULN that persists ≥2 weeks	24 hours[b]	"Liver Event" Documents[c]	24 hours	Updated "Liver Event" Documents[c]
ALT≥3×ULN and <5xULN and bilirubin <2×ULN	24 hours[b]	"Liver Event" Documents do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[c]	24 hours	Updated "Liver Event" Documents, if applicable[c]

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRF=case report form; CV=cardiovascular; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

a. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.
b. Novartis must be contacted at onset of liver chemistry elevations to discuss subject safety
c. Liver Event Documents (ie, "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF," as applicable) should be completed as soon as possible.

The SPM provides direction regarding the recording, reporting/transmitting, and follow-up of SAEs.

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from Novartis will file it with the Investigator's Brochure [Ofatumumab/OMB157/GSK1841157 Investigator's Brochure, 2016] and will notify the IRB/IEC, if appropriate according to local requirements.

6.3.10. Laboratory Assessments

6.3.10.1. Clinical Laboratory Data

All protocol required laboratory assessments listed in Table 6-5 must be performed by the central laboratory (unless otherwise specified). Laboratory assessments must be conducted in accordance with the [redacted] investigator manual and Protocol Time and Events Schedule (Table 6-1). Laboratory requisition forms must be completed and samples must be clearly labeled with the subject number, protocol number, site number, and visit date. Details for the preparation and shipment of samples and reference ranges for all safety parameters will be provided to the site by the central laboratory.

If additional laboratory assessments not specified in the protocol are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE), the event(s) must be recorded in the subject's case report form (CRF). Refer to the [redacted] investigator manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 6-5 Laboratory Testing

Chemistry	Hematology	Urinalysis	Other
Total protein	Platelet count	Appearance	Hepatitis B: [b] - HBV surface antigen - HBV surface antibody - anti-HBc - HBV DNA PCR
Albumin	RBC count	Specific gravity	
ALT	Hemoglobin	pH	
AST	Hematocrit	Protein	
Alkaline phosphatase	WBC count	Glucose	
Gamma-glutamyl transferase	WBC differential (automated) - Neutrophils - Lymphocytes[a] - Monocytes[a] - Bands - Eosinophils[a] - Basophils[a]	Ketones	Hepatitis C antibody [b]
Total bilirubin		Leukocyte esterase (leukocytes)	Immunoglobulins IgG, IgA, IgM[a]
Blood urea nitrogen		Hemoglobin (RBCs)	Pneumococcal antibody assay (*Streptococcus pneumoniae* IgG antibody assay) [a,b]
Creatinine		Microscopy: - RBC/HPF - WBC/HPF - Epithelial cells - Trichomonas - Bacteria - Yeast - Crystals - Ammonium urates - Mucous threads - Amorphous sediment - Casts	
Creatinine clearance (calculated)			Toxoid antibody assay (Tetanus toxoid IgG antibody assay) [a,b]
Sodium			
Potassium	Nucleated RBCs		High sensitivity C-reactive protein [a]
Chloride	CD19+ B-lymphocyte counts [a]		B-lymphocyte chemokine [a]
Calcium			[redacted]
Bicarbonate	CD3 [a]		
Glucose	CD4 [a]		[redacted]
	CD8 [a]		
	CD4:CD8 ratio [a]		
		Microalbumin	Human anti-human antibody [a]
		Creatinine	
		Microalbumin: creatinine ratio	

Abbreviations: ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; AST=aspartate aminotransferase; [redacted]; BlyS= B-lymphocyte stimulator; [redacted]; HBV=hepatitis B virus; HPF=high powered field; Ig=immunoglobulin; PCR=polymerase chain reaction; RBC=red blood cell; WBC=white blood cell.

a. To maintain study blinding, values will not be reported to investigators during the Treatment or Individualized Follow-up Periods. After the Week 60 visit and all Individualized Follow-up visits, the central laboratory (or designee) will provide the laboratory values and notify the investigator whether or not a subject needs to remain in Follow-up.
b. Screening and Week 60/early withdrawal only.
c. **Note**: Refer to the Time and Events Schedule (Table 6-1) and the [redacted] investigator manual for specific timing of individual laboratory assessments. Laboratory reference ranges are provided in Appendix 13.

6.3.10.2. Hepatitis B Screening and Monitoring

Exclude subjects who are HBsAg positive, regardless of other hepatitis B serologies. If a subject is HBsAg negative and anti-HBc positive, perform HBV DNA. Exclude subjects who are HBV DNA positive.

** In **Japan**, if a subject is HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive, an HBV DNA test will be performed and the subject will be excluded if results are positive (refer to Appendix 2).**

Subjects who are HBsAg negative, anti-HBc positive, and HBV DNA negative may be included in the study, but must undergo HBV DNA PCR monitoring at a minimum of every 12 weeks during the Treatment Period and for 6 months after the last dose. Consult with a physician experienced in the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Antiviral therapy to be initiated if required.

Table 6-6 Hepatitis B Virus Test Result Scenarios for Subject Eligibility

HBsAg	**anti-HBc** (HBcAb)	**HBsAb**	**HBV DNA**	**Subject Eligibility and Monitoring**
All subjects:				
+ / -	+ / -	+ / -	positive	Exclude subject if positive at screening; discontinue study treatment if positive during study
positive	+ / -	+ / -	+ / -	Exclude subject if positive at screening
negative	positive	+ / -	negative	May enroll subject with physician consult and HBV DNA monitoring during study
Additional for **Japan**: negative	negative	positive	negative	May enroll subject with physician consult and HBV DNA monitoring during study

+ / - = either positive or negative test result
Abbreviations: HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.

If a subject becomes HBV DNA positive during the course of the study, notify the medical monitor. Discontinue further treatment with investigational product and continue to follow the subject for safety as part of the Follow-up Period.

Extra visits outside those defined in the protocol may be needed for subjects who require hepatitis monitoring.

6.3.11. Other Safety Outcomes

6.3.11.1. Vital Signs

The following vital sign assessments will be measured by the investigator or medically qualified designee at the visits described in Table 6-1:

- Sitting systolic and diastolic blood pressure after at least 5 minutes of rest. Use the same arm at each visit.
- Heart rate in the sitting position and at the time of the blood pressure measurement.
- Temperature.

6.3.11.2. Twelve-lead Electrocardiogram (ECG)

The investigator or medically-qualified designee will perform a standard 12-lead ECG as part of the Screening assessments. The ECG should be obtained as per the study center's usual practice. The investigator or medically-qualified designee will evaluate the ECG

for any abnormalities that should exclude the subject from the study. If the QTc exceeds ≥450 msec (≥480 msec for subjects with a bundle branch block), the subject will be excluded from participation in the study.

Ofatumumab, by its mechanism of action (lysis of CD20+ B-lymphocytes), does not affect QTc; therefore, QTc is not routinely monitored during this study. A repeat ECG will be obtained at Week 60 or early withdrawal.

6.3.12. Medical Device Incidents

** In **Japan**, medical devices that are approved in other countries but not approved in Japan will be provided by Novartis for use in this study. Refer to Appendix 2 for medical device incident definitions and details on documenting, reporting, and follow-up of device incidents.**

6.5. Pharmacokinetics

The following pharmacokinetic endpoints will be evaluated, as data permit:

- Plasma (trough) concentrations of ofatumumab
- Exposure-response relationship

For subjects in the pharmacokinetic-pharmacodynamic substudy: pharmacokinetic endpoints will include model-based estimation of the following, as data permit:

- Maximum ofatumumab concentration (C_{max})
- Time of maximum concentration (T_{max})
- Area under the time-concentration curve (AUC)

Data permitting, there will also be an examination of the effect of demographic factors, including baseline covariates, on the pharmacokinetic endpoints.

Plasma analysis will be performed under the control of Novartis. The details of sample collection, processing, storage, and shipping are included in the [redacted] investigator manual. Concentrations of ofatumumab will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site, as per Novartis protocol.

Once the plasma has been analyzed for ofatumumab, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate Novartis protocol.

6.6. Pharmacodynamics

The following pharmacodynamic endpoints will be evaluated:

- Change from baseline in B-lymphocyte counts in peripheral blood.
- Time to repletion of CD19+ B-cells to either ≥baseline level or ≥LLN, whichever is lower.
- B-cell depletion and re-population as measured by CD19+ peripheral blood B-lymphocyte count via routine fluorescent activated cell sorting analysis.
- *For subjects in the pharmacokinetic-pharmacodynamic substudy*: CD19+ peripheral blood B-lymphocyte count via routine fluorescent activated cell sorting analysis with subsets including, but not restricted to, naïve and memory phenotypes.

6.7. Pharmacogenetics (PGx)

Information regarding pharmacogenetic (PGx) research is included in Appendix 1.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK-defined eCRFs, transmitted electronically to Novartis or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), the World Health Organization Drug Dictionary, and an internal validated medication dictionary. An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced. Electronic CRFs (including queries and audit trails) will be retained by 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 Novartis according to Novartis policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The overall null hypothesis is that there is no difference in time to SR on minimal steroid therapy by Week 60, and there is no difference in duration of remission on minimal steroid therapy between subjects in the ofatumumab SC group versus subjects in the placebo group. The alternative hypothesis is that ofatumumab SC is superior to placebo in at least one of the co-primary endpoints.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Assuming that the proportion of subjects achieving SR on minimal steroid therapy status is 54% and 80% in the placebo and the ofatumumab SC groups, respectively [Beissert, 2010], with proportional hazards across the various strata, a sample size of 68 subjects per group will give ≥90% power for a statistically significant difference between the two groups in time to SR on minimal steroid therapy, using a two-sided 0.05 level of significance. Note that for the purpose of sample size calculation of time to SR, "survival" means: "Not in SR", and hence (100-54=) 46%, and (100-80=) 20% are the survival rates for the placebo and ofatumumab SC treatment groups respectively needed to calculate sample size for the log-rank test. The study is designed to detect a hazard ratio of 0.48248 (median time to response on ofatumumab SC/median time to response on placebo). It is assumed that no more than 13% of the subjects in both groups will be lost to follow-up before their Week 60 visit. With the projected 54% and 80% SR rates in the placebo and active groups respectively, a total of approximately 80 subjects with SR in both treatment groups combined are needed at the end of the study. Because this study has 2 co-primary efficacy endpoints, an evaluation of the overall power to detect at least one significant endpoint was made using simulations. The analysis proposed for the

co-primary endpoints is a sequential test based on the method of Alosh and Huque [Alosh, 2010]. Results of the simulations are displayed in Table 8-2.

8.2.2. Sample Size Sensitivity

The sample size projected for this study is based on the assumption of 54% and 80% SR rates in the placebo and ofatumumab SC treatment groups respectively. For a log rank test, the projected hazard ratio is 0.48248 (ofatumumab SC/placebo) and the projected number of subjects with SR on minimal steroid therapy is 80. If the hazard ratio is indeed 0.48248, but the response rates in both groups are lower, then more subjects will need to be enrolled in order to have at least 80 subjects with SR at the end of the study. Table 8-1 shows the sensitivity of the sample size to the response rates in each treatment arm, assuming a hazard ratio of 0.48248.

Table 8-1 Sample Size Sensitivity

Placebo Response Rate	Ofatumumab SC Response Rate	Total Sample Size Needed for At Least 80 Responses (Assuming a 13% Dropout Rate)
0.42	0.68	166
0.44	0.70	160
0.46	0.72	154
0.48	0.74	148
0.50	0.76	144
0.52	0.78	140
0.54 [a]	0.80	136

a. Projected for the study.

The primary analysis is based on a sequential test of the 2 co-primary endpoints: time to SR on minimal steroid therapy, and duration of remission, using the method of Alosh and Huque [Alosh, 2010], described in detail in Section 8.3.6.5. In this method, a sequential testing of the co-primary endpoints is made using critical points that provide consistency results for the 2 co-primary endpoints. Two parameters were considered in the simulation: time to SR on minimal steroid therapy, and duration of remission on minimal steroid therapy. Simulations were made using an exponential time to event (time to remission, and time to flare), and using the protocol definitions of SR and duration of remission. The ranges of values for these parameters were selected to provide approximately 54% and 80% remission rates in the placebo and active groups respectively, assumed for this study.

Table 8-2 Overall Power for the Co-primary Endpoints

Parameter	Placebo	Ofatumumab SC	Overall Power
Time to remission (weeks) Duration of remission (weeks)	28 8	16 17	95%
Time to remission (weeks) Duration of remission (weeks)	32 9	16 17	90%
Time to remission (weeks) Duration of remission (weeks)	44 10	20 19	93%

Abbreviation: SC=subcutaneous.
Note: Based on simulation of 100 trials with 59 subjects per group.

8.2.3. Blinded Sample Size Re-estimation

The power of 90% for this study assumes that 80 subjects will have SR on minimal steroid therapy by the end of the study. This number will be monitored in a blinded way, and if necessary, more than 136 subjects will be randomized to ensure that at least 80 subjects will have SR on minimal steroid therapy at the end of the study. Because the sample size re-estimation is done in a blinded manner, based on the total number of SRs, no penalty for type-1 error inflation is warranted. The reporting and analysis plan (RAP) will specify the method of monitoring and adjustment to the sample size.

8.3. Data Analysis Considerations

Additional details of data analyses will be specified in the RAP.

8.3.1. Analysis Populations

The Intent-to-Treat (ITT) population will consist of all subjects randomized to treatment. This will be the primary population used for the efficacy analyses. The Per Protocol (PP) population will consist of those members of the ITT population who have no major protocol violations. If the PP population comprises more than 95% or less than 50% of the ITT population, it will not be analyzed. This population will be used for a confirmatory analysis of the primary efficacy endpoint and any key secondary efficacy endpoints. The primary population for safety analyses will be the safety population which will consist of all subjects who were randomized and were administered least 1 dose of investigational product. The Pharmacokinetic Population will include all subjects in the ITT population providing analyzed pharmacokinetic samples.

The Pharmacogenetic Population will include all subjects in the ITT population who consented to providing a genetics sample, provided a sample, and did not withdraw their consent.

8.3.2. Analysis Data Sets

The Observed Case dataset makes no assumptions about missing data and will lead to missing assessments being excluded from the analysis. The primary analysis dataset for the analysis of time to SR on minimal steroid therapy will be the Observed Case dataset.

Subjects who discontinue from the study before they reach SR, or finish the study without an SR will be considered as censored at their last visit. For the analysis of duration of remission on minimal steroid therapy, subjects who discontinued prior to the end of the study will be considered as not in remission from their last known visit till Week 60. For the analysis of proportion of subjects who achieve remission at Week 60, subjects who discontinued before Week 60 will be considered as not in remission.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparison of interest of this study is between placebo and ofatumumab SC on time to SR on minimal steroid therapy, and duration of remission on minimal steroid therapy. These comparisons will be made using the sequential method of Alosh and Huque [Alosh, 2010], described in Section 8.3.6.5.

8.3.3.2. Other Comparisons of Interest

Secondary comparisons of interest will be made between placebo and ofatumumab SC on the secondary endpoints, sequentially in the order presented in Section 6.2.2, only if the 2 co-primary endpoints have been found significant. All tests will be done at two-sided 0.05 level of significance. To protect against an inflation of type-1 error, if any of the comparisons are found not statistically significant, no subsequent tests of significance will be performed on the secondary endpoints.

Comparisons of interest will be made between placebo and ofatumumab SC on the other endpoints.

8.3.4. Interim Analysis

An interim analysis for futility will be conducted when 60 events of SR on minimal steroid therapy have been observed. The analysis will be conducted by an unblinded statistician not involved in the conduct of the study and results will be presented to the IDMC. A conditional power analysis will be conducted based primarily on projecting the observed trend of the difference between ofatumumab and placebo in time to remission on minimal steroid therapy. If the analysis indicates that the conditional power for a positive outcome for time to remission on minimal steroid therapy ($p<0.025$ one-sided) is less than 30%, the IDMC will communicate to designated Sponsor's representatives that the study is unlikely to meet its primary objectives. The Sponsor may evaluate additional information such as pharmacokinetics and pharmacodynamics and make a final decision regarding continuation of the study.

If enrollment is substantially slower than anticipated and/or the rate of SRs is much smaller than projected, consideration will be given to performing the interim analysis for futility at an earlier time point. If a decision is made to perform an early interim analysis, the IDMC will be notified of this decision and preparation will be made for an unscheduled IDMC meeting. After review of the interim data, the IDMC may:

- Recommend continuing the study as planned.

- Determine that continuation of the study is unlikely to reach a successful conclusion on the basis of the slow enrollment and/or low rate of remissions and thus recommend stopping the study early for futility.

The interim analysis will not be used to stop the study early for a positive outcome; therefore, no adjustment to the final analysis type-1 error is indicated. Details of the interim analysis will be specified in the IDMC charter, as well as in the RAP.

8.3.5. Reporting Time Points

Reporting of the study will occur at 2 time points:

- Sponsor unblinding for analyses to support regulatory submissions will occur after all subjects have completed the Week 60 visit (primary analysis time point) or been withdrawn from the Treatment Period; all data will be cleaned and the database up to this time point will be frozen.
- The final analysis will occur after the last subject's last visit in the Individualized Follow-up Period (ie, after all subjects have completed the full study or been withdrawn prematurely); data from the Individualized Follow-up Period will be reported in an addendum to the clinical study report.

8.3.6. Key Elements of Analysis Plan

8.3.6.1. Missing Data

The co-primary efficacy endpoint of time to SR on minimal steroid therapy will be analyzed using the ITT Observed Case dataset. Subjects who discontinue from the study before the end of the study, or reach their last planned visit without achieving SR on minimal steroid therapy, will be censored in the analysis at their last visit. If discontinuations from the study are for reasons that are independent of this endpoint, then this analysis is not biased. If discontinuations are for reasons that are correlated with the endpoint, the statistical test may be biased, particularly, if 1 of the treatment arms has a markedly larger number of discontinuations. An early discontinuation of a subject before achieving an endpoint may have an unduly favorable bias towards the treatment arm that has more discontinuations, since the time-to-event analysis uses the shortened exposure time due to the discontinuation. One can make an assumption that if the discontinuation is due to lack of efficacy, or for safety reasons, that subject would not have achieved the endpoint had the subject continued to the end of the study. Therefore, as a sensitivity analysis, subjects who discontinued before the end of the study will be considered as censored at the end of the study rather than at their last visit. For the other co-primary endpoint, duration of remission on minimal steroid therapy, subjects who discontinued before the end of the study will be considered as not in remission from the last known visit till Week 60.

For the secondary endpoint of the proportion of subjects in remission on minimal steroid therapy at Week 60, subjects who discontinued prior to Week 60 will be considered as not in remission at Week 60.

8.3.6.2. Derived and Transformed Data

For variables that require the analysis of change from baseline, the post-baseline assessment value minus the baseline assessment value will be used to derive change from baseline. If either value is missing then the change from baseline will also be missing.

Full details on the derivation of endpoints and any data transformations to be performed will be described in the RAP.

8.3.6.3. Assessment Windows

The RAP will define details of visit slotting and visit windows of relevance to the conduct of the analysis. All data collected will be listed even if it is not used in summary tables/figures or statistical analyses.

8.3.6.4. Randomization and Stratification

A central randomization procedure will be used to allocate subjects to the two treatment arms. Because the possibility exists for a small number of subjects in many sites, the randomization will not be stratified by site. Rather, stratification will be made on disease duration (≤1 year, >1 year), and baseline prednisone dose (<60 mg, ≥60 mg). Randomization will be set up to minimize treatment imbalances within stratification factors.

8.3.6.5. Efficacy Analyses

Graphical displays and tables will present and summarize all efficacy measures over the course of the study. Means, SDs, medians, maximum, minimum, and number of subjects will summarize continuous data. Categorical data will be summarized by counts and percentages. Confidence intervals (Cis) (95%) and p-values will be displayed where applicable.

Primary Endpoint Analyses

Baseline prednisone/prednisolone dose and disease duration will be used to stratify all primary and secondary analyses. The primary analysis for the co-primary endpoints will use the ITT population.

The co-primary efficacy endpoint of time to SR on minimal steroid therapy by Week 60 will be analyzed using a log-rank test stratified by baseline prednisone/prednisolone dose and disease duration strata. Subjects who discontinue prematurely (prior to Week 60) will be censored at the time they discontinued. Subjects who reach Week 60 without remission will be censored at their last visit. Calculation of time to SR will be made from randomization date to the first time the subject was in remission for 8 consecutive weeks while on minimal steroid therapy and sustained that remission until Week 60.

The co-primary endpoint of duration of remission on minimal steroid therapy will be analyzed using a rank analysis of covariance (ANCOVA) [Stokes, 2000], with treatment as a main effect, and baseline prednisone/prednisolone dose and disease duration strata as covariates. If a subject went into remission, then relapsed, and then went into remission

again (or possibly more than 2 episodes of remission), the duration of remission will be the total time (sum) of all periods of remission while on minimal steroid therapy up to Week 60. If a subject discontinued the study prior to Week 60, the subject will be considered as not in remission from the last known visit till Week 60.

To protect the overall type-1 error at 0.05 (one-sided 0.025), the analysis of the co-primary endpoints will follow the procedure proposed by Alosh and Huque [Alosh, 2010]. In this procedure, a consistency criterion is applied, so that the co-primary endpoints can be deemed significant only if one of the following events occur:

1. The time to SR on minimal steroid therapy is significant at one-sided 0.02. If significant, then duration of remission on minimal steroid therapy is tested at one-sided 0.025.
2. If time to SR on minimal steroid therapy has a one-sided p-value (P) between 0.02 and 0.025, then duration of remission) on minimal steroid therapy can be rejected at a one-sided level:

   $0.025-((0.025-\gamma1)/(0.025-0.02))*(P-0.02)$.

   If duration of remission is rejected, so is time to SR on minimal steroid therapy.
3. If time to SR on minimal steroid therapy has a one-sided p-value (P) between 0.025 and 0.1, then duration of remission on minimal steroid therapy must be significant at a one-sided level:

   $0.018-((\gamma1-\gamma2)/(0.1-0.025))*(P-0.025)$.

   Time to SR on minimal steroid therapy cannot be rejected in this case.

The values $\gamma1$ and $\gamma2$ are selected to control the overall type-1 error. Because the co-primary endpoints are expected to be correlated, we use Table 2 of Alosh and Huque [Alosh, 2010] to determine $\gamma1$ and $\gamma2$. As displayed in that table, selecting $\gamma2=0.001$, and $\gamma1=0.018$, lead to a conservative (<0.025 one-sided) type-1 error for all correlations ≤ 0.9. Our simulations suggest that the correlation between the co-primary endpoints is expected to be ≤ 0.9, hence the values selected for $\gamma1$ and $\gamma2$ will lead to an overall one-sided type-1 error <0.025.

To illustrate the above procedure, we consider the following hypothetical outcomes:

1. P1=time to SR on minimal steroid therapy p-value=0.01. P2=duration of remission on minimal steroid therapy p-value=0.024. Since $P1\leq 0.02$, time to SR is significant. Since $P2\leq 0.025$, duration of remission is significant.

   Overall, we conclude that ofatumumab SC is superior to placebo (on both endpoints).
2. P1=0.01, P2=0.03. Since $P1\leq 0.02$, time to SR is significant. Since $P2>0.025$, duration of remission is not significant.

   Overall, we conclude that ofatumumab SC is superior to placebo (on time to SR).
3. P1=0.023, P2=0.015. Since $0.02\leq P1\leq 0.025$, we test duration of remission at level: $0.025-((0.025-\gamma1)/(0.025-0.02))*(P-0.02)=0.0208$ (substituting 0.018 for $\gamma1$ and

0.023 for P). Since P2≤0.0208, duration of remission is rejected, and hence also time to SR.

Overall, we conclude that ofatumumab SC is superior to placebo (on both endpoints).

4. P1=0.06, P2=0.006. Since 0.025≤P1≤0.1, we test duration of remission at level:

   0.018-((γ1-γ2)/(0.1-0.025))*(P-0.025).=0.010067. Since P2<0.010067, duration of remission is rejected, but not time to SR.

   Overall, we conclude that ofatumumab SC is superior to placebo (on duration of remission).

Secondary Endpoint Analyses

The secondary endpoint of the proportion of subjects with remission on minimal steroid therapy at Week 60 will be analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by baseline prednisone/prednisolone dose and disease duration strata. This analysis will be conducted on the ITT population. In this analysis, subjects who discontinued prior to Week 60 will be considered as not having remission at Week 60. Other secondary analyses based on time to event endpoints will be analyzed using a stratified log-rank test similarly to the primary endpoint analyses. Secondary endpoints that are based on proportions will be analyzed using a stratified CMH test. Continuous data will be analyzed using ANCOVA with Treatment as a main effect and the strata as covariates. If a continuous endpoint is based on a change from baseline, then baseline will be included as an additional covariate. Summary statistics will also be provided for the primary and key secondary variables by study center.

All statistical tests will be performed with significance interpreted at the two-sided 5% significance level.

8.3.6.6. Pharmacokinetic Analyses

The ofatumumab plasma concentration data will be analyzed using nonlinear mixed effects modeling. The effect of demographic factors will be examined if data permit.

8.3.6.7. Pharmacodynamic Analyses

Peripheral blood B-lymphocyte counts will be used as a pharmacodynamic marker. These data will be tabulated by sex at each time point with the tables showing N, mean, SD, median, and range. Similar summaries will be provided for neutrophil counts, which are considered a negative control.

8.3.6.8. Pharmacokinetic/Pharmacodynamic Analyses

The ofatumumab plasma concentration and peripheral lymphocyte counts will be analyzed using nonlinear mixed effects modeling and related to study primary and secondary endpoints if data permit. The effect of demographic factors and baseline covariates will be examined if data permit.

8.3.6.9. Safety Analyses

The analysis of safety data will use the Safety population. These data will not undergo any formal statistical analysis.

Adverse Events

Adverse events will be coded using the MedDRA and summarized by system organ class and preferred term.

Summaries by treatment groups, of the number and percentage of subjects with the following AEs will be provided:

- All AEs
- Adverse event frequency, severity, and relationship to investigational product
- Frequency and severity of infections
- Frequency of SAEs
- Percentage of subjects withdrawing due to AEs assessed by the investigators as at least possibly related to treatment
- Adverse events leading to permanent discontinuation of investigational product
- Adverse events of special interest (see Section 6.3.2.3)
- Postinjection systemic reactions
- Injection site reactions

The hierarchical relationship between MedDRA, system organ classes, and preferred terms and verbatim text will be displayed for relevant AEs.

Clinical Laboratory Evaluations

Summary statistics will be presented for each laboratory test, and change from baseline, at each assessment time point by treatment group. Laboratory test values will be flagged to show whether they are a value within, below, or above the normal range and if they are a value of potential clinical concern. The number and percentage of subjects with values in each of these categories at each assessment time point will be summarized for each laboratory test.

Vital Signs

Each variable and change from baseline in each variable will be summarized at each assessment time point by treatment group. In addition, the number and percentage of subjects with vital sign values within, below, and above values of potential clinical concern will be summarized for each variable.

8.3.6.10. Clinical Measures

Summary statistics will be provided for all other efficacy and safety endpoints.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study center, Novartis will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favorable opinion/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.

In approving the clinical protocol, the IEC/IRB and, where required, the applicable regulatory agency must also approve the PGx assessments (ie, approval of Appendix 1), unless otherwise indicated. Where permitted by regulatory authorities, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

** In **Japan**, refer to Appendix 2 for country-specific regulatory and ethical considerations.**

9.3. 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.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis may conduct a quality assurance assessment and/or 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 assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

The end of the study will occur when the last remaining randomized subject has completed the final visit (ie, date of last subject last visit) and all queries relating to subject data have been answered.

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 noncompliance. If Novartis determines 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.

9.6. 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 (eg, 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 (eg, 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.

Novartis 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, Novartis standard operating procedures, and/or institutional requirements.

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.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

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.

Novartis will also 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. Novartis will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or

received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. 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 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 analyses and the analysis plan for IDMC review is described in the charter, which is available upon request.

9.9. Progressive Multifocal Leukoencephalopathy (PML) Adjudication

Any case of suspected or confirmed PML will go through independent PML adjudication and an opinion will be provided to the Sponsor.

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11. APPENDICES

11.1. Appendix 1 – Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (ie, genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* 57:01 (Human Leukocyte Antigen B)	Carriage of the HLA-B*57:01 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*57:01 screening and exclusion of HLA-B*57:01 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*57:01 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*57:01 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	HLA-B*15:02	Independent studies indicated that patients of East Asian ancestry who carry HLA-B*15:02 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, including neutropenia following initiation of irinotecan treatment. The irinotecan drug label indicates that individuals who have 2 copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to ofatumumab.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to ofatumumab. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with ofatumumab that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the pharmacokinetics and/or pharmacodynamics of ofatumumab
- Relationship between genetic variants and safety and/or tolerability of ofatumumab
- Relationship between genetic variants and efficacy of ofatumumab

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives study treatment may take part in the PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for DNA extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labeled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of ofatumumab has been completed and the study data reviewed.

In some cases, the samples may not be studied (eg, if no questions are raised about how people respond to ofatumumab).

Novartis will securely store samples and may keep them for up to 15 years after the last subject completes the study; or Novartis may destroy the samples sooner. Novartis or those working with Novartis (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has had a sample taken for PGx research withdraws from the clinical study for any reason other than being lost to follow-up, then the subject will be given a choice of 1 of the following options concerning the PGx sample:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent from the PGx research or requests sample destruction, the investigator must request sample destruction by completing the appropriate documentation within the specified timeframe, and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to Novartis as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (absorption, distribution, metabolism, and excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to ofatumumab. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (eg, single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study RAP or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

Novartis may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

Novartis does not inform the investigator, subject, or anyone else (eg, family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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11.2. Appendix 2 – Country Specific Requirements

Unless otherwise specified, no country-specific requirements are applicable.

11.2.1. Appendix 2 – Country-Specific Requirements: Japan

The following country-specific information and study conduct considerations for OPV116910 Protocol Amendment 8 are applicable to all subjects enrolled at study centers in Japan.

These protocol modifications were requested during review by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) (note: agreements with agency were based on the Japanese language version). This information was previously included in an 'addendum' to Protocol Amendment 3.

Protocol Modifications and Supplementary Details

(Note: Section numbers refer to the corresponding section of the protocol)

Section 4.2 Inclusion Criteria – Criterion 7b

7.b. In the list of "acceptable methods of contraception," the **following methods are not applicable in Japan**:

- Oral contraceptives with progestogen alone
- Injectable progesterone
- Levonorgestrel implants
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Vaginal spermicidal foam, gel, film, and cream

Section 4.3 Exclusion Criterion 6 (added additional sub-criteria)

6. Evidence or history of clinically significant infection **or medical condition** including…

– Pneumocystis pneumonia or interstitial pneumonia (based on results of **screening** posterior-anterior **chest X-ray, KL-6**, and **β-D glucan**). Order these tests from a local laboratory during screening and as part of a work-up for a subject with signs or symptoms of potential concern during the study.

– Based on the Japanese Guideline for Hepatitis B, for subjects who are HBsAg negative, anti-HBc (HBcAb) negative, but **HBsAb positive**, an HBV DNA test will be performed and the subject will be excluded from the study if results are positive.

– If any of the following criteria for TB screening are met:

- Past medical history for latent or active TB before screening.
- Sign(s) or symptom(s) suggestive of active TB in medical history on examination.
- Recent close contact with a patient with active TB.
- Positive interferon-gamma release assay (QuantiFERON-TB Gold In-Tube) or tuberculin skin test within 1 month before the first dose of study treatment.

- Chest x-ray, taken within 3 months before first dose of study treatment, shows evidence indicating currently active or previous TB.

Section 4.4.3 Withdrawal from the Study

In Japan, "Sponsor request (after discussion with the investigator)" will be made in the case of subjects lost to follow-up or when the (sub)investigator considers it necessary to withdraw the subject from the study.

The study center should make 3 contact attempts by 2 types of correspondence procedures (eg, phone calls, cell-phone text messaging, e-mail, certified letter) before considering a subject lost to follow-up. Correspondence must be documented.

Section 5.3 Product Accountability

In Japan, unused investigational products will be collected at the end of the study by the Sponsor or Sponsor's consignor.

Section 5.6.2 Prohibited Medications and Non-Drug Therapies

In Japan, alemtuzumab (Campath) and anti-CD4 treatments are not approved. Immunoglobulin therapy is prohibited as an immunosuppressive agent.

Section 6.1. Critical Baseline Assessments

In Japan, increased incidences of pneumocystis pneumonia and interstitial pneumonia have been noted in Japanese patients taking other biologic agents. It is recommended to screen for TB by conducting a medical interview, performing interferon-gamma release assay or tuberculin skin test, and chest x-ray, prior to the start of biologic treatment. Therefore, the following assessments should be conducted for subjects in Japan during the Screening Period and repeated if clinically-indicated during study participation:

- Chest x-ray
- KL-6 assay
- β-D-glucan assay
- Interferon-gamma release assay (QuantiFERON-TB Gold In-Tube) or tuberculin skin test within 1 month before the first dose of study treatment.

Section 6.3.11 Medical Devices Incidents

Medical devices that are approved in other countries but not approved in Japan (Nonapproved Medical Devices in Japan) will be provided by Novartis for use in this study.

Nonapproved Medical Device in Japan incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the (sub)investigator throughout the study.

General Name	Manufacturer name	Catalog No./ Product No.
Vacuum blood collection tube	Streck	Cyto-Chex BCT
Prefilled syringe with needle	Becton Dickinson and Company	Hypak-SCF

Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

Incidents include the followings:

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration in health

A serious deterioration in state of health can include:

- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)
- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic (IVD) test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Malfunction – A failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

Remedial Action – Any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable incident (including any amendment to the design to prevent recurrence).

Documenting Medical Device Incidents

Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the (sub)investigator's normal clinical practice, and on the "Medical Device Incident Report Form". In addition, for incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE data collection tool in the CRF will be completed as previously described.

The form will be completed as thoroughly as possible and signed by the (sub)investigator before transmittal to Novartis. It is very important that the (sub)investigator provides his/her assessment of causality to the medical device provided by Novartis at the time of

the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Transmission of Medical Device Incident Reports

Immediate facsimile transmission of the Medical Device Incident Report Form is the preferred method to transmit this information to Novartis.

In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the Medical Device Incident Report Form sent by overnight mail or delivery service.

	Initial Report		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Medical device incident	24 hours	Medical Device Incident Report Form	24 hours	Updated Medical Device Incident Report Form

Time Period of Detecting Medical Device Incident

Medical device incidents will be collected from the start of the study until the follow-up contact.

Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The (sub)investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the (sub)investigator.

Post-Study Medical Device Incidents

The (sub)investigators are not obligated to actively seek reports of medical device incidents in former subjects. However, if the (sub)investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a Novartis medical device provided for the study, the (sub)investigator will promptly notify Novartis.

Regulatory Reporting Requirements for Medical Devices

The (sub)investigator will promptly report all incidents occurring with any Novartis medical device provided for use in the study to Novartis. Novartis notifies appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents by the

(sub)investigator to Novartis is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.

The (sub)investigator or head of corresponding clinical institute, will comply with the applicable local regulatory requirements relating to the reporting of incidents and near-incidents to the IRB/IEC.

Section 9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No. 28 dated 27 March 1997)" and Article 14-3 and 80-2 of the Pharmaceutical Affairs Law.

The statement "I acknowledge that I am responsible for overall study conduct." On the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

Novartis will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract with study centers for the conduct of the study.

Informed Consent

Prior to participation in the study, the (sub)investigator should fully inform the potential subject and/or the subject's legally acceptable representative (Note: in Japan, the description of legally acceptable representative is applicable when the subject is younger than 20 years old) about the study including providing written information. The (sub)investigator should provide the subject and/or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study. The subject and/or the subject's legally acceptable representative should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The (sub)investigator should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy of the form to the subject and/or the subject's legally acceptable representative.

11.3. Appendix 3 – Liver Chemistry Stopping and Follow-up Criteria

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT – Absolute	ALT ≥8xULN
ALT – Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin [1,2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR [2]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic [3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow-Up Assessments**
• Immediately discontinue study treatment • Report the event to Novartis **within 24 hours** • Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **Monitoring** below) • **Do not restart** subject with study treatment unless allowed per protocol and Novartis Medical Governance approval is granted • If restart is not allowed or not granted, permanently discontinue study treatment and may continue subject in the study for any protocol-specified follow-up	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5] • Blood sample for pharmacokinetic (PK) analysis, obtained within 6 weeks after last dose[6] • 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 liver injury or hypersensitivity on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake CRF

MONITORING:	
For bilirubin or INR criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours** • A specialist or hepatology consultation is recommended • Monitor subjects twice weekly until liver chemistries resolve, stabilize, or return to within baseline **For all other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor subjects weekly until liver chemistries resolve, stabilize, or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high-performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **Note: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

b. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).

d. Includes: 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.

e. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

f. PK sample may not be required for subjects known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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.

Liver Chemistry Increased Monitoring Criteria with Continued Therapy – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the Novartis medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue study treatment. • Subject 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 subject meets the liver chemistry stopping criteria, proceed as described above. • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

11.4. Appendix 4 – Algorithm for PML Monitoring

Monitoring for progressive multifocal leukoencephalopathy (PML) will be an important part of the safety monitoring for this study.

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.

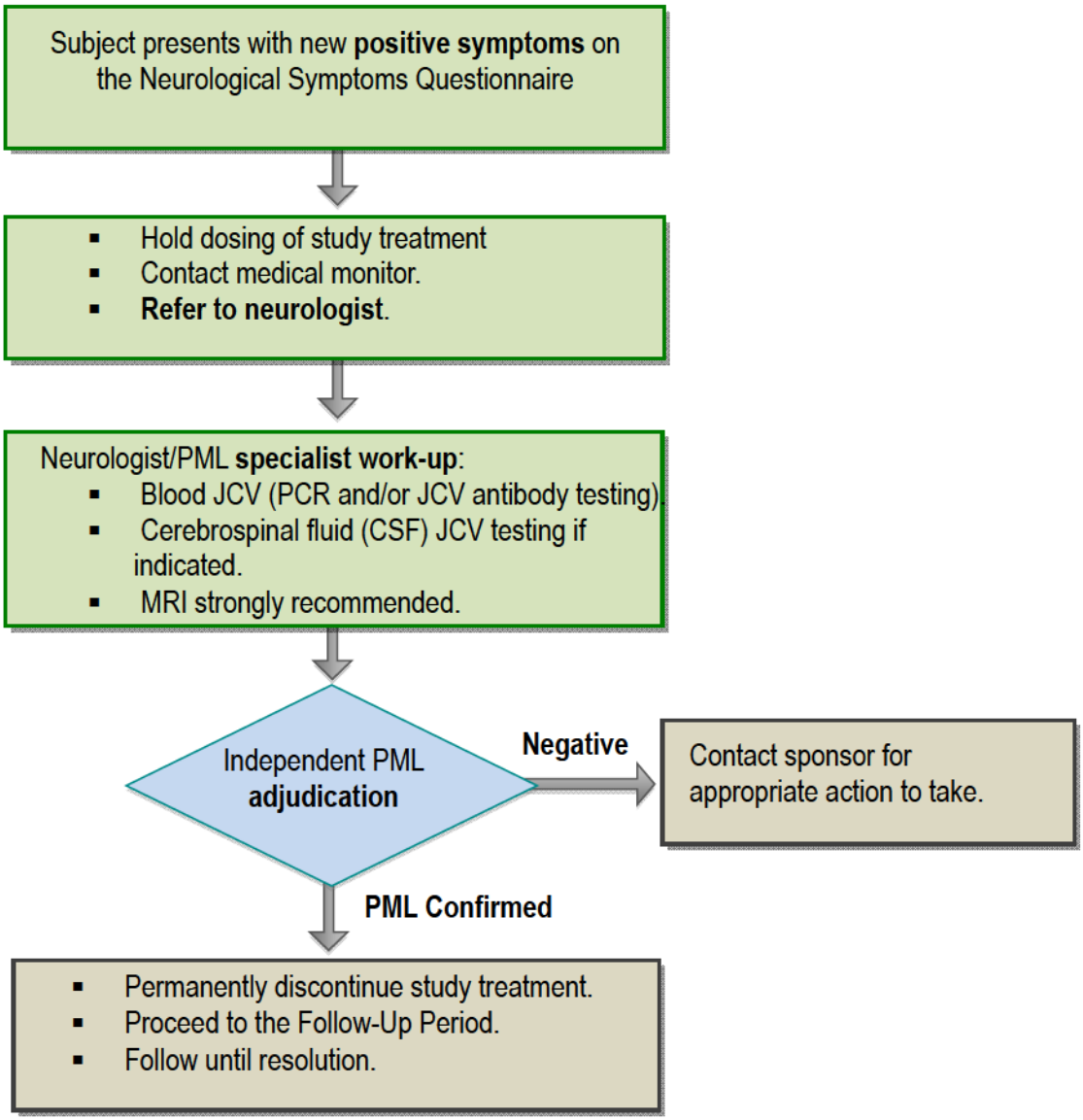
These symptoms are not an exhaustive list, and the investigator should exercise judgment in deciding to report signs and symptoms to Sponsor promptly. If a subject develops neurological signs or symptoms consistent with PML, treatment should be halted and the subject referred to a neurologist for evaluation. Blood JCV (PCR and/or JCV antibody testing) should be performed. If indicated, cerebrospinal fluid (CSF) JCV testing should also be performed. Magnetic resonance imaging (MRI) is strongly recommended. If test results are negative, the investigator should contact the Sponsor for appropriate action to be taken. If PML is confirmed, the subject should be withdrawn from treatment, proceed to the Follow-Up Period, and be followed until resolution. Serum banked from the Baseline visit may also be tested for JCV as part of the PML work-up.

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 basic components of this monitoring include:

1. Prior to study start, the Sponsor will provide information regarding PML and its presentation.
2. Qualified site staff will administer the Neurological Symptoms Questionnaire at every visit.
3. In the event of positive symptoms on the Neurological Symptoms Questionnaire, the investigator will contact the medical monitor and the subject will be referred to a neurologist.
4. Any case of suspected or confirmed PML will go through independent PML adjudication and an opinion will be provided to the Sponsor. The independent PML adjudicator can request additional testing and further data collection.

Figure 11-1 Algorithm for PML Monitoring

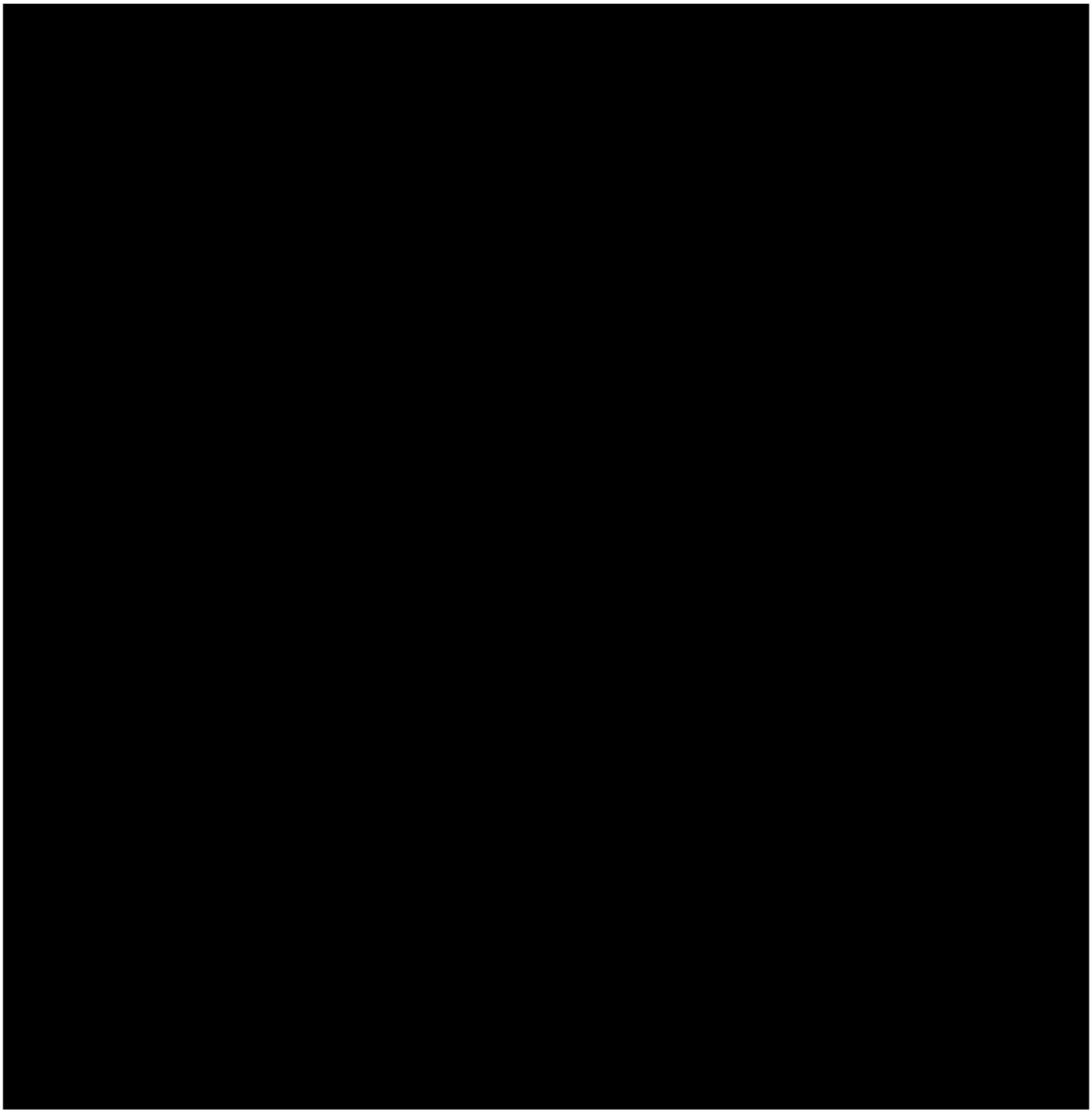


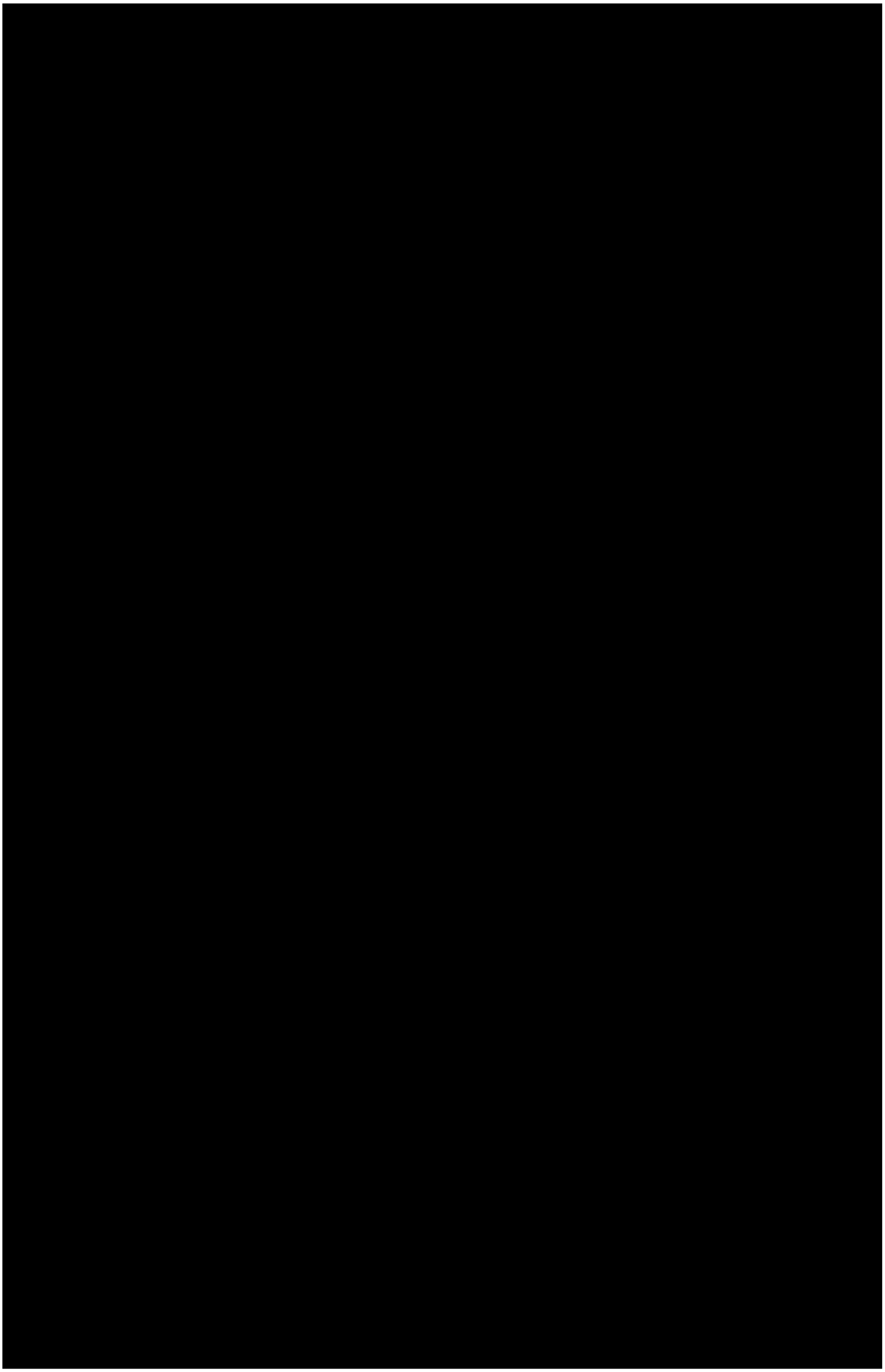
11.5. Appendix 5 – Neurological Symptoms Questionnaire

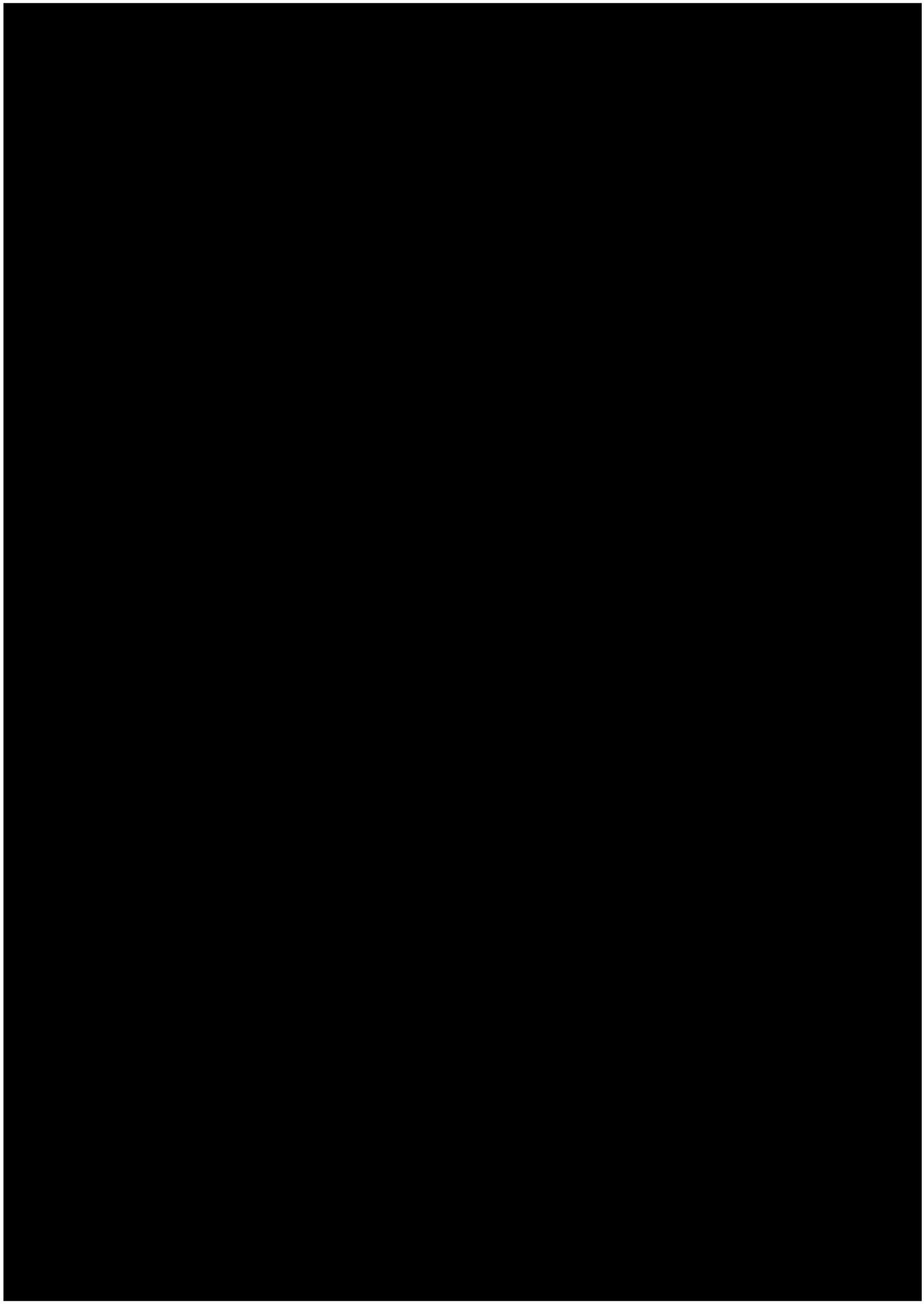
		YES	NO
1.	Does the subject report any new focal weakness?		
2.	Does the subject report any new difficulty with coordination or walking?		
3.	Does the subject report any new signs of confusion, impaired memory, or attention?		
4.	Does the subject appear apathetic compared to previous contacts?		
5.	Does the subject report any new visual disturbances?		
6.	Has the subject had any new trouble speaking, either slurring speech, difficulty getting out words, difficulty understanding words, or difficulty comprehending spoken language?		
7.	Does the subject have any other new neurological symptoms, including but not limited to: • New onset seizure • New sensory loss • New emotional lability		

If any of the above are answered "Yes" at any visit, the investigator will contact the medical monitor.

Any neurological symptom that cannot be directly attributed to a concurrent medical condition or concomitant medication **must be referred to a neurologist**.







ABSIS SCORING SHEET

Date:
Patient's weight (kg):

Legend for weighting factor (most dominant appearance of skin lesions):	
1.5	*Erosive, exudative lesions*
1	*Erosive, dry lesions*
0.5	*Reepithelialized lesions*

Skin Involvement (Max BSA)	**Patient's BSA**	**Weighting factor**
Head & neck (9%):		
L Arm including hand (9%):		
R Arm including hand (9%)		
Trunk (front & back) (36%):		
L Leg (18%):		
R Leg (18%):		
Genitals (1%):		

(Skin involvement total score: % BSA x weighting factor = 0-150 points)

Oral Involvement:

I. Extent (enter 1 for presence of lesions, 0 absence of any lesion):

Upper gingival mucosa		Tongue	
Lower gingival mucosa		Floor of the mouth	
Upper lip mucosa		Hard palate	
Lower lip mucosa		Soft palate	
Left buccal mucosa		Pharynx	
Right buccal mucosa			

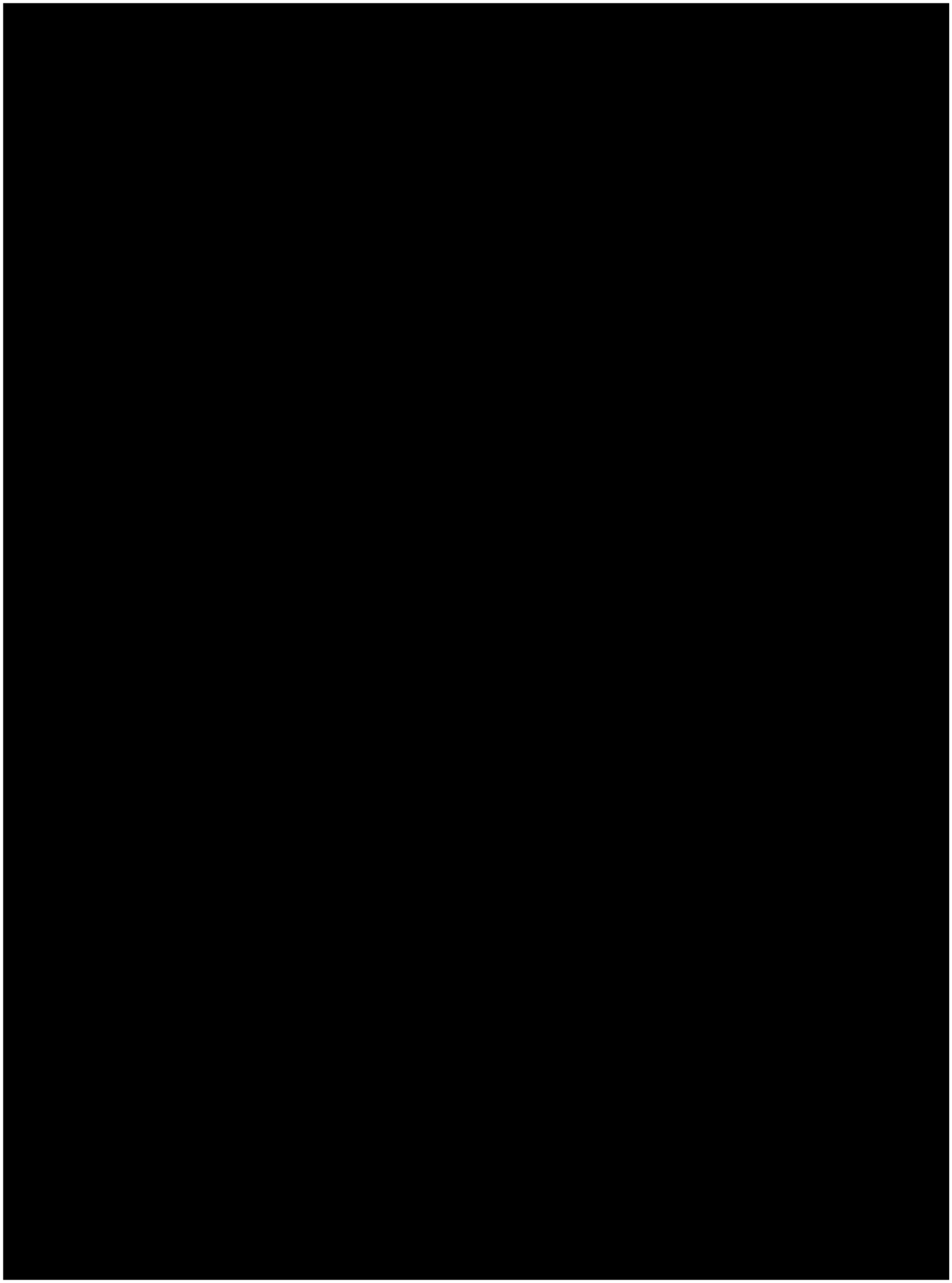
(Total score ranges from 0-11)

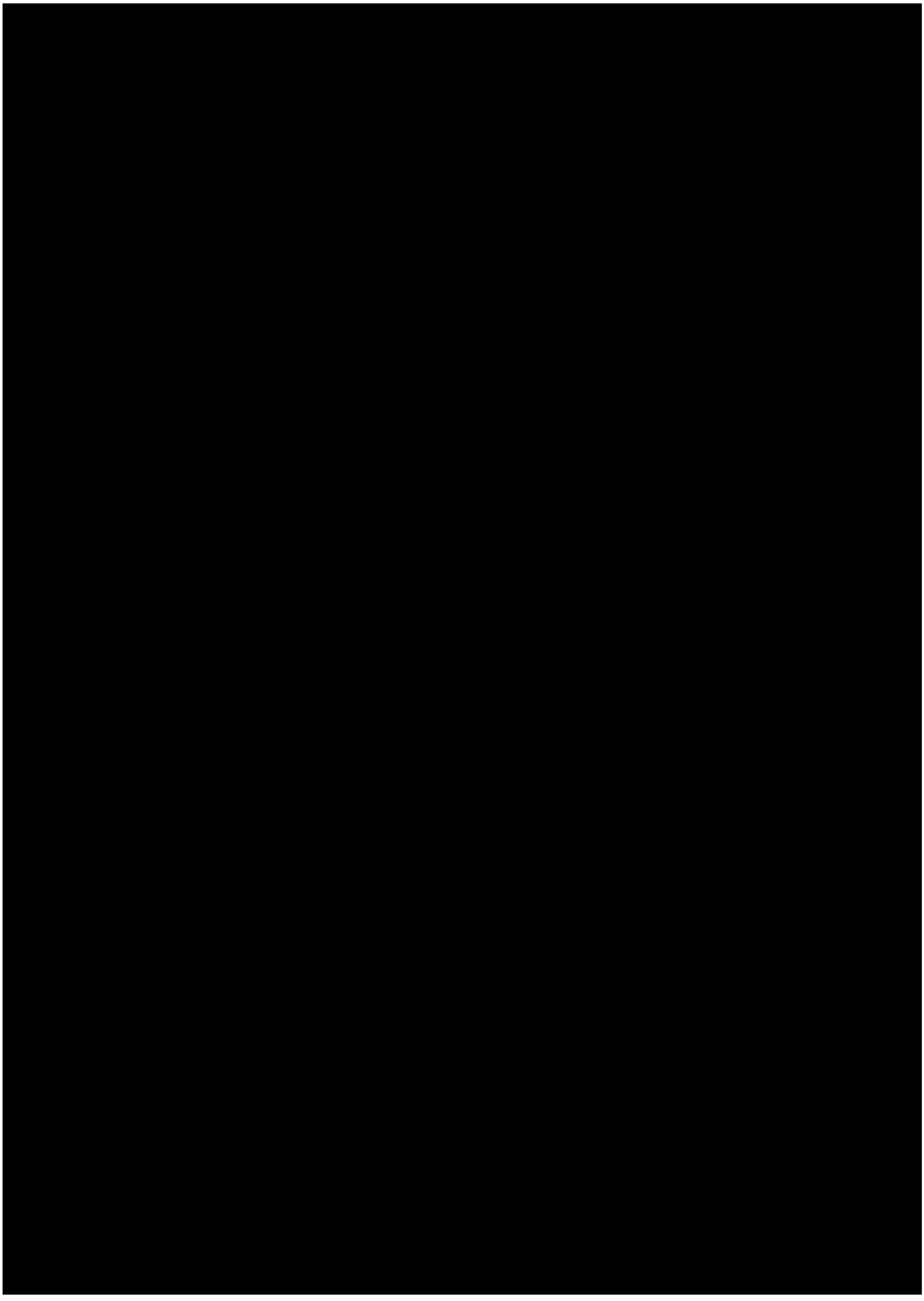
Severity (discomfort during eating/drinking)

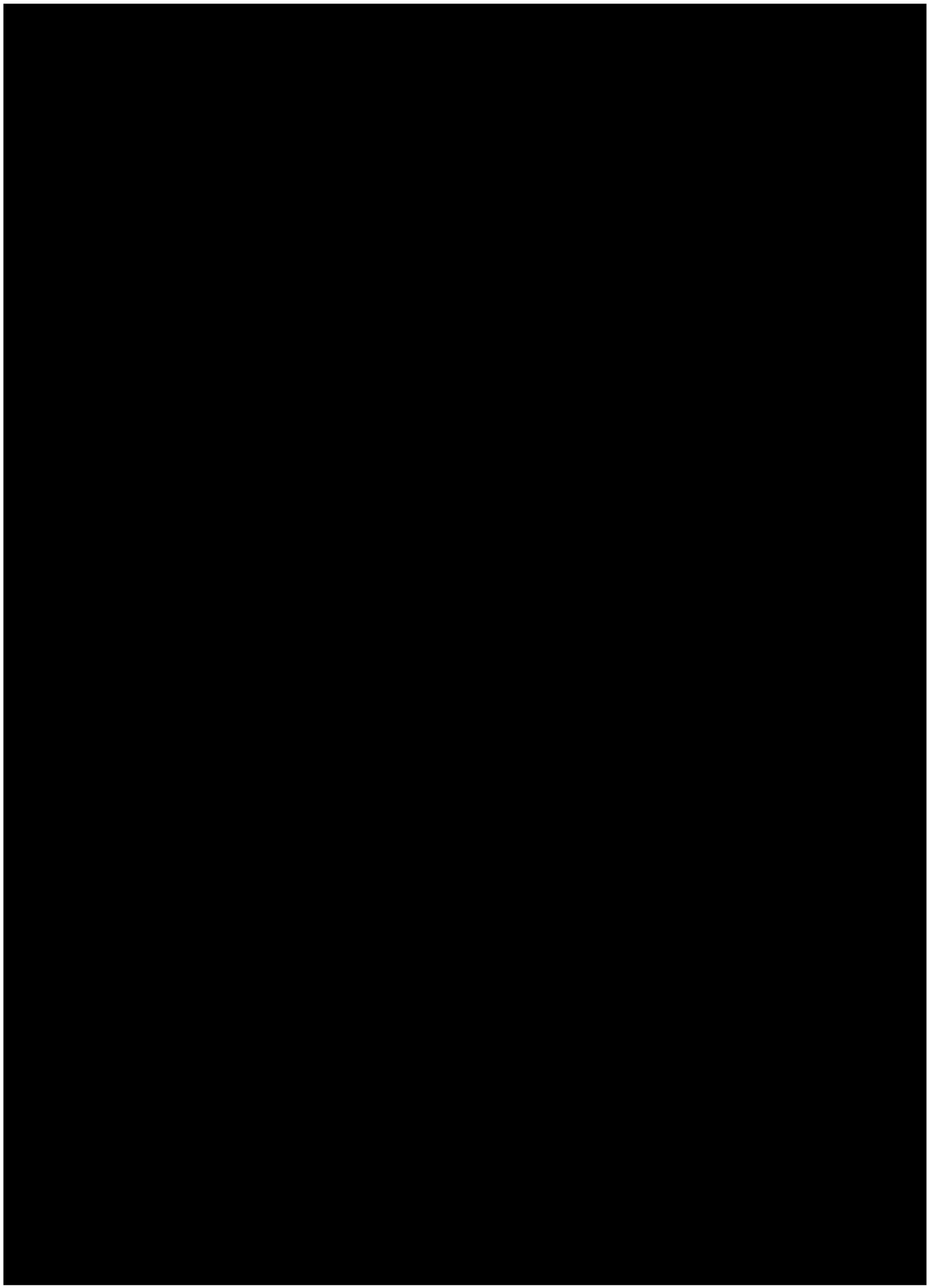
Food	Level	Factor of Discomfort	Severity score
Water	1		
Soup	2		
Yogurt	3		
Custard	4		
Mashed potatoes/ scrambled egg	5		
Baked fish	6		
White bread	7		
Apple/ raw carrot	8		
Fried steak/ whole-grain bread	9		

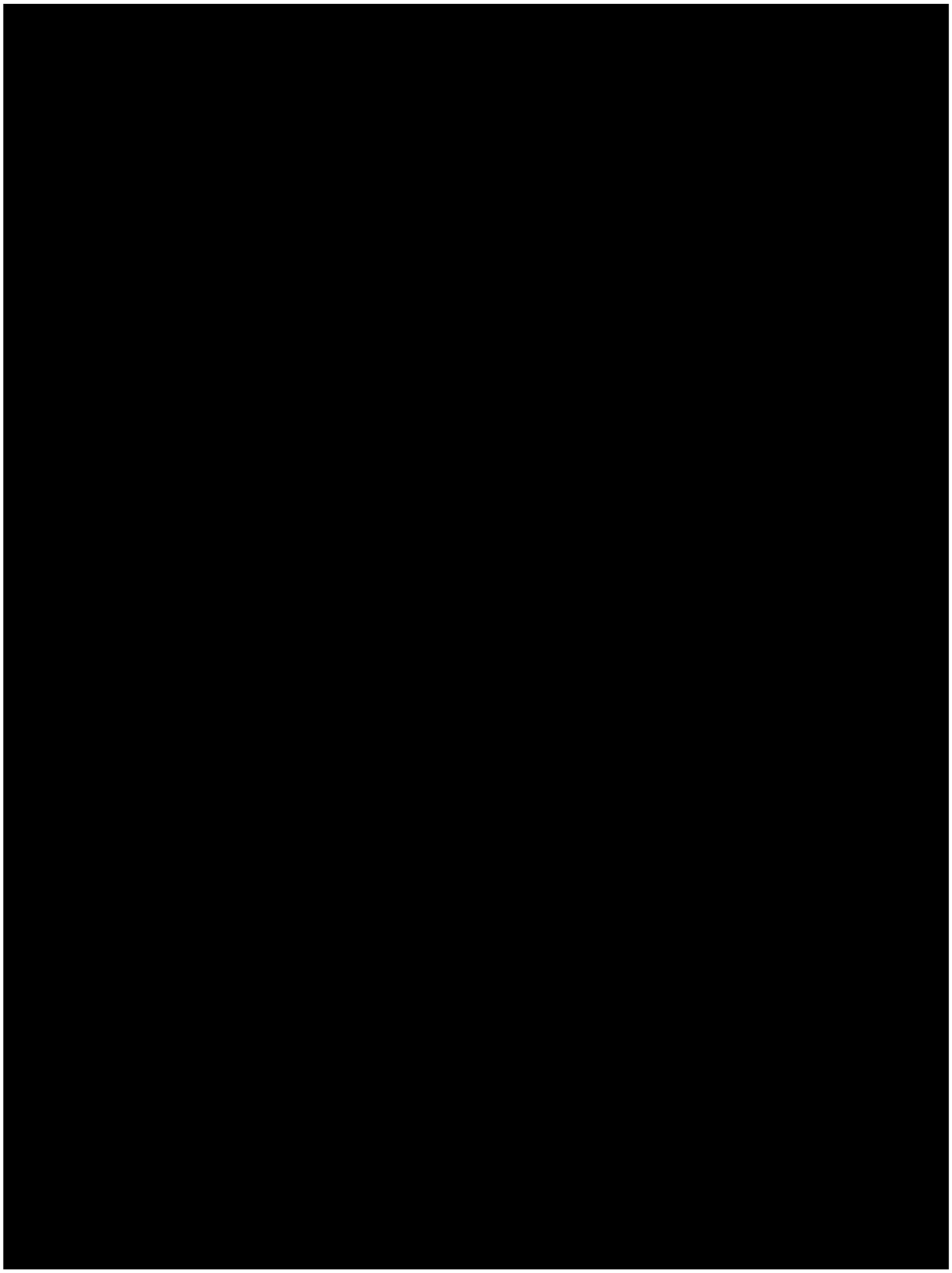
(Severity score= Level multiplied by the factor of discomfort= 0-45 points)

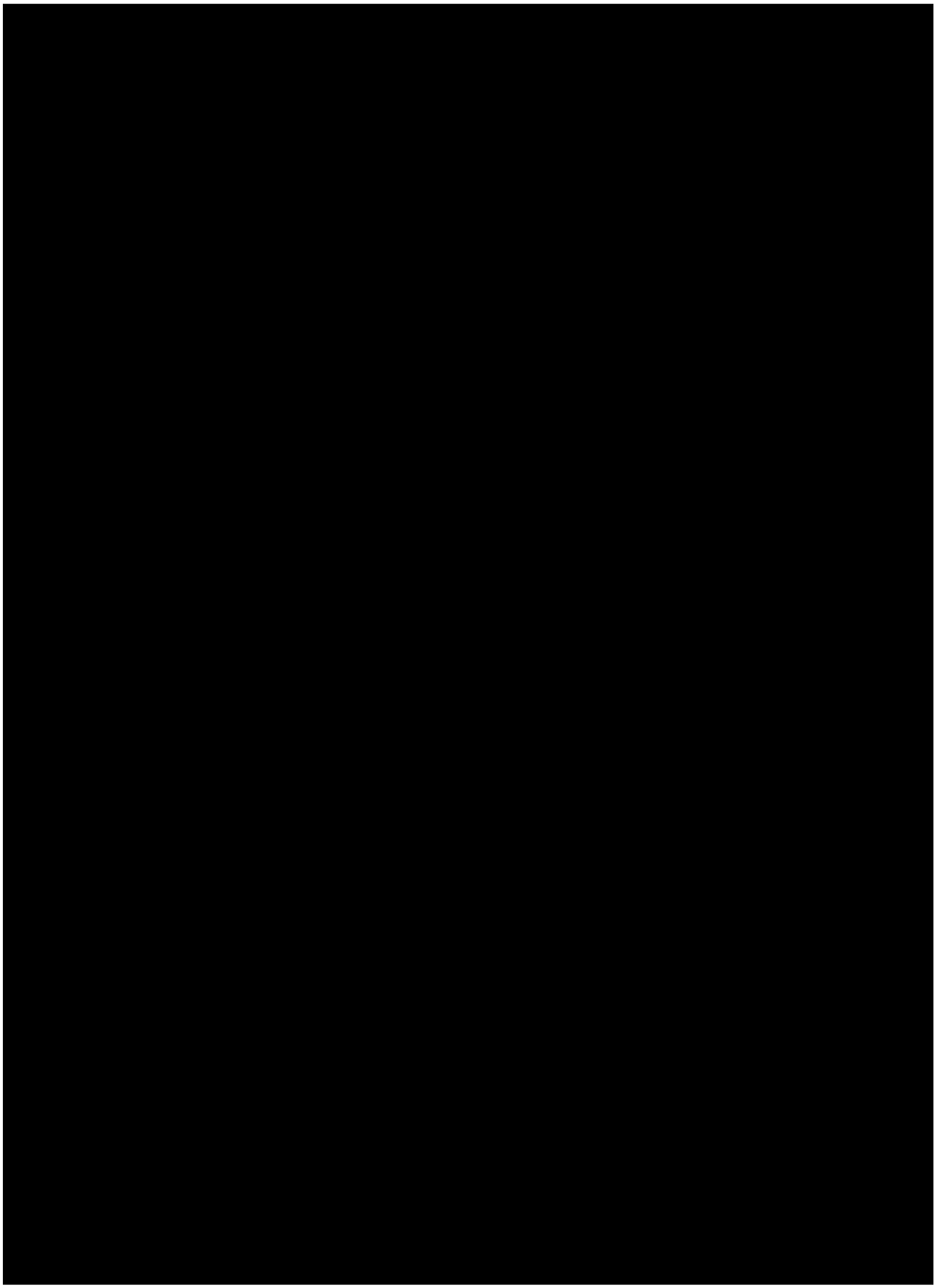
Legend for factor of discomfort	
1	*Pain/bleeding occurred always*
0.5	*Pain/bleeding occurred sometimes*
0	*Never experienced problems*

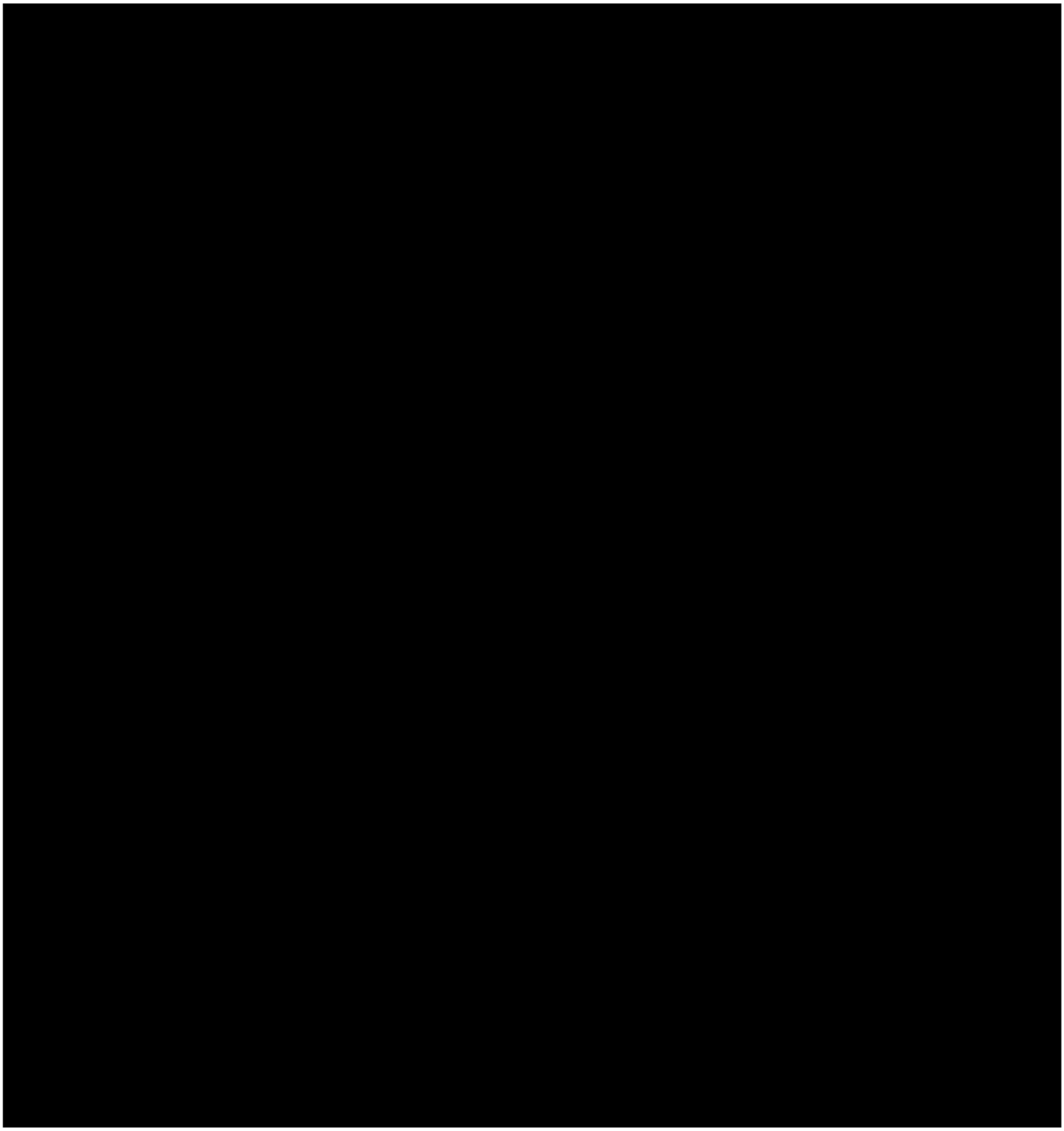


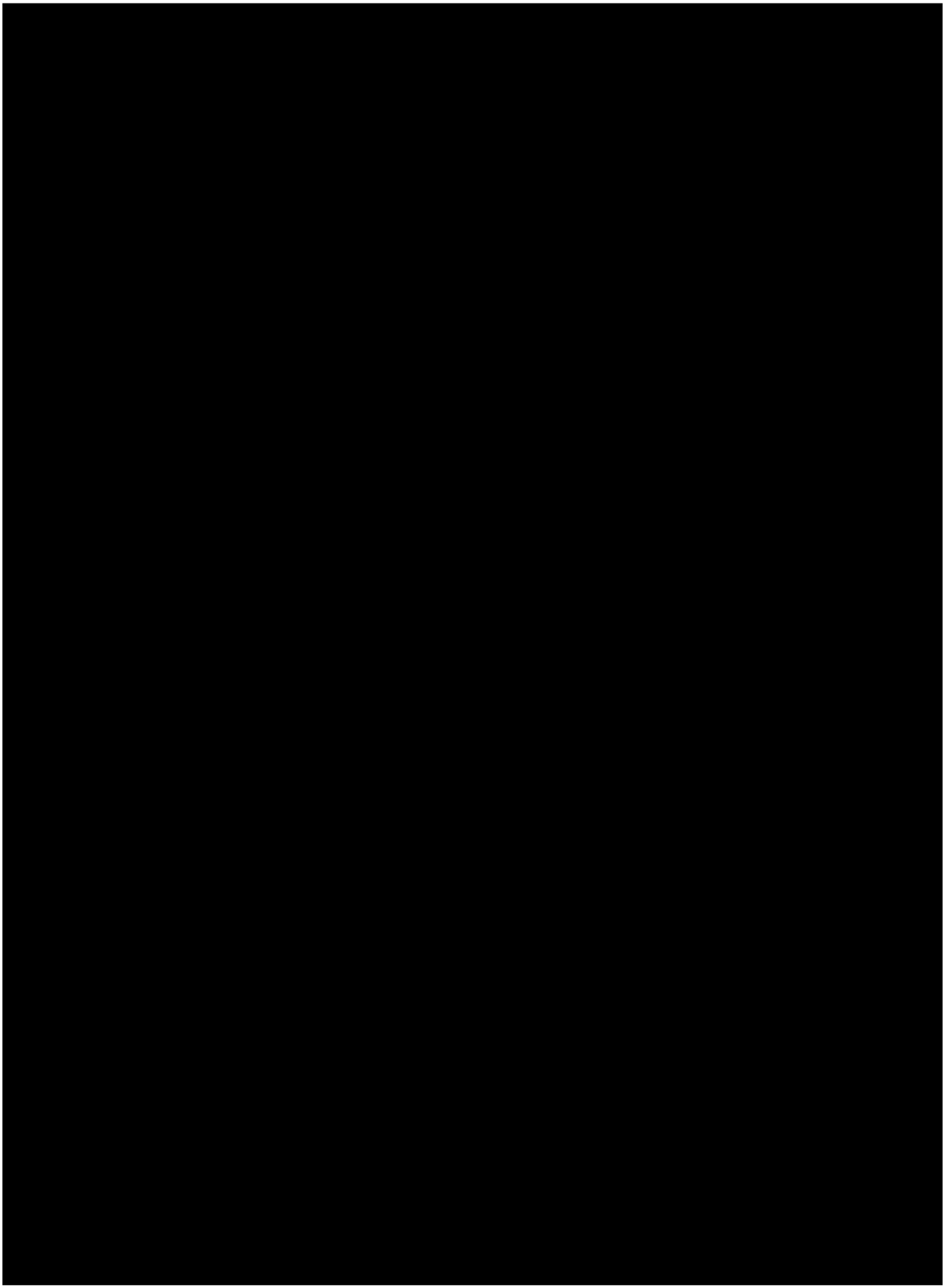


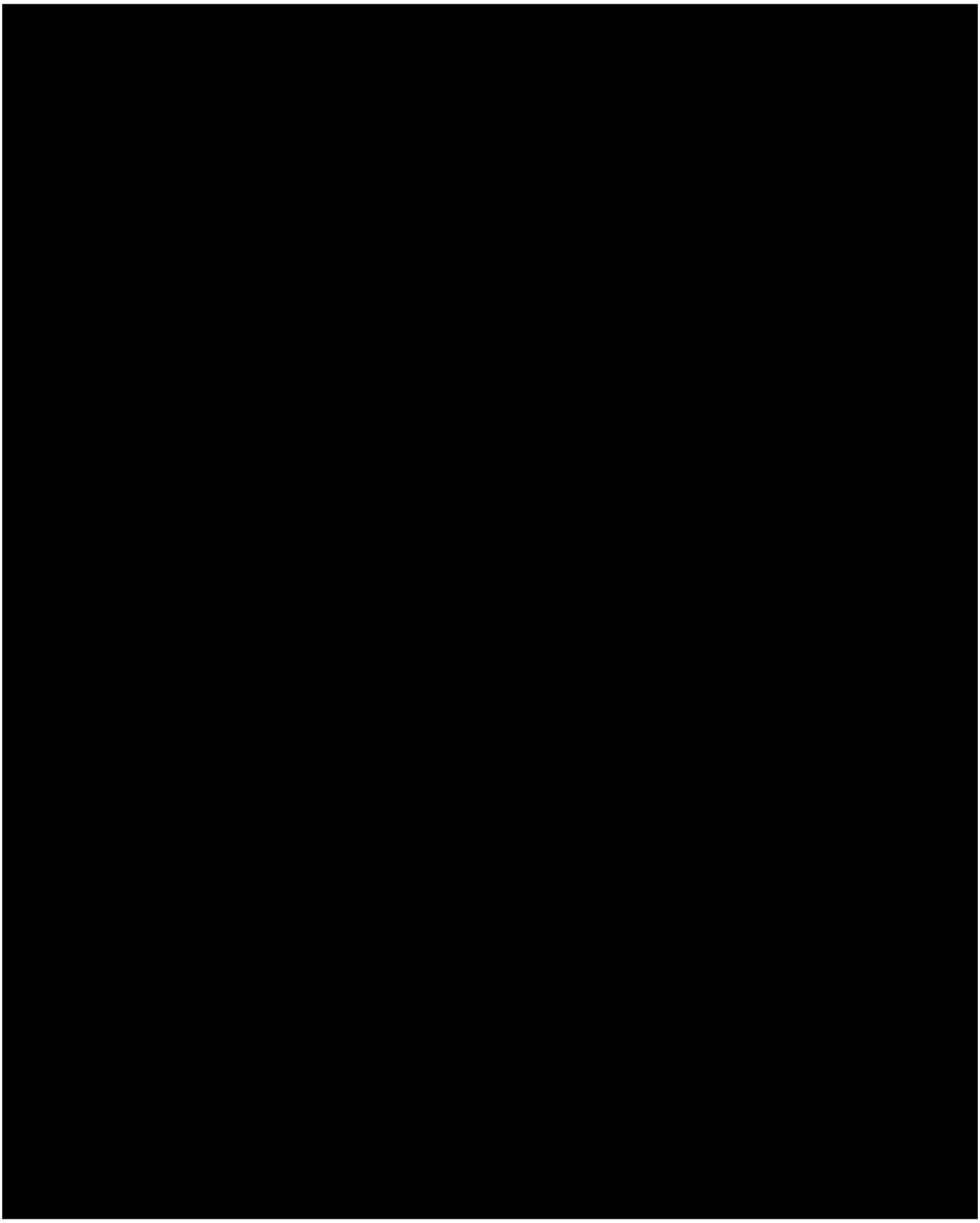


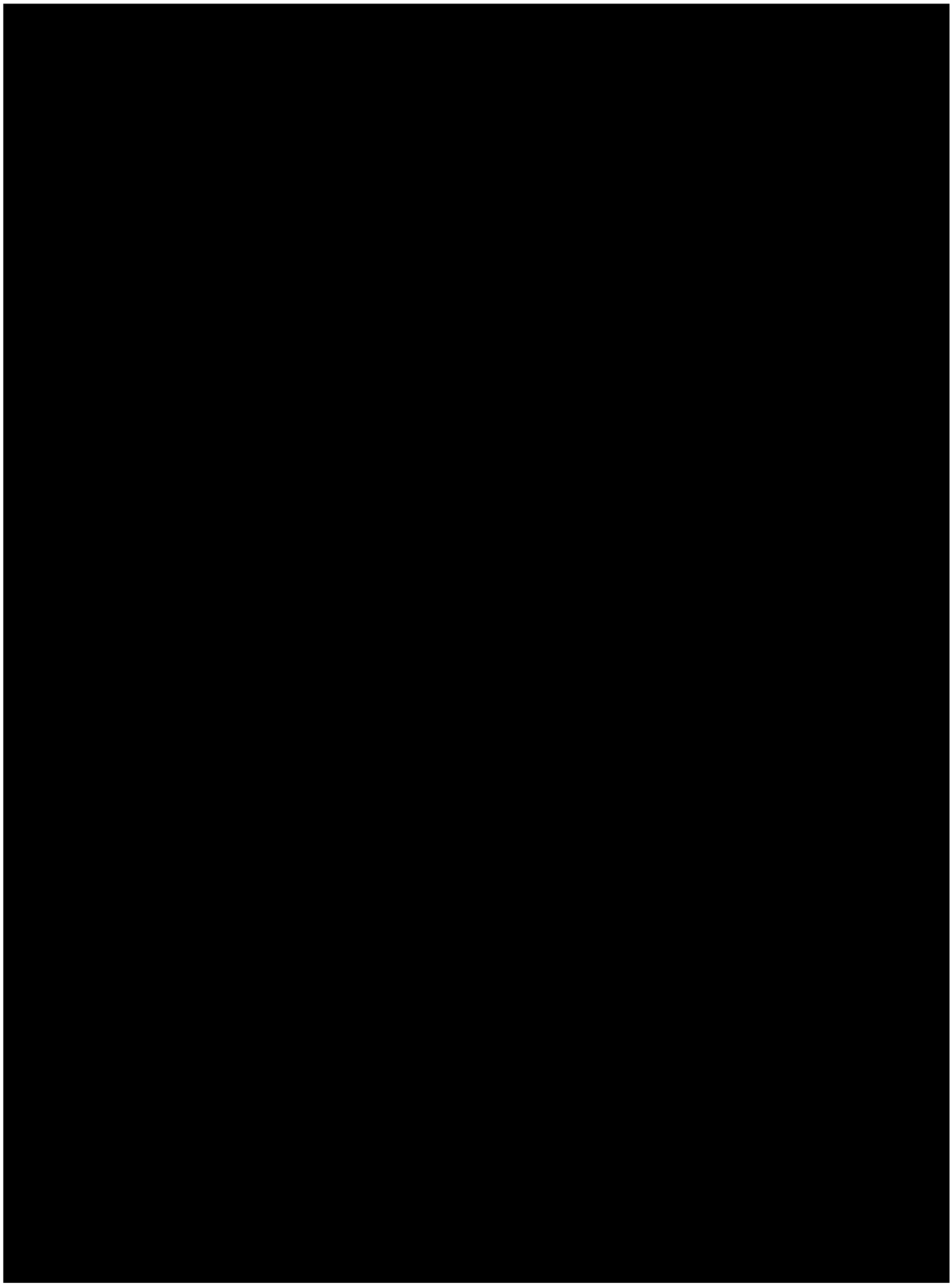












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 [Clinical Trial Version]

11.13. Appendix 13 – Central Laboratory Reference Ranges

Note: refer to the [redacted] Investigator Manual for the current reference ranges.

[redacted]	REFERENCE RANGES
The reference ranges reported are gender and age specific and represent a heterogeneous clinical trials population. Any value that is outside of the established reference range will be indicated on the laboratory report. Protocol specific and Sponsor-defined alerts will be indicated on the laboratory report.	

CHEMISTRY PANEL – CONVENTIONAL UNITS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
PROTEIN, TOTAL	G/DL	6.0-8.5 (13-64y) 5.8-8.1 (65+y)	
ALBUMIN	G/DL	3.2-5.0 (3+y)	
ALT (SGPT)	U/L	0-48 (13+y)	
AST (SGOT)	U/L	0-42 (3-64y) 0-55 (65+y)	
ALKALINE PHOS.	U/L	M : 30-225 (16-19y) ■ F : 30-165 (16-19y) ■ 20-125 (20+y)	
GGT	U/L	M : 0-65 (13-64y) F : 0-45 (13-64y) 0-75 (65+y)	
BILIRUBIN, TOTAL	MG/DL	0.0-1.3 (1+y)	
BILIRUBIN, DIRECT	MG/DL	0.0-0.4 (0+y)	
UREA NITROGEN	MG/DL	7-25 (13-64y) 7-30 (65+y)	
CREATININE, ENZ	MG/DL	M : 0.67-1.26 (18-19y) F : 0.48-1.01 (18-19y) M : 0.80-1.30 (20-29y) F : 0.57-1.03 (20-29y) M : 0.79-1.33 (30-39y) F : 0.58-1.06 (30-39y) M : 0.78-1.34 (40-49y) F : 0.59-1.07 (40-49y) M : 0.76-1.46 (50-59y) F : 0.60-1.10 (50-59y) M : 0.76-1.46 (60-69y) F : 0.60-1.18 (60-69y) M : 0.67-1.54 (>69y) F : 0.63-1.22 (>69y)	
SODIUM	MEQ/L	135-146 (0+y)	<120 or >160
POTASSIUM	MEQ/L	3.5-5.3 (13+y)	< 2.8 or > 6.5
CHLORIDE	MEQ/L	95-108 (0+y)	
y = years			

- In individuals between 12-18 years of age, alkaline phosphatase levels vary according to period of maximum bone growth.

CHEMISTRY PANEL – CONVENTIONAL UNITS (cont'd)

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
CALCIUM	MG/DL	8.5-10.3 (3+y)	< 6.0 or > 13.0
CO2 CONTENT	MEQ/L	20-32 (13+y)	
GLUCOSE	MG/DL	70-115 (13-49y) 70-125 (50+y)	< 40 or > 500
y = years			

LE, L1, L2, L3, LQ, LR, LP

EVENT OCCURRENCE	REPORT FLAG	GUIDANCE COMMENTS ON REPORT AND IN WEB RESULT\VIEW
ALT ≥3X ULN and Bilirubin ≥2X ULN (>35% Direct Bilirubin) **All Phases**	**LE**	**Call subject; stop study drug immediately. Request specialist or hepatologist consult. Follow up clinic and lab evaluation within 24 hours**
ALT ≥3X ULN **Phase I**	**L1**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥5X ULN **Phase II**	**L2**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥8X ULN **Phase III/IV**	**L3**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥3X ULN and <5X ULN and Bilirubin <2X ULN **Phase II**	**LQ**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT and Bilirubin in Quick Trend)**
ALT ≥5X ULN and <8X ULN Bilirubin <2X ULN **Phase III-IV**	**LR**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT and Bilirubin in Quick Trend)**
ALT ≥3X ULN **Phases II-IV**	**LP**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT in Quick Trend)**

CHEMISTRY PANEL – SI UNITS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
PROTEIN, TOTAL	G/L	60-85 (13-64y) 58-81 (65+y)	
ALBUMIN	G/L	32-50 (3+y)	
ALT (SGPT)	U/L	0-48 (13+y)	
AST (SGOT)	U/L	0-42 (3-64y) 0-55 (65+y)	
ALKALINE PHOS.	U/L	M : 30-225 (16-19y) ■ F : 30-165 (16-19y) ■ 20-125 (20+y)	
GGT	U/L	M : 0-65 (13-64y) F : 0-45 (13-64y) 0-75 (65+y)	
BILIRUBIN, TOTAL	UMOL/L	0-22 (1+y)	
BILIRUBIN, DIRECT	UMOL/L	0-6 (0+y)	
UREA NITROGEN	MMOL/L	2.5-9.0 (13-64y) 2.5-10.5 (65+y)	
CREATININE, ENZ	UMOL/L	M : 59.2-111.4 (18-19y) F : 42.4-89.3 (18-19y) M : 70.7-114.9 (20-29y) F : 50.4-91.1 (20-29y) M : 69.8-117.6 (30-39y) F : 51.3-93.7 (30-39y) M : 69.0-118.5 (40-49y) F : 52.2-94.6 (40-49y) M : 67.2-129.1 (50-59y) F : 53.0-97.2 (50-59y) M : 67.2-129.1 (60-69y) F : 53.0-104.3 (60-69y) M : 59.2-136.1 (>69y) F : 55.7-107.8 (>69y)	
SODIUM	MMOL/L	135-146 (0+y)	< 120 or > 160
POTASSIUM	MMOL/L	3.5-5.3 (13+y)	< 2.8 or > 6.5
CHLORIDE	MMOL/L	95-108 (0+y)	
CALCIUM	MMOL/L	2.12-2.56 (3+y)	< 1.50 or > 3.24
CO2 CONTENT	MMOL/L	20-32 (13+y)	
GLUCOSE	MMOL/L	3.9-6.4 (13-49y) 3.9-6.9 (50+y)	< 2.2 or > 27.8
y = years			

- In individuals between 12-18 years of age, alkaline phosphatase levels vary according to period of maximum bone growth.

LE, L1, L2, L3, LQ, LR, LP

EVENT OCCURRENCE	REPORT FLAG	GUIDANCE COMMENTS ON REPORT AND IN WEB RESULT\VIEW
ALT ≥3X ULN and Bilirubin ≥2X ULN (>35% Direct Bilirubin) **All Phases**	**LE**	**Call subject; stop study drug immediately. Request specialist or hepatologist consult. Follow up clinic and lab evaluation within 24 hours**
ALT ≥3X ULN **Phase I**	**L1**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥5X ULN **Phase II**	**L2**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥8X ULN **Phase III/IV**	**L3**	**Stop drug immediately; call subject for prompt clinic evaluation required, as per protocol**
ALT ≥3X ULN and <5X ULN and Bilirubin <2X ULN **Phase II**	**LQ**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT and Bilirubin in Quick Trend)**
ALT ≥5X ULN and <8X ULN Bilirubin <2X ULN **Phase III-IV**	**LR**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT and Bilirubin in Quick Trend)**
ALT ≥3X ULN **Phases II-IV**	**LP**	**Call subject; prompt clinic evaluation required, as per protocol (Review ALT in Quick Trend)**

HEMATOLOGY – CONVENTIONAL UNITS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
PLATELET COUNT	PER CUMM	130,000-400,000 (1+y)	< 31,000 or > 1,499,000
RED CELL COUNT	MILL/MCL	M : 4.4-5.8 (18-64y) M : 3.7-5.5 (65+y) F : 3.9-5.2 (18-64y) F : 3.6-5.1 (65+y)	
HEMOGLOBIN	G/DL	M : 13.8-17.2 (18-64y) M : 11.8-16.8 (65+y) F : 12.0-15.6 (18-64y) F : 11.1-15.5 (65+y)	< 7.1 or > 19.9
HEMATOCRIT	%	M : 41.0-50.0 (18-64y) M : 36.0-49.0 (65+y) F : 35.0-46.0 (18-64y) F : 33.0-46.0 (65+y)	< 20.1 or > 59.9
WHITE CELL COUNT	THOU/MCL	3.8-10.8 (18+y)	< 1.1
TOTAL NEUTROPHILS, ABS.	THOU/MCL	1.80-8.00 (1+y)	
TOTAL NEUTROPHILS	%	40.0-75.0 (18+y)	
NEUTROPHILS, SEGS. ABS.	THOU/MCL	1.80-8.00 (1+y)	
NEUTROPHILS, SEGS.	%	40.0-75.0 (18+y)	
NEUTROPHILS, BANDS, ABS.▪	THOU/MCL	0.00-0.86 (18+y)	
NEUTROPHILS, BANDS▪	%	0.0-8.0 (18+y)	
LYMPHOCYTES, ABS.	THOU/MCL	0.85-4.10 (1+y)	
LYMPHOCYTES	%	16.0-46.0 (18+y)	
MONOCYTES, ABS.	THOU/MCL	0.20-1.10 (1+y)	
MONOCYTES	%	0.0-12.0 (18+y)	
EOSINOPHILS, ABS.	THOU/MCL	0.05-0.55 (0+y)	
EOSINOPHILS	%	0.0-7.0 (18+y)	
BASOPHILS, ABS.	THOU/MCL	0.00-0.20 (1+y)	
BASOPHILS	%	0.0-2.0 (0+y)	
y = years			

▪ Neutrophil, Bands are reported only if seen on a manual differential.

HEMATOLOGY – SI UNITS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
PLATELET COUNT	GI/L	130-400 (1+y)	< 31 or > 1,499
RED CELL COUNT	TI/L	M : 4.4-5.8 (18-64y) M : 3.7-5.5 (65+y) F : 3.9-5.2 (18-64y) F : 3.6-5.1 (65+y)	
HEMOGLOBIN	G/L	M : 138-172 (18-64y) M : 118-168 (65+y) F : 120-156 (18-64y) F : 111-155 (65+y)	< 71 or > 199
HEMATOCRIT	1	M : 0.410-0.500 (18-64y) M : 0.360-0.490 (65+y) F : 0.350-0.460 (18-64y) F : 0.330-0.460 (65+y)	< 0.201 or > 0.599
WHITE CELL COUNT	GI/L	3.8-10.8 (18+y)	< 1.1
TOTAL NEUTROPHILS, ABS.	GI/L	1.80-8.00 (1+y)	
TOTAL NEUTROPHILS	%	40.0-75.0 (18+y)	
NEUTROPHILS, SEGS. ABS.	GI/L	1.80-8.00 (1+y)	
NEUTROPHILS, SEGS.	%	40.0-75.0 (18+y)	
NEUTROPHILS, BANDS, ABS.▪	GI/L	0.00-0.86 (18+y)	
NEUTROPHILS, BANDS▪	%	0.0-8.0 (18+y)	
LYMPHOCYTES, ABS.	GI/L	0.85-4.10 (1+y)	
LYMPHOCYTES	%	16.0-46.0 (18+y)	
MONOCYTES, ABS.	GI/L	0.20-1.10 (1+y)	
MONOCYTES	%	0.0-12.0 (18+y)	
EOSINOPHILS, ABS.	GI/L	0.05-0.55 (0+y)	
EOSINOPHILS	%	0.0-7.0 (18+y)	
BASOPHILS, ABS.	GI/L	0.00-0.20 (1+y)	
BASOPHILS	%	0.0-2.0 (0+y)	
y = years			

▪ Neutrophil, Bands are reported only if seen on a manual differential.

URINALYSIS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
APPEARANCE		CLEAR	
SPECIFIC GRAVITY		1.001-1.035	
URINE REACTION pH		4.6-8.0	
PROTEIN QUAL.		NEGATIVE	
GLUCOSE		NEGATIVE	
KETONE		NEGATIVE	
LEUKOCYTES		NEGATIVE	
OCCULT BLOOD		NEGATIVE	
MICROSCOPIC:			
RBC	PER HPF	M: 0-3 F: 0-3	
WBC	PER HPF	M: 0-5 F: 0-10	
OTHER FINDINGS WILL BE REPORTED ONLY IF OBSERVED UNDER MICROSCOPIC EXAMINATION			

OTHER TESTS – CONVENTIONAL UNITS

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
CREATININE CLEARANCE, ESTIMATED (using serum creatinine only)	ML/MIN	REFERENCE RANGE NOT ESTABLISHED	
MICROALBUMIN/ CREATININE RATIO	MG/G CREAT.	< 30	
HEPATITIS Bs Ag		NON REACTIVE OR NEGATIVE	
HEPATITIS BsAb		NON-REACTIVE	
HEPATITIS B CORE Ab TOTAL		NON REACTIVE OR NEGATIVE	
HEPATITIS B DNA PCR QUANTITATIVE:			
HBV DNA PCR	IU/ML	< 20	
HBV DNA LOG	LOG IU/ML	< 1.30	
HBV DNA PCR COPIES	COPIES/ML	< 116	
HEPATITIS C ANTIBODY		NON REACTIVE	
PREGNANCY TEST SERUM		Males and Non-Pregnant Females = NEGATIVE Pregnant = POSITIVE	
FSH	MIU/ML	F : Follicular Phase: 2.5-10.2 F : Midcycle Peak: 3.1-17.7 F : Luteal Phase: 1.5-9.1 F : Postmenopausal: 23.0-116.3	
ESTRADIOL, LC/MS/MS	PG/ML	ADULT FEMALE (18+y): Follicular Stage: 39-375 Mid Cycle Stage: 94-762 Luteal Stage: 48-440 Postmenopausal: ≤ 10	
y = years			

OTHER TESTS – CONVENTIONAL UNITS (cont'd)

ANALYTE	UNITS	REFERENCE RANGES	**PHONE ALERT RANGE
C-REACTIVE PROTEIN (CRP) HIGHLY SENSITIVE	MG/L	< 3.1 (18+y)	
SERUM BANKING FOR JCV		NOT DETECTED	
IMMUNO-GLOBULIN G (IgG)	MG/DL	694-1,618 (16+y)	
IMMUNO-GLOBULIN M (IgM)	MG/DL	48-271 (16+y)	
IMMUNO-GLOBULIN A (IgA)	MG/DL	81-463 (16+y)	
B-LYMPH STIMULATOR	PG/ML	REFERENCE RANGE NOT ESTABLISHED	
B-LYMPH CHEMOKINE	PG/ML	REFERENCE RANGE NOT ESTABLISHED	
DESMOGLEIN ANTIBODIES (1 AND 3)		REFERENCE RANGE NOT ESTABLISHED	
TETANUS ANTITOX AB	IU/ML	> OR = 0.50	
PNEUMOCOCCAL AB ASSAY		REFERENCE RANGE NOT ESTABLISHED	
TBNK (CD4/CD8/CD19-B CELL COUNT)	PER CMM	REFERENCE RANGE NOT ESTABLISHED	
B CELL PANEL		REFERENCE RANGE NOT ESTABLISHED	
y = years			

FLOW CYTOMETRY – CONVENTIONAL UNITS

ANALYTE	UNITS	REFERENCE RANGES
FLOW CYTOMETRY – T & B CELLS:		
%CD3 (Mature T Cells)	%	61-82 (13-18y) 57-85 (19+y)
Absolute CD3+	PER CMM	860-2420(13-18y) 840-3060(19+y)
%CD8 (Suppressor T Cells)	%	17-36(13-18y) 12-42 (19+y)
Absolute CD8	PER CMM	240-890(13-18y) 180-1170(19+y)
%CD4 (Helper Cells)	%	33-53(13-18y) 30-61(19+y)
Absolute CD4+	PER CMM	510-145(13-18y) 490-1740(19+y)
%CD19 (B Cells)	%	9-30(13-18y), 6-6-29(19+y)
Absolute CD19+	PER CMM	130-800(13-18y) 110-660(19+y)
Absolute Lymphocyte (CD45+)	PER CMM	850-4100
%CD4 (Helper Cells) / %CD8 (Suppressor T Cells)	NONE	1.0-2.9(13-18y) 0.86-5.0(19+y)
FLOW CYTOMETRY – B-CELL PANEL:		
CD19+ CD27+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+ Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10+ Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10- %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10- Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+bright CD10+%	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+bright CD10+ Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD+ Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD- %	% CD19c	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD- Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD- %	% CD19	REFERENCE RANGE NOT

FLOW CYTOMETRY – CONVENTIONAL UNITS

ANALYTE	UNITS	REFERENCE RANGES
		ESTABLISHED
CD19+ CD27+IgD- Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+bright CD38+bright %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+bright CD38+bright Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD69+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD69+ Absolutes	PER CUMM	REFERENCE RANGE NOT ESTABLISHED
y = years		

OTHER TESTS – SI UNITS

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
CREATININE CLEARANCE, ESTIMATED (using serum creatinine only)	ML/MIN	REFERENCE RANGE NOT ESTABLISHED	
MICROALBUMIN/ CREATININE RATIO	MG/MMOL CREAT.	< 3.4	
HEPATITIS BsAg		NON REACTIVE OR NEGATIVE	
HEPATITIS BsAb		NON-REACTIVE	
HEPATITIS B CORE Ab TOTAL		NON REACTIVE OR NEGATIVE	
HEPATITIS B DNA PCR QUANTITATIVE:			
HBV DNA PCR	IU/ML	< 20	
HBV DNA LOG	LOG IU/ML	< 1.30	
HBV DNA PCR COPIES	COPIES/ML	< 116	
HEPATITIS C ANTIBODY		NON REACTIVE	
PREGNANCY TEST SERUM		Males and Non-Pregnant Females = NEGATIVE Pregnant = POSITIVE	
FSH	IU/L	F : Follicular Phase: 2.5-10.2 F : Midcycle Peak: 3.1-17.1 F : Luteal Phase: 1.5-9.1 F : Postmenopausal: 23.0-116.3	
ESTRADIOL, LC/MS/MS	PMOL/L	ADULT FEMALE (18+y): Follicular Stage: 143-1377 Mid Cycle Stage: 345-2797 Luteal Stage: 176-1615 Postmenopausal: ≤ 37	
y = years			

OTHER TESTS – SI UNITS

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
SERUM BANKING FOR JCV		NOT DETECTED	
IMMUNO-GLOBULIN G (IgG)	G/L	6.94-16.18 (16+y)	
IMMUNO-GLOBULIN M (IgM)	G/L	0.48-2.71 (16+y)	
IMMUNO-GLOBULIN A (IgA)	G/L	0.81-4.63 (16+y)	
B-LYMPH STIMULATOR	NG/L	REFERENCE RANGE NOT ESTABLISHED	
B-LYMPH CHEMOKINE	NG/L	REFERENCE RANGE NOT ESTABLISHED	
DESMOGLEIN ANTIBODIES (1 AND 3)		REFERENCE RANGE NOT ESTABLISHED	
TETANUS ANTITOX AB	IU/ML	> OR = 0.50	
PNEUMOCOCCAL AB ASSAY		REFERENCE RANGE NOT ESTABLISHED	
C-REACTIVE PROTEIN (CRP) HIGHLY SENSITIVE	MG/L	< 3.1 (18+y)	
TBNK (CD4/CD8/CD19-B CELL COUNT)	PER CMM	REFERENCE RANGE NOT ESTABLISHED	
B CELL PANEL		REFERENCE RANGE NOT ESTABLISHED	
y = years			

FLOW CYTOMETRY – SI UNITS

ANALYTE	UNITS	REFERENCE RANGES
FLOW CYTOMETRY – T & B CELLS:		
%CD3 (Mature T Cells)	%	61-82 (13-18y) 57-85 (19+y)
Absolute CD3+	GI/L	0.860-2.42(13-18y) 0.840-3.060(19+y)
%CD8 (Suppressor T Cells)	%	17-36(13-18y) 12-42 (19+y)
Absolute CD8	GI/L	0.240-0.890(13-18y) 0.180-1.170(19+y)
%CD4 (Helper Cells)	%	33-53(13-18y) 30-61(19+y)
Absolute CD4+	GI/L	0.510-1.450(13-18y) 0.490-1.740(19+y)
%CD19 (B Cells)	%	9-30(13-18y) 6-29(19+y)
Absolute CD19+	GI/L	0.130-0.800(13-18y) 0.110-0.660(19+y)
Absolute Lymphocyte (CD45+)	GI/L	0.850-4.100
%CD4 (Helper Cells) / %CD8 (Suppressor T Cells)	NONE	1.0-2.9(13-18y) 0.86-5.0(19+y)
FLOW CYTOMETRY – B-CELL PANEL:		
CD19+ CD27+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+ Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10+ Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10- %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+ CD10- Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+bright CD10+%	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD+ CD38+bright CD10+ Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD+ Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD- %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27-IgD- Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD- %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+IgD- Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+bright CD38+bright %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD27+bright CD38+bright Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD69+ %	% CD19	REFERENCE RANGE NOT ESTABLISHED
CD19+ CD69+ Absolutes	GI/L	REFERENCE RANGE NOT ESTABLISHED
y = years		

CHEMISTRY PANEL – LIVER EVENT ASSESSMENT – CONVENTIONAL

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
ALT (SGPT)	U/L	0-48 (13+y)	
AST (SGOT)	U/L	0-42 (3-64y) 0-55 (65+y)	
ALKALINE PHOS.	U/L	M: 30-225 (16-19y) F: 30-165 (16-19y) 20-125 (20+y)	
BILIRUBIN, TOTAL	MG/DL	0.0-1.3 (1+y)	
BILIRUBIN, DIRECT♦	MG/DL	0.0-0.4 (0+y)	
CPK, TOTAL	U/L	M : 0-235 (0+y) F : 0-190 (0+y)	
LACTATE DEHYDROGENASE	U/L	0-250 (3-64y) 0-270 (65+y)	
y = years			

♦ If Total Bilirubin is > 2.5 mg/dl, Direct Bilirubin will be reported.

CHEMISTRY PANEL – LIVER EVENT ASSESSMENT – SI

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
ALT (SGPT)	U/L	0-48 (13+y)	
AST (SGOT)	U/L	0-42 (3-64y) 0-55 (65+y)	
ALKALINE PHOS.	U/L	M: 30-225 (16-19y) F: 30-165 (16-19y) 20-125 (20+y)	
BILIRUBIN, TOTAL	UMOL/L	0-22 (1+y)	
BILIRUBIN, DIRECT♦	UMOL/L	0-6 (0+y)	
CPK, TOTAL	U/L	M : 0-235 (0+y) F : 0-190 (0+y)	
LACTATE DEHYDROGENASE	U/L	0-250 (3-64y) 0-270 (65+y)	
y = years			

♦ If Total Bilirubin is > 43 umol/l, Direct Bilirubin will be reported.

HEMATOLOGY – LIVER EVENT ASSESSMENT – CONVENTIONAL

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
PLATELET COUNT	PER CUMM	130,000-400,000 (1+y)	< 31,000 or > 1,499,000
RED CELL COUNT	MILL/MCL	M : 4.4-5.8 (18-64y) M : 3.7-5.5 (65+y) F : 3.9-5.2 (18-64y) F : 3.6-5.1 (65+y)	
HEMOGLOBIN	G/DL	M : 13.8-17.2 (18-64y) M : 11.8-16.8 (65+y) F : 12.0-15.6 (18-64y) F : 11.1-15.5 (65+y)	< 7.1 or > 19.9
HEMATOCRIT	%	M : 41.0-50.0 (18-64y) M : 36.0-49.0 (65+y) F : 35.0-46.0 (18-64y) F : 33.0-46.0 (65+y)	< 20.1 or > 59.9
WHITE CELL COUNT	THOU/MCL	3.8-10.8 (18+y)	< 1.1
TOTAL NEUTROPHILS, ABS.	THOU/MCL	1.80-8.00 (1+y)	
TOTAL NEUTROPHILS	%	40.0-75.0 (18+y)	
NEUTROPHILS, SEGS. ABS.	THOU/MCL	1.80-8.00 (1+y)	
NEUTROPHILS, SEGS.	%	40.0-75.0 (18+y)	
NEUTROPHILS, BANDS, ABS.▪	THOU/MCL	0.00-0.86 (18+y)	
NEUTROPHILS, BANDS▪	%	0.0-8.0 (18+y)	
LYMPHOCYTES, ABS.	THOU/MCL	0.85-4.10 (1+y)	
LYMPHOCYTES	%	16.0-46.0 (18+y)	
MONOCYTES, ABS.	THOU/MCL	0.20-1.10 (1+y)	
MONOCYTES	%	0.0-12.0 (18+y)	
EOSINOPHILS, ABS.	THOU/MCL	0.05-0.55 (0+y)	
EOSINOPHILS	%	0.0-7.0 (18+y)	
BASOPHILS, ABS.	THOU/MCL	0.00-0.20 (1+y)	
BASOPHILS	%	0.0-2.0 (0+y)	
y = years			

▪ Neutrophil, Bands are reported only if seen on a manual differential.

HEMATOLOGY – LIVER EVENT ASSESSMENT – SI

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
PLATELET COUNT	GI/L	130-400 (1+y)	< 31 or > 1,499
RED CELL COUNT	TI/L	M : 4.4-5.8 (18-64y) M : 3.7-5.5 (65+y) F : 3.9-5.2 (18-64y) F : 3.6-5.1 (65+y)	
HEMOGLOBIN	G/L	M : 138-172 (18-64y) M : 118-168 (65+y) F : 120-156 (18-64y) F : 111-155 (65+y)	< 71 or > 199
HEMATOCRIT	1	M : 0.410-0.500 (18-64y) M : 0.360-0.490 (65+y) F : 0.350-0.460 (18-64y) F : 0.330-0.460 (65+y)	< 0.201 or > 0.599
WHITE CELL COUNT	GI/L	3.8-10.8 (18+y)	< 1.1
TOTAL NEUTROPHILS, ABS.	GI/L	1.80-8.00 (1+y)	
TOTAL NEUTROPHILS	%	40.0-75.0 (18+y)	
NEUTROPHILS, SEGS. ABS.	GI/L	1.80-8.00 (1+y)	
NEUTROPHILS, SEGS.	%	40.0-75.0 (18+y)	
NEUTROPHILS, BANDS, ABS.▪	GI/L	0.00-0.86 (18+y)	
NEUTROPHILS, BANDS▪	%	0.0-8.0 (18+y)	
LYMPHOCYTES, ABS.	GI/L	0.85-4.10 (1+y)	
LYMPHOCYTES	%	16.0-46.0 (18+y)	
MONOCYTES, ABS.	GI/L	0.20-1.10 (1+y)	
MONOCYTES	%	0.0-12.0 (18+y)	
EOSINOPHILS, ABS.	GI/L	0.05-0.55 (0+y)	
EOSINOPHILS	%	0.0-7.0 (18+y)	
BASOPHILS, ABS.	GI/L	0.00-0.20 (1+y)	
BASOPHILS	%	0.0-2.0 (0+y)	
y = years			

▪ Neutrophil, Bands are reported only if seen on a manual differential.

LIVER EVENT ASSESSMENT

ANALYTE	UNITS	REFERENCE RANGES	** PHONE ALERT RANGE
HEPATITIS Bs Ag		NON REACTIVE	
HEPATITIS B CORE Ab IgM		NON REACTIVE	
HEPATITIS A IgM		NON REACTIVE	
CMV IgM Ab	INDEX	< 0.9	
EBV IgM Ab	 ISR	NEGATIVE ≤ 0.90 (Strength of Signal)	
HEPATITIS C VIRUS RNA	IU/ML LOG IU/ML	< 43 < 1.63	
HEPATITIS E IgM		NOT DETECTED	
ANA SCREEN W/ REFLEX TO TITER AND PATTERN	TITER	NEGATIVE (Screen) < 40 (IFA Titer)	
ACTIN	UNITS	< 20	
TYPE 1 ANTI-LIVER KIDNEY MICROSOMAL Ab	UNITS	≤ 20	
TOTAL IgG:	MG/DL (Conv. Unit)	694-1618 (16-99y)	
	G/L (SI Unit)	6.94-16.18 (16-99y)	
ACETAMINOPHEN ADDUCT ASSAY	NMOL/ML	REFERENCE RANGE NOT ESTABLISHED	
HEPATITIS B DNA PCR QUANTITATIVE:			
HBV DNA PCR	IU/ML	< 20	
HBV DNA LOG	LOG IU/ML	< 1.30	
HBV DNA PCR COPIES	COPIES/ML	< 116	
HEPATITIS D Ab		NEGATIVE	
y = years			

11.14. Appendix 14 – Phone Visit Questionnaire

Phone visits will be conducted at Week 10, Week 14, Week 18, and Week 22. During each of these phone visits, the following questions should be discussed:

Ask open-ended and nonleading questions to inquire about the occurrence of AEs. Appropriate questions include the following:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

Ask about changes to concomitant medications and the subject's current steroid dose and progress with the steroid taper.

- Have you changed the dosage of any of your other medicines?
- What dose of prednisone/prednisolone are you currently taking?
- When did you last change your dose of prednisone/prednisolone?
- What was the reason for your last change in dose of prednisone/prednisolone (eg, decreased according to scheduled taper or increased because of disease flare)?

Ask questions from the neurological symptoms questionnaire (see Appendix 5).

Give subjects the opportunity to ask any additional questions and to discuss any potential concerns.

11.15. Appendix 15 – Protocol Changes

Protocol Amendment 1: 21 June 2013

Applicable to all countries and study centers.

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number and revision chronology	NA
Sponsor information	Glaxo Group Limited d/b/a GlaxoSmithKline ~~Glaxo Wellcome House Berkeley Avenue, Greenford~~, Middlesex, ~~UB6 0NN~~, UK	Glaxo Group Limited, **England** d/b/a GlaxoSmithKline **980 Great West Road Brentford**, Middlesex, **TW8 9GS**, UK	Change of Sponsor's legal registered address
Protocol-specific definitions	Absence of new or nonhealing (established) lesions for ≥8 weeks	Absence of new or nonhealing (established) lesions for ≥8 weeks **(Note: Subjects with existing, healing lesions may be considered in remission if other criteria are met.)**	Clarification
Protocol summary; Section 3.1	Subjects will visit the clinic during Screening, at Baseline (Week 0), at Weeks 2 and 4, and every 4 weeks from ~~Week 4~~ through Week 60. Subjects will also have structured phone visits between each of the clinic visits from ~~Week 6~~ through Week 22.	Subjects will visit the clinic during Screening; at Baseline (Week 0); at Weeks 2, 4, **6, and 8**; and then every 4 weeks from **Week 8** through Week 60. Subjects will also have structured phone visits between each of the clinic visits from **Week 10** through Week 22.	Updated to reflect change from a phone visit to a clinic visit at Week 6.
Figure 3-1; Table 6-1	Week 6 = ~~Phone~~ visit	Week 6 = **Clinic** visit	Additional clinic visit to monitor progress with steroid taper.
Protocol summary; Section 3.1	…eligible subjects will be centrally randomized…	…eligible subjects will be centrally randomized **1:1 across 2 strata (disease duration [≤1 year, >1 year] and baseline prednisone dose [<60 mg, ≥60 mg])**…	Additional description of randomization in study design section for clarity
Protocol summary; Section 3.1 & Section 3.1.3; Table 6-1	NA	Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.	Clarification that all subjects, including early withdrawals from treatment, should be transitioned to the Individualized Follow-up Period.

Section	Original Text	Changes	Rationale
Table 3-2	NA	a. … For subjects at a starting dose >160 mg, taper dose by 20 mg every 2 weeks until the dose is 160 mg, at which point the decrements shown on the table above should be used.	Added guidance for initiation of steroid taper for subjects at starting doses >160 mg
Section 4.2	2. History of biopsy consistent with PV…	2. History of biopsy consistent with PV... **If no history, a biopsy may be performed during the Screening Period.**	There is a chance that not all potential subjects will have had a biopsy prior to screening.
Section 4.3	4. Prior treatment with… ~~Systemic antibiotic pemphigus treatments (eg, minocycline or doxycycline)~~	4. Prior treatment with… **methotrexate**	The effect of antibiotics for treating pemphigus lesions is minimal, but subjects may require treatment for infection during the study. Added exclusion for methotrexate as it is used by some physicians for the treatment of pemphigus.
Section 5.6.2	Any other systemic treatment for PV (including rituximab, mycophenolate, azathioprine, dapsone, ~~systemic antibiotic treatments such as minocycline, doxycycline)~~ even if not specifically being prescribed for PV.	Any other systemic treatment for PV (including rituximab, mycophenolate, azathioprine, dapsone, and **methotrexate**) even if not prescribed specifically for PV.	
Section 4.3	6. Evidence or history of clinically significant infection including: ~~Prior treatment with any lymphocyte-depleting therapies, including, but not limited to cladribine, anti-CD4, total body irradiation, or bone marrow transplantation.~~	4. Prior treatment with … **total body irradiation, bone marrow transplantation, cladribine**	More accurately represented under heading of treatment restrictions than clinically significant infections.
Section 4.3	6. For HBsAg negative, but HB~~s~~Ab positive (regardless of HBsAb status)…	6. For HBsAg negative, but HB**c**Ab positive (regardless of HBsAb status)…	Correction
Section 4.3	9. Platelets ~~<1.3 x 105 GI/L~~	9. Platelets **<130 GI/L (<130,000/mm^3)**	Correction
Section 4.3; Table 6-1	11. ~~Plans to change smoking status during the course of the study.~~	Collect smoking status at Screening, Baseline, Week 24, Week 60, and early withdrawal	Considered more relevant to collect information on smoking status rather than exclude subjects who may be planning a change

Section	Original Text	Changes	Rationale
Section 4.3	NA	11. Electrocardiogram (ECG) showing a clinically significant abnormality or showing a QTc interval ≥450 msec (≥480 msec for subjects with a bundle branch block) (ECG to be obtained during Screening/prior to receiving the first dose of study drug).	Exclusion of subjects with a potential risk factor for adverse cardiac outcomes.
Table 6-1; Section 6.3.10.2	ECG at ~~Baseline~~	ECG at **Screening**	To allow time to obtain the ECG and results before the first dose of investigational product.
Section 4.4.1	Neutropenia Grade 3 (<1000~~-500~~/mm^3; <1.0~~-0.5~~ x10^9/L) ~~or Grade 4 (<500/mm^3; <0.5 x 10^9/L)~~	Neutropenia **with an absolute neutrophil count <1 GI/L** (<1000/mm^3; <1.0 x10^9/L) **(ie, CTCAE Grade 3 and higher)**	Clarification of dose-holding threshold value
Section 4.4.2	Any subject who discontinues treatment should enter the Follow-up Period…	Any subject who discontinues treatment **prior to study completion** should enter the **Individualized** Follow-up Period…	Clarification
Section 5.1.1	Trained site personnel will administer investigational product at Weeks 0, 12, 24, 36, and 48…	Trained site personnel will administer **0.6 mL of** investigational product at Weeks 0, 12, 24, 36, and 48…	Clarification that each dose will be 0.6 mL (inclusive of doses from vials and from prefilled syringes)
Section 5.1.2	… premedication with acetaminophen/paracetamol and an antihistamine, as described in Table 5-1.	… premedication with acetaminophen/paracetamol and an antihistamine (see Table 5-1), **which will be administered at the clinic.**	Clarification that all premedication will be administered at the study center.
Section 5.3	After the Week 60 visit and ~~all~~ Individualized Follow-up visit~~s~~…	After the Week 60 visit and **each** Individualized Follow-up visit…	Clarification that notification will be after each visit not after all follow-up visits have been completed.
Table 6-1	NA	Added IgG, IgM, IgA at Screening	Immunoglobulin levels are part of the exclusion criteria, but were not specified as part of screening laboratory tests.

Section	Original Text	Changes	Rationale
Table 6-1	Note: Visits should be scheduled within ±3 days of the specified time point.	Note: Visits **from Week 0 through Week 60** should be scheduled within ±3 days of the specified time point. **Visits during the Individualized Follow-up Period should be scheduled within ±7 days of the specified time point.**	A wider visit window is more practical during the Individualized Follow-up Period and variations in timing of the assessments will not impact the analyses.
Table 6-2	Day 0 blood draws will occur predose and ~~12 hours~~ postdose.	Day 0 blood draws will occur predose and **4 hours** postdose.	Feasibility at the study centers.
Section 6.3.2.3	Subjects should be withdrawn from investigational product (and GSK medical monitor notified as soon as possible) for the following reasons:	The medical monitor should be notified of the following AEs of special interest. Refer to Section 4.4.2 and Section 4.4.3 for discontinuation criteria.	Correction/clarification
Section 6.3.10.1	~~Oral~~ temperature	Temperature	Subjects with oral lesions may require other means of obtaining a temperature.
Section 8.3.4	An interim analysis for futility… will be conducted by the IDMC.	An interim analysis for futility… will be conducted by **an unblinded statistician not involved in the conduct of the study and presented to** the IDMC.	Clarification
Section 8.3.5.5	… lead to a conservative (<0.025 one-sided) type-1 error for all correlations ~~<~~0.9.	… lead to a conservative (<0.025 one-sided) type-1 error for all correlations ≤0.9.	Correction (changed from < to ≤)
Appendix 4	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…	At a minimum, blood JCV (PCR and/or **JCV antibody testing) with or without an** MRI should be performed; if **any** test is positive, cerebrospinal fluid (CSF) JCV **testing** should be performed. If blood JCV **testing** and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If blood JCV **testing** and/or MRI are positive…	JCV antibody testing may be used instead of PCR
Appendix 13	NA	Central laboratory reference ranges	For reference

Protocol Amendment 2: 26 September 2013

Applicable to all countries and study centers.
** This amendment was superseded by Protocol Amendment 3 before implementation at any study center **

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number and revision chronology	
Sponsor information	NA	Medical monitor name and contact information for Asia Pacific region.	
Protocol summary; Section 1.2, Section 10	… reducing mortality to approximately 5% to ~~10%~~ [Robinson, 1997]. … response to rituximab has correlated with B-cell depletion [Mouquet, 2008; Eming, 2008].	… reducing mortality to approximately 5% to **15%** [Robinson, 1997; **Langan 2008**]. … response to rituximab has correlated with B-cell depletion [Mouquet, 2008; Eming, 2008; **Colliou, 2013**].	More recent references regarding PV mortality and clinical response to rituximab.
Protocol summary; Section 3.1	… ofatumumab SC in subjects with ~~active~~ PV…	… ofatumumab SC in subjects with PV…	Clarity.
Protocol summary; Table 3-1; Section 2.3	Other Objectives: • To assess the pharmacodynamics of ofatumumab...	Other Objectives: • To assess the **population** pharmacodynamics of ofatumumab….	Clarification.
Protocol summary; Table 3-1; Section 6.5	NA	Pharmacokinetic endpoints: • **Plasma (trough) concentrations of ofatumumab** • **Exposure-response relationship**	New endpoints to determine ofatumumab plasma concentrations across the whole study population.
Section 3.1.1	A Screening Period of up to 12 weeks will allow subjects ~~who have active lesions at the initial Screening Visit~~ to achieve disease control using a stable dose of 20 mg/day up to 120 mg/day…	A Screening Period of up to 12 weeks will allow subjects to achieve disease control **(ie, no new lesions for ≥2 weeks)** using a stable dose of 20 mg/day up to 120 mg/day... **Refer to the study procedures manual (SPM) for retesting and/or rescreening procedures**.	Clarification.
Table 3-2	Footnote c. … an attempt at reducing the steroid ~~taper~~ further need only be attempted...	Footnote c. … an attempt at reducing the steroid **dose** further need only be attempted…	Clarification.
Section 3.1.4	The substudy … will enroll approximately ~~15~~ subjects.	The substudy … will enroll approximately **25** subjects.	Increase likelihood of obtaining data from at least 10 evaluable subjects.

Section	Original Text	Changes	Rationale
Table 3-3	Placebo group: Maximum -42.15 ~~Footnote b: The low minimum % change in CD19+ B-cells…~~	Placebo group: Maximum **+**42.15	Error correction. Footnote was not applicable to Day 85 time point.
Section 4.3	6. Positive test for HBsAg. For HBsAg negative, but ~~HBcAb~~ positive (regardless of HBsAb status), an HBV DNA test will be performed and the subject will be excluded if results are positive.	6. Positive test for HBsAg. For HBsAg negative, but **anti-HBc** positive (regardless of HBsAb status), an HBV DNA test will be performed and the subject will be excluded if results are positive. **Consult with a physician experienced in the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive.**	Consistency with recent proposed change to US prescribing information for ARZERRA.
Section 4.3	9. Any of the following screening laboratory values: • Bilirubin >1.5 x ULN. ~~• CD4 count <500 cells/mm³.~~	9. Any of the following screening laboratory values: • Bilirubin >1.5 x ULN **(except in cases of isolated predominantly indirect hyperbilirubinemia due to Gilbert's syndrome).**	Gilbert's syndrome is a benign, but fairly prevalent, condition. CD4 count is not typically assessed prior to initiation of anti-CD20 treatment (primarily rituximab) in PV, and CD4 count has not been a required exclusion criterion across the ofatumumab program. Removing the exclusion of subjects with CD4 count <500 cells/mm³ is not expected to adversely impact subject safety during the study. Excluding subjects on the basis of underlying Gilbert's syndrome or baseline CD4 count may unnecessarily limit the study population and may not be representative of the overall PV population.
Section 5.1.1	Dose preparation instructions ~~will be~~ provided in the SPM. ~~See the SPM for~~ detailed instructions related to the destruction of unused materials.	Dose preparation instructions are provided in **the unblinded pharmacist manual**. Detailed instructions related to the destruction of unused materials **are provided in the unblinded pharmacist manual.**	Clarification of site reference document.

Section	Original Text	Changes	Rationale
Section 5.3	Full details for ~~contacting the central IVR system~~ to unblind a subject are contained within the SPM.	Emergency unblinding will be available via the central IVR system **(refer to the SPM and IVRS guidelines for appropriate procedures to follow)**.	Clarity – the study center should not unblind via IVR without first attempting to contact the medical monitor.
Table 6-1 Time and events table	NA	Plasma samples will be collected from all subjects predose at Baseline and at Weeks 12, 24, 36, 48, and 60 (or early withdrawal) to determine ofatumumab trough concentrations.	To determine ofatumumab plasma concentrations across the whole study population.
Table 6-2 Substudy	NA	Predose pharmacokinetic samples added to Week 24 and Week 36.	Samples will be collected from all subjects at these time points.
Section 6.3.1	Instructions for sample handling and shipping are in the ~~SPM~~.	Instructions for sample handling and shipping are provided in the [redacted] **investigator manual**.	Clarification of site reference document.
Section 6.3.2.1	~~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. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.~~	NA	Erroneous text.
Section 6.3.9	The SPM provides ~~the method of~~ recording, ~~evaluating, and~~ follow-up of ~~AEs and~~ SAEs, ~~procedures for completing and transmitting SAE reports to GSK, and procedures for post-study AEs/SAEs.~~	The SPM provides **direction regarding the** recording, **reporting/ transmitting,** and follow-up of SAEs.	Clarification/correction of supplemental information provided in the SPM.
Section 6.3.9.2	Refer to the ~~SPM~~ for appropriate processing and handling of samples...	Refer to the [redacted] **investigator manual** for appropriate processing and handling of samples...	Clarification of site reference document.

Section	Original Text	Changes	Rationale
Section 6.3.9.2	~~For subjects who are HBcAb positive and HBV DNA negative, perform HBV DNA PCR testing at a minimum of every 2 months during the Treatment and Follow-up Periods. If a subject becomes HBV DNA + during the course of the study, discontinue further treatment … Subjects may receive further treatment per local guidelines at discretion of investigator. Subjects who are HBcAb positive may receive prophylaxis at the investigator's discretion~~.	**Subjects 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 the care and management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Antiviral therapy to be initiated if required.**	Consistency with recent proposed change to US prescribing information for ARZERRA.
Section 6.5	Plasma analysis will be performed under the control of GSK PTS-DMPK/Scinovo, the details of ~~which will be included in the SPM~~. … Raw data will be archived at the bioanalytical site ~~(detailed in the SPM).~~	Plasma analysis will be performed under the control of GSK PTS-DMPK/Scinovo. **The details of sample collection, processing, storage, and shipping are** included in the [redacted] **investigator manual**. … Raw data will be archived at the bioanalytical site, **as per GSK PTS-DMPK protocol**.	Clarification of site reference document.
Appendix 4	~~At a minimum~~, blood JCV (PCR and/or JCV antibody testing) ~~with or without an MRI~~ should be performed~~; if any test is positive~~, cerebrospinal fluid (CSF) JCV testing should be performed. If ~~blood~~ JCV testing and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If ~~blood JCV testing and/or MRI are positive~~…	Blood JCV (PCR and/or JCV antibody testing) should be performed. **If indicated,** cerebrospinal fluid (CSF) JCV testing should also be performed. **Magnetic resonance imaging (MRI) is strongly recommended.** If blood JCV testing and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If **PML is confirmed**… 4. The independent PML adjudicator can request additional testing and further data collection.	Changes requested by independent PML adjudicator.
[redacted]			
Appendix 14	NA	Specification of suggested questions to ask subjects during the scheduled phone visits.	Additional information regarding structure of phone visits per FDA request.
Appendix 15	Appendix ~~14~~	Appendix **15. List of all changes in Protocol Amendment 2.**	

Protocol Amendment 3: 13 March 2014

Applicable to all countries and study centers.
At the time of this amendment, no subjects had been randomized in the study.

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number, date, revision chronology, and authors.	
Throughout	NA	Minor changes in text and formatting.	To improve clarity.
List of definitions	Sum of all periods of remission on minimal steroid therapy up to Week 60 …and maintained ~~dose at~~ ≤10 mg/day…	**Total time** (sum) of all periods of remission **while** on minimal steroid therapy **(oral prednisone/ prednisolone dose ≤10 mg/day)** up to Week 60 …and maintained ≤10 mg/day **of oral prednisone/prednisolone…**	Consistency of wording between definitions and endpoints.
Title page; Protocol summary; Section 1.4; Section 2.1; Section 3.1; Figure 3-1; Table 3-1	… ~~60~~ mg administered every ~~12~~ weeks… … ~~60~~ mg administered every ~~12~~ weeks for ~~48~~ weeks… … every ~~12~~ weeks for a total of ~~48~~ weeks (~~5~~ doses, ~~with the first dose occurring on Day 0 subsequent to enrollment and randomization~~).	… **20** mg administered every **4** weeks **(with an additional 20-mg 'loading' dose [ie, 40 mg total] at both Week 0 and Week 4)**… … **20** mg administered every **4** weeks for **56** weeks… … every **4** weeks **(with an additional 20-mg 'loading' dose at both Week 0 and Week 4)** for a total of **56** weeks (**total of 17 injections across 15 monthly dosing visits**).	Change in dose and dosing interval.
Protocol summary; Section 3.1; Table 3-1; Figure 3-1	…~~48~~-week Treatment Period … …a ~~48~~-week Treatment Period, and a ~~12~~-week Follow-up ~~Period~~… After the last dose … at Week ~~48~~… followed-up for a minimum of ~~12~~ weeks, with visits scheduled at Weeks ~~52~~, ~~56, and~~ 60.	…**56**-week Treatment Period … …a **56**-week Treatment Period and a **4**-week Follow-up **visit**… After the last dose … at Week **56**… followed-up for a minimum of **4** weeks, with a visit scheduled at Week 60.	Change timing of last dose with subsequent change in initial Follow-up to align with change in dosing interval (no change to Individualized Follow-up).
Protocol summary; Section 2.2; Table 3-1	Secondary Objectives: • …tolerability of ofatumumab SC ~~at a dose of 60 mg administered every 12 weeks~~. • …and repletion following ofatumumab SC ~~at a dose of 60 mg administered every 12 weeks~~.	Secondary Objectives: • …tolerability of ofatumumab. • …and repletion following ofatumumab SC.	Simplification.

Section	Original Text	Changes	Rationale
Protocol summary; Section 6.2.2; Section 6.3; Table 3-1	~~Safety~~: • Cumulative dose of corticosteroids Safety: • ~~Percentage of subjects~~ withdrawing due to AEs ~~assessed by the investigators as at least possibly related to treatment~~	**Secondary Endpoints**: • Cumulative dose of corticosteroids Safety: • **Frequency of** withdrawals due to **treatment-related** AEs. • **Frequency of AEs of special interest, postinjection systemic reactions, and injection site reactions.**	Consistency across sections.
Section 2.3	• To ~~evaluate~~ the population pharmacodynamics of ofatumumab ~~SC administered at a dose of 60 ...~~	• To **assess** the population pharmacodynamics of ofatumumab SC…	Consistency across sections.
Section 3.1.3	…Week 60 study assessments will be completed ~~prior to initiating the baseline visit of~~ the OLE study. NA	…Week 60 study assessments will be completed **before the first dose of ofatumumab SC in** the OLE study. **Note: Subjects who are HBsAg negative, anti-HBc positive, and HBV DNA negative must continue HBV DNA PCR monitoring at a minimum of every 2 months for 6 months after the last dose of study treatment.**	Clarification.
Section 3.2	NA	**Within the protocol, reference to GlaxoSmithKline (GSK) and/or [redacted], a GSK company ([redacted]) is inclusive of tasks and responsibilities that will be performed by a contract research organization (eg, [redacted]).**	Clarification.
Section 3.3	*** Data from small single-dose study of ofatumumab SC in subjects with rheumatoid arthritis used to support dosing regimen of 60 mg every 12 weeks.*	*** Entire dose rationale section revised to include data from repeat-dose study of ofatumumab SC in subjects with RRMS, which indicate a dosing regimen of 20 mg every 4 weeks will be more likely to maintain desired B-cell depletion.*	Newly-available data and pharmacometric modeling support changing the dose and dosing regimen.
Section 4.2	…diagnosis of PV for >2 months and <~~5~~ years.	…diagnosis of PV for >2 months and <**10** years.	Investigator feedback has indicated that permitting a longer period since diagnosis may increase feasibility without adversely impacting subjects. Up to 10 years is still not considered recalcitrant disease.

Section	Original Text	Changes	Rationale
Section 4.4.1	Investigational product dosing will be held ~~for up to 2 weeks~~ in the following situations:	Investigational product dosing will be held in the following situations: **If the condition resolves within 1 week, administer the held dose and then return to the regular dosing schedule. If the condition does not resolve within 1 week….**	Window for dose holding shortened to accommodate the change in dosing interval. Added guidance for when to administer a held dose.
Section 5.1.1	…~~provided in 3 mL glass vials containing 1 mL of concentration 100 mg/mL drug product~~ … …will administer ~~0.6~~ mL of investigational product at Weeks 0, 12, 24, 36, and 48… …dosing on the specific visit schedule ~~(eg, every 12 weeks)~~.	**Initially, syringes** containing 0.6 mL **(60 mg)** of concentration 100 mg/mL drug product **will be provided.** **For study centers initiated using the dilution method for study treatment preparation an unblinded pharmacist (or appropriately-qualified designee) at the study center will prepare each dose via a dilution process…** **When available, GSK will supply ofatumumab SC in prefilled glass syringes containing 0.4 mL (20 mg) of concentration 50 mg/mL drug product and matching placebo prefilled glass syringes containing 0.4 mL of normal saline.** …will administer **0.4** mL of investigational product… …dosing on the specific visit schedule **as shown in Table 6-1**.	Change in how investigational product will be supplied, dose, and dosing interval.
Section 5.3	Each site must designate an unblinded pharmacist (or designee) for drug preparation; ~~an unblinded clinical research assistant will monitor sites to ensure drug accountability.~~	Each site **that prepares study injections using the dilution method** must designate an unblinded pharmacist (or **appropriately-qualified** designee) for drug preparation.	Clarification that unblinded pharmacist is only needed if study treatment will be mixed at the site. Labels will be blinded; therefore, an unblinded clinical research assistant is not required.

Section	Original Text	Changes	Rationale
Table 6-1	Treatment Period (~~48~~ Weeks) Investigational product administration, vital signs, and pregnancy testing every ~~12~~ weeks. Clinical assessments, [redacted], BLC [redacted] PD mark [redacted] [redacted].	Treatment Period (**56** Weeks) Investigational product administration, vital signs, and pregnancy testing every **4** weeks. Clinical assessments [redacted], BLC, [redacted], PD markers, and PK samples [redacted]	Assessment time points updated to reflect change in dosing interval.
Table 6-1	NA	**Neurological symptoms questionnaire at screening.**	To be consistent with exclusion criterion 5.
Table 6-2	… Day ~~0~~ through Day 7, pharmacokinetic samples … (±2 hours)…	… Day **1** through Day 7, pharmacokinetic samples … (±2 hours)… *PK and PD samples added at Week 16 and 20. PD samples added at Weeks 4 and 8.* *Footnote that samples should be collected predose on dosing days.*	Collection window of ±2 hours does not apply to Day 0 samples. Updated to reflect change in dosing interval.
Section 6.1	…factors will be assessed at Baseline.	…factors will be assessed at **Screening**/Baseline.	Information may be collected at either visit.
Section 6.2.1	…total time of all periods ~~during 60 weeks, from when the subject initially tapered his/her oral prednisone/prednisolone dose to ≤10 mg/day and had remission, until initial flare/relapse or~~ Week 60, ~~whichever comes first.~~	…total time **[sum]** of all periods **of remission while on minimal steroid therapy** [oral prednisone/ prednisolone dose of ≤10 mg/day] **up to** Week 60.	Consistency of definition wording with endpoints.
Section 6.3.1, Appendix 3	** *Liver chemistry stopping and follow-up criteria: detailed information in text and figure in appendix.*	** *Liver chemistry stopping and follow-up criteria: detailed information in appendix and figures in text.*	Updated formatting and presentation of flow diagrams and instructional text to improve clarity.
[redacted]			

Section	Original Text	Changes	Rationale
Section 6.3.9.2; Table 6-4	Table Footnote ~~c. For subjects who are anti-HBc positive and HBV DNA negative, perform HBV DNA PCR testing at a minimum of every 2 months during the Treatment and Follow-up Periods.~~	Hepatitis B Screening and Monitoring … must undergo HBV DNA PCR monitoring **at a minimum of every 2 months during the Treatment Period and for 6 months after the last dose.**	Moved from table footnote to Section 6.3.9.2 to keep all relevant information together. Added time period for postdose monitoring to account for variations in the Follow-up Period duration.
Section 8.3; Section 8.3.5.9	~~The RAP will provide complete details of the safety analyses.~~	Additional details of data analyses will be specified in the RAP.	Text added to Section 8.3.
Section 8.3.4	An interim analysis for futility will be conducted when 60 events of remission…	An interim analysis for futility will be conducted when 60 events of **sustained** remission …	Clarification that futility analysis should be based on sustained remissions.
	NA	**If enrollment is substantially slower than anticipated and/or the rate of sustained remissions is much smaller than projected, consideration will be given to performing the interim analysis for futility at an earlier time point…**	It is difficult to predict enrollment rates for this rare disease; therefore, an earlier futility analysis may be considered appropriate.
Section 8.3.5.6	…plasma concentration data ~~obtained from the pharmacokinetic substudy~~ will be analyzed…	…plasma concentration data will be analyzed…	Plasma concentration data will be evaluated in all subjects.
Appendix 5	1. Does the subject report any new weakness?	1. Does the subject report any new **focal** weakness?	Clarification.
Appendix 15	NA	**List of all changes in Protocol Amendment 3.**	

Protocol Amendment 4: 18 September 2014

Applicable to all relevant countries with country-specific requirements.
At the time of this amendment, no subjects had been randomized in the study.

** This amendment was superseded by Protocol Amendment 5 before implementation at any study center **

Section	Original Text	Changes	Rationale
Section 3	NA	Added: ** **Refer to Appendix 2 (or protocol addendum) for any applicable country-specific requirements.** **	Regulatory authorities from the UK and France requested protocol change(s) that have been added to Appendix 2, *Country-Specific Requirements*; therefore, cross-references to this appendix have been added within the protocol.
Section 4	NA	Added: ** **Refer to Appendix 2 (or protocol addendum) for any applicable country-specific requirements for subject inclusion in this study.** **	
Appendix 2 – France and Appendix 2 – UK	Change regarding Section 4.2, Inclusion criterion 7b. … use of acceptable methods of contraception… informed consent and lasting until ~~6 months~~ after last dose,,,	… use of acceptable methods of contraception… informed consent and lasting until **12 months** after last dose,,,	Request by France and UK national competent authorities for alignment with ARZERRA (ofatumumab for IV infusion) EU SPC.
Appendix 2 – UK	Change regarding Section 4.2, Inclusion criterion 7b. … Complete abstinence from heterosexual intercourse	Complete abstinence from heterosexual intercourse, **when this is in line with the preferred and usual lifestyle of the subject**	Request by UK national competent authority.

Protocol Amendment 5: 02 April 2015

Applicable to all countries and study centers, unless otherwise specified as a country-specific requirement. At the time of this amendment, 5 subjects had been randomized in the study.

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number, date, and revision chronology.	Amendment 5.
Throughout	NA	Corrections and clarifications for consistency throughout protocol, Cross-references to country-specific criteria, as applicable.	To address inconsistencies and questions identified while initiating study centers and subject enrollment.
Definitions	NA	Added definitions for study periods	Added study period definitions to list of clinical definitions for ease of locating.
Summary; Section 1.2	…mortality rate of ~~<10%.~~ …mortality ~~to approximately 5% to 15% [Robinson, 1997~~; Langan, 2008].	…mortality rate of **<20%.** …mortality **from 70% to less than 20% [Carson, 1996**; Langan, 2008].	Updated with publication of a retrospective analysis of mortality rates.
Summary; Table 3-1	To determine the extent of B-cell depletion and repletion following ofatumumab SC. To assess the population pharmacodynamics of ofatumumab SC in subjects with PV.	To assess population pharmacodynamics and the extent of B-cell depletion and repletion following ofatumumab SC.	Combine similar objectives for clarity.
Summary	[redacted]	[redacted]	Consistency with Table 3-1, Objectives and Endpoints and Section 6.2.3.
Summary; Section 6.3	NA	**Frequency of AEs leading to permanent discontinuation of investigational product.**	Consistency with Table 3-1, Objectives and Endpoints
Figure 3-2	NA	New figure to show flow of subjects from Core Study Period to the extension study, IFU Period, and study exit.	Improve clarity.

Section	Original Text	Changes	Rationale
Section 3.1	The study includes a Screening Period, a 56-week Treatment Period, and a 4-week Follow-up visit. … enter the Individualized Follow-up Period.	The study includes a Screening Period, **a Core Study Period (consisting of the** 56-week Treatment Period and 4-week Follow-up visit**), and an Individualized Follow-up Period (as applicable).** … enter the Individualized Follow-up Period **(as applicable; guidance will be provided within the [redacted] visit report, laboratory values will remain blinded).**	Improve clarity.
Table 3-2	Oral Prednisone/Prednisolone Dose-taper Schedule – by ~~study week and starting dose~~	Oral Prednisone/Prednisolone Dose-taper Schedule – by **current dose and disease status** (tapering or dose increase for flare/relapse)	To improve clarity and include dose increase guidelines for flares and reinitiating dose taper.
Section 3.1.2	…prior to each administration of investigational product.	…prior to each administration of investigational product **to lessen the likelihood of localized reactions**.	Include rationale for premedication.
Section 3.1.3	NA	Until… **Other criteria for study withdrawal/exit are met (see Section 4.4.3).**	Subjects withdrawing from the study will not continue in the Individualized Follow-up Period.
Section 3.1.3	For subjects who participate in the ~~OLE~~ study, Week 60 study assessments will be completed before ~~the first dose of ofatumumab SC in the OLE~~ study..	For subjects who participate in the **extension** study, **OPV116910** Week 60 study assessments will be completed before **any study-related assessments are performed for the extension** study.	Clarification because not all subjects will receive ofatumumab at the baseline visit of extension study.
Section 3.1.3; Section 6.3.10.2	…HBV DNA PCR monitoring at a minimum of every ~~2 months~~…	…HBV DNA PCR monitoring at a minimum of every **12 weeks**…	Revised monitoring interval considered acceptable to monitor for hepatitis B reactivation.

Section	Original Text	Changes	Rationale
Section 4.2	3. At least 1 previous episode of a failed steroid taper (ie, disease flare/relapse at a prednisone/prednisolone dose >10 mg/day).	3. At least 1 previous episode of a failed steroid taper (ie, disease flare/relapse) at a prednisone/ prednisolone dose >10 mg/day, **with a Pemphigus Severity of Clinical Disease score of moderate (2)or severe (3) (may be historical/retrospective assessment [see Appendix 6 and SPM for guidance]), where severity of disease at flare/relapse necessitated an increase of >20mg/day.** ***Note: prednisone/prednisolone dose should not be increased for the sole purpose of entry into this study.***	Request by France for more specific clinical disease severity criteria related to status at the time of the failed steroid taper (change incorporated as a global requirement). Clarification that steroid dosing should be independent of study.
Section 4.2	7b. … use of acceptable methods of contraception… informed consent and lasting until ~~6 months~~ after last dose… Complete abstinence from heterosexual intercourse.	7b. … use of acceptable methods of contraception… informed consent and lasting until **12 months** after last dose… Complete abstinence from heterosexual intercourse, **when this is in line with the preferred and usual lifestyle of the subject.**	Change from country-specific requirement in Amendment 4 to global requirement in Amendment 5.
Section 4.3	NA	4. Added exclusions for tacrolimus, alemtuzumab, mitoxantrone, and CD-20 treatments.	Consistency with prohibited medications sections.
Section 4.4.1	NA	**Positive symptoms on neurological symptoms questionnaire (see Appendix 4 and Appendix 5).**	Dose-holding for positive symptoms was included in the PML algorithm but not in the dose-holding section.
Section 4.4.2	Any subject who discontinues ~~treatment prior to completion~~ should enter the Individualized Follow-up Period unless he/she meets a criterion for mandatory withdrawal from the study.	Any subject who discontinues **from the Treatment Period should complete an Early Withdrawal Visit and transition into** the Individualized Follow-up Period for important safety monitoring (as applicable; see Section 3.1.3), unless he/she meets a criterion for mandatory withdrawal from the study.	Improve clarity.
Section 4.4.3	NA	**Subject initiates treatment with a prohibited PV disease modifying drug that depletes B cells (eg, rituximab).**	If subject initiates new B-cell depleting therapy, monitoring has limited utility for assessing repletion after ofatumumab treatment.

Section	Original Text	Changes	Rationale
Section 5.1.1, Section 5.3	NA	**In countries (including Japan) and/or study centers not using the dilution method to prepare study injections, Kendall 5 micron filter needles will not be used and there is no need to designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation.**	Clarification
Section 5.2	~~GSK will not collect electronic case report form (eCRF) information for screen failures unless the subject experiences an SAE during the Screening Period.~~	**In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials publishing requirements, and respond to queries from regulatory authorities, a minimal set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any SAEs.**	GSK policy has been updated to collect minimal information on subjects who are screen failures.
Section 5.3	NA	**Sponsor unblinding for analyses will occur after all subjects have completed the Week 60 visit or been withdrawn from the treatment period (see Section 8.3.4).**	Clarification
Section 5.6.2	~~Bulleted list of prohibited medications~~	**Tabular format for prohibited medications with washout periods.**	List washout periods in same section as medications.
Figure 6-1	NA	**New figure to show relative timing ofatumumab SC dosing.**	
Table 6-1	NA	**Document steroid dose (all visits)**	Specified to improve clarity.
Table 6-1 Footnotes	Visits from ~~Week 0~~ through Week 60 to be scheduled within ±3 days…	Visits from **Week 2** through Week 60 to be scheduled within ±3 days…	Day 0 does not have a visit window.
		b. **Subjects requiring additional HBV testing will return for IFU visits every 12 weeks for 6 months after the last dose.**	Consistency with HBV testing requirements in Section 6.3.9.2 and convenience of subject in overall visit scheduling.
	d. AEs will be collected from the start of study treatment through the ~~protocol-specified Follow-up~~ Period.	d. AEs will be collected from the start of study treatment through the **Core Study** Period.	Only SAEs and AEs of special interest will be collected during Individualized Follow-up Period.

Section	Original Text	Changes	Rationale
Table 6-2	NA	Added separate table for Individualized Follow-up Period. Added document steroid dose, neurological symptoms questionnaire, hematology, and pregnancy testing to the IFU visits.	Separated due to confusion regarding visit schedule. To continue monitoring for safety. The onset of PML may occur after discontinuation of study treatment.
[redacted]			
Section 6.3.2.3	NA	**• Hepatitis B virus reactivation (see Section 6.3.10.2).** **• Severe mucocutaneous reactions (eg, toxic epidermal necrolysis and Stevens Johnson syndrome).** **• Cytopenias.** **• Cardiovascular events (see Section 6.3.4).**	Updated list of AEs of special interest for consistency with the IB. These potential AEs are not new concerns, but were not specified in the previous version of the protocol.

Section	Original Text	Changes	Rationale
Section 6.3.10.2	…HBV DNA PCR monitoring at a minimum of every ~~2 months~~…	… HBV DNA PCR monitoring at a minimum of every **12 weeks…**	Alignment with the American Association for the Study of Liver Disease guidance and other ofatumumab clinical programs.
Table 6-6	NA	**Added table of hepatitis B test results scenarios for eligibility.**	To improve clarity over text-only descriptions.
Section 8.3.5	NA	**New heading inserted: Reporting Time Points**	To separate data reporting time points from description of interim analyses.
Appendix 2	~~Appendix 2 – France~~ ~~Appendix 2 – UK~~	NA	Changed from country-specific to global requirements.
Appendix 2 – Japan (with cross-references from applicable sections within body of protocol)	NA	Addition of county-specific requirements for Japan: methods of contraception; additional screening procedures; exclusion criteria specifications; clarification of withdrawal from study due to Sponsor request; only ofatumumab 20 mg prefilled syringes will be utilized; unblinded pharmacists not required; prohibited medications; medical devices; and regulatory and ethics considerations.	Protocol modifications and supplementary details requested during review by the PMDA were initially presented in a Japan-specific 'addendum' to Protocol Amendment 3. These details are now specified with the current global protocol.
Appendix 4, Figure 11-3	NA	Added PML monitoring algorithm **flowchart**.	Visual representation of PML evaluation flow.
Appendix 5	If any of the above are answered "Yes" at any visit, the investigator will contact the medical monitor ~~and the subject will be referred to a neurologist~~.	If any of the above are answered "Yes" at any visit, the investigator will contact the medical monitor. **Any neurological symptom that cannot be directly attributed to a concurrent medical condition or concomitant medication must be referred to a neurologist.**	If symptoms have an identifiable cause, then referral to a neurologist may not be appropriate.
Appendix 6	… (ie, historical assessment).	… (ie, **may be a** historical/ **retrospective** assessment). **Refer to the SPM for additional guidance.**	Clarification
[redacted]			

Section	Original Text	Changes	Rationale
[redacted]			
Appendix 15	NA	**List of all changes in Protocol Amendment 5.**	

Protocol Amendment 6: 28 September 2015

Applicable to all countries and study centers, unless otherwise specified as a country-specific requirement. At the time of this amendment, 21 subjects had been randomized in the study.

** GSK asked that the sites revert back to Amendment 5 and the Ethics Committees in the USA were notified; therefore, none of the changes in this amendment were implemented at any study center. This amendment was then superseded by Protocol Amendment 7**

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number, date, and revision chronology.	Amendment 6
Throughout	NA	Corrections and clarifications for consistency throughout protocol	To address inconsistencies and questions identified while initiating study centers and subject enrollment.
Abbreviations	NA	**hsCRP High sensitivity C-reactive protein**	Clarification
Protocol-specific definitions, Study Periods	*Core Study Period*	*Core Study Period* ***(also referred to as complete treatment course)***	Clarification
Protocol-specific definitions, Study periods, Individualized Follow-up	~~If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in~~ Individualized Follow-up Period until ~~either~~ the CD19+ B-cell counts or circulating IgG levels are ≥LLN ~~or until~~ 2 years after the last dose of investigational product (whichever comes first). ~~Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.~~	**After completing the Core Study Period (or early discontinuation of treatment), subjects who do not enroll in the extension study will enter the Individualized Follow-up Period for a minimum of 1 year. After the first year, subjects will remain in the** Individualized Follow-up Period until the CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN), **study withdrawal criteria are met, or for a maximum of** 2 years after the last dose of investigational product (whichever comes first).	A minimum 1-year Individualized Follow-up Period for subjects who do not enroll in the extension study will allow the collection of additional safety data following the completion of treatment. The 1st year of Individualized Follow-up is expected to provide adequate time for B-cell repletion in the majority of subjects. The 2nd year will continue to monitor for B-cell repletion in the remaining subjects.
Protocol-specific definitions, Clinical definitions	NA	**B-cell recovery/repletion: CD19+ B-cell counts greater than or equal to the lower limit of normal or baseline levels (if less than the lower limit of normal). Note: B-cell counts and IgG results will be blinded after the Screening visit and throughout the study.**	Definition added for completeness and clarity.

Section	Original Text	Changes	Rationale
Protocol-specific definitions, Clinical definitions, *Remission*	Absence of new or nonhealing (established) lesions for ≥8 weeks *(Note: Subjects ~~with~~ existing, healing lesions may be considered in remission ~~if other criteria are met~~.)*	Absence of new or nonhealing (established) lesions for ≥8 weeks *(Note: Subjects **who only have** existing, healing lesions may be considered in remission.)*	Clarification
Trademark Information	**Trademarks of the GlaxoSmithKline group of companies** ~~ARZERRA~~ **Trademarks not owned by the GlaxoSmithKline group of companies** Campath EQ-5D QuantiFERON	**Trademarks of the GlaxoSmithKline group of companies** **None** **Trademarks not owned by the GlaxoSmithKline group of companies** **ARZERRA** Campath EQ-5D **MabCampath** QuantiFERON	Updated information
Protocol summary, Other objectives; Protocol summary Other endpoints; Section 2.3; Table 3-1; Section 6.2.3	NA	*Other Objective:* **To evaluate disease remission and disease flare/relapse after the completion of treatment with ofatumumab SC** *Other Endpoints:* • **Duration of remission on minimal steroid therapy by the end of the Individualized Follow-up Period** • **Duration of remission off steroid therapy by the end of Individualized Follow-up Period.** • **Time to flare/relapse between Week 60 and the end of the Individualized Follow-up Period.**	Objective and corresponding endpoints added to assess duration of remission on minimal steroid therapy and time to flare/relapse in the Individualized Follow-up Period after completion of a treatment course. These results, in conjunction with those obtained in extension study OPV117059, will be used to assess if continuous treatment with ofatumumab SC is necessary or if intermittent treatment courses are effective.

Section	Original Text	Changes	Rationale
Protocol summary, Section 2.2 and Section 2.3	**Protocol Summary, Secondary Objectives**: To assess population pharmacodynamics ~~and~~ the extent of B-cell depletion and repletion following ofatumumab SC **2.2 Secondary Objectives**: ~~To determine~~ the extent of B-cell depletion and repletion following ofatumumab SC. **2.3 Other Objectives** ~~To assess the population pharmacodynamics of ofatumumab SC in subjects with PV~~	**Protocol Summary, Secondary Objectives**: To assess population pharmacodynamics **including** the extent of B-cell depletion and repletion following ofatumumab SC **2.2 Secondary Objectives**: **To assess population pharmacodynamics including** the extent of B-cell depletion and repletion following ofatumumab SC. **2.3 Other Objectives** NA	Clarification and corrections for consistency between sections.
Table 3-1	Secondary Efficacy Endpoints- supporting primary objective: • Time to remission while on minimal steroid therapy Secondary Objectives- *Efficacy and Pharmacodynamic:* To ~~determine~~ population pharmacodynamics ~~and~~ the extent of B-cell depletion and repletion following ofatumumab SC	Secondary Efficacy Endpoints- supporting primary objective: • Time to remission while on minimal steroid therapy **by Week 60** Secondary Objectives- *Efficacy and Pharmacodynamic:* To **assess** population pharmacodynamics **including** the extent of B-cell depletion and repletion following ofatumumab SC	

Section	Original Text	Changes	Rationale
Protocol summary, Study design	The study includes a Screening Period, a 56-week Treatment Period, and a 4-week Follow-up visit. Subjects will visit the clinic ~~during Screening~~; at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have structured phone visits between each of the clinic visits from Week 10 through Week 22. ~~It is anticipated that~~ total duration of participation in ~~this~~ study will be approximately ~~72 weeks~~.	The study includes a Screening Period, **a Core Study Period (consisting of** a 56-week Treatment Period, and a 4-week Follow-up visit) **and an Individualized Follow-up Period. For subjects not enrolling in extension study OPV117059, the duration of the Individualized Follow-up Period will be a minimum of 1 year with a maximum follow-up of 2 years depending on timing of B-cell or IgG repletion.** The total duration of participation in the study will be approximately **2 years, with a maximum of 3 years including the full 2-year duration of the Individualized Follow-up Period.** **Core Study Period** Subjects will visit the clinic at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have structured phone visits between each of the clinic visits from Week 10 through Week 22.	A minimum 1-year Individualized Follow-up Period for subjects not enrolling into extension study OPV117059 will allow the collection of additional safety data following the completion of treatment. The 1st year of Individualized Follow-up is expected to provide adequate time for B-cell repletion in the majority of subjects. The 2nd year will continue to monitor for B-cell repletion in the remaining subjects. Total duration of study participation revised for consistency. Subheadings (Screening Period, Core Study Period, Individualized Follow-up Period) have been added to this section for clarity. The description of the visit schedule is now included under each appropriate subheading.
Protocol summary, Study design	~~After the last dose of ofatumumab SC or placebo at Week 56, subjects will be followed up for a minimum of 4 weeks, with a visit scheduled at Week 60. Subjects completing the study and meeting all entry criteria will be offered the option to participate in an extension study (OPV117059), which will start after completion of the Week 60 visit.~~ ~~If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until either the CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN) or until 2 years after the last dose of investigational~~	**Subjects who withdraw early from the Treatment Period will complete an early withdrawal visit and transition directly into the OPV116910 Individualized Follow-up Period.** **Subjects who complete the Treatment Period will be followed for a minimum of 4 weeks, with a Follow-up Visit scheduled at Week 60. At the Week 60 visit, the subject's remission status will be confirmed to determine if the subject is potentially eligible for the extension study (OPV117059) or if the subject will transition directly into the OPV116910 Individualized Follow-up Period. Eligible and consenting subjects will enter the extension study within 4**	Subjects who are in sustained remission on minimal steroid therapy will enter the Individualized Follow-up Period to allow assessment of duration of remission and time to initial flare/relapse off treatment. These subjects will be eligible for the extension study if a disease flare/relapse is experienced during the 1st year of the Individualized Follow-up Period. Subjects in sustained remission on minimal steroid therapy who become eligible for and enroll into the extension study may be in the Individualized Follow-up Period for less than 1 year.

Section	Original Text	Changes	Rationale
	~~product (whichever comes first). Individualized Follow-up visits will be scheduled every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period~~	**weeks of completing the OPV116910 Week 60 visit.** **Subjects who complete Study OPV116910 through Week 60 with one of the following outcomes may be eligible for the OPV117059 extension study if all entry criteria are met:** • **Did not achieve sustained remission (no new or non-healing lesions for ≥8 weeks that is sustained until Week 60) on minimal steroid therapy (≤10 mg/day)** • **Achieved sustained remission (no new or non-healing lesions for ≥8 weeks that is sustained until Week 60) on minimal steroid therapy (≤10 mg/day) but is experiencing a disease flare/relapse in the first year of the Individualized Follow-up Period.** **<u>Individualized Follow-up Period</u>** **Subjects who do not enroll into the extension study will enter the OPV116910 Individualized Follow-up Period for a minimum of 1 year. The following types of subjects will transition directly into the OPV116910 Individualized Follow-up Period after the Week 60 Visit:** • **Subjects who are in sustained remission (no new or non-healing lesions for ≥8 weeks that is sustained until Week 60) on minimal steroid therapy (≥10 mg/day) at the time of the Week 60 visit. *If this type of subject experiences a disease flare/relapse during the first year of the OPV116910 Individualized Follow-up Period, then consenting subjects may be screened and enrolled into the extension study at***	Clarification of the period of time allowed between the Week 60 visit and the start of the extension study. Consistency with the new requirement for a minimum 1-year Individualized Follow-up Period for subjects who do not enroll into the extension study.

Section	Original Text	Changes	Rationale
		the time of the initial flare/relapse. **(See Protocol-Specific Definitions for the definition of disease flare/relapse.)** ***Subjects who enroll into the extension study may be in the Individualized Follow-up Period for less than one year.*** • **Subjects who withdraw from the OPV116910 Core Study Period.** • **Subjects who do not consent to participation in the extension study.** • **Extension study screen failures.** **After the first year in the OPV116910 Individualized Follow-up Period, subjects will remain in the Individualized Follow-up Period for up to 1 more year until one of the following events occurs (whichever comes first):** • **CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN) (guidance will be provided within the [redacted] visit report, lab values will remain blinded)** • **Criteria for withdrawal from the study are met** • **Two years after the last dose of investigational product** **Visits during the Individualized Follow-up Period will be scheduled approximately every 12 weeks.**	
Protocol summary, Study endpoints/ assessments	**Note: definitions are provided with the list of abbreviations ~~and in Section 6.2.~~*	**Note: definitions are provided with the list of abbreviations.*	The cross-reference to the body of the protocol has been removed as the Protocol Summary is sometimes used as a standalone document.

Section	Original Text	Changes	Rationale
Section 1.3; Section 4.2	…is provided in the Investigator's Brochure.	…is provided in the Investigator's Brochure **[GlaxoSmithKline Document Number GM2008/00147/10, 2015].**	Clarification
Section 3	…Time and Events Table (Table 6-1)…	…Time and Events Table (Table 6-1 **and Table 6-2**)…	Clarification
Section 3.1	The study includes a Screening Period, a Core Study Period (consisting of the 56-week Treatment Period and 4-week Follow-up visit), and an Individualized Follow-up Period ~~(as applicable).~~	The study includes a Screening Period, a Core Study Period (consisting of the 56-week Treatment Period and 4-week Follow-up visit), and an Individualized Follow-up Period **(which includes a 1 year minimum follow-up for subjects not enrolling in extension Study OPV117059 with a maximum follow-up of 2 years depending on timing of B-cell or IgG repletion). The total duration of participation in the study will be approximately 2 years, with a maximum of 3 years including the full 2-year duration of the Individualized Follow-up Period.**	Consistency with the new requirement for a minimum 1-year Individualized Follow-up Period for subjects who do not enroll into the extension study.
Section 3.1	~~Subjects will visit the clinic during Screening; at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have structured phone visits between each of the clinic visits from Week 10 through Week 22 (see Appendix 14).~~ …using a stable oral dose of prednisone/prednisolone (20 mg/day up to 120 mg/day or 1.5 mg/kg/day [whichever is higher] for ≥2 weeks). ~~Multiple visits to the clinic are permitted during this Screening Period to assess disease status and to adjust the oral prednisone/prednisolone dose~~. Once disease control is achieved, subjects who continue to satisfy the eligibility criteria may be randomized. ~~All screening procedures should be completed within 12 weeks of informed consent being given.~~	…using a stable oral dose of prednisone/prednisolone (20 mg/day up to 120 mg/day or 1.5 mg/kg/day [whichever is higher] for ≥2 weeks) **(see Section 3.1.1)**. Once disease control is achieved, subjects who continue to satisfy the eligibility criteria may be randomized.	Deleted statements have been moved to Section 3.1.1. Screening Period and Section 3.1.2 Core Study Period as appropriate.

Section	Original Text	Changes	Rationale
Section 3.1	~~It is anticipated that total duration of participation in the Core Study Period will be approximately 72 weeks.~~	NA	Incorrect statement removed. (Duration of the Core Study Period is 60 weeks; however, this statement is no longer needed in this section as the minimum and maximum duration of the subject's participation in the study is now stated.)
Section 3.1	~~After the last dose of ofatumumab SC or placebo at Week 56, subjects will be followed up for a minimum of 4 weeks, with a visit scheduled at Week 60. Subjects completing the study and meeting all entry criteria will be offered the option to participate in an extension study (OPV117059), which will start after completion of the Week 60 visit.~~ ~~If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until either the CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first) (see Figure 3-2). Individualized Follow-up visits will be scheduled every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period (as applicable; guidance will be provided within the [redacted] visit report, lab values will remain blinded).~~	**Subjects who complete the Treatment Period will be followed for a minimum of 4 weeks, with a Follow-up visit scheduled at Week 60. At the Week 60 visit, the subject's remission status will be confirmed to determine if the subject is potentially eligible for the extension study (OPV117059) or if the subject will transition directly into the OPV116910 Individualized Follow-up Period. For subjects not enrolling in extension study OPV117059, the duration of the Individualized Follow-up Period will be a minimum of 1 year with a maximum follow-up of 2 years depending on timing of B-cell or IgG repletion (see Figure 3-2, Section 3.1.2.1, and Section 3.1.3).**	Revisions made for consistency with the new requirement for a minimum 1-year Individualized Follow-up Period for subjects not enrolling into the extension study and for consistency with eligibility criteria for the extension study. Details regarding the Week 60 visit and the Individualized Follow-up Period are now described in Section 3.1.2.1 and Section 3.1.3, respectively.

Section	Original Text	Changes	Rationale
Section 3.1; Section 9.8	Section 3.1: An independent data monitoring committee (IDMC) will evaluate ~~risks relative to benefits through review of~~ safety ~~and efficacy~~ data… Section 9.8: An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and efficacy issues…	Section 3.1: An independent data monitoring committee (IDMC) will evaluate safety data… **The IDMC will review efficacy data for an interim analysis for futility (Section 8.3.4) and as needed**. Section 9.8: An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and**/or** efficacy issues…	Correction and clarification
Figure 3-2	*Previous Study Flowchart deleted*	*New Study Flowchart added*	Revised for clarification and consistency with the changes contained in this amendment.
Section 3.1.1	NA	**Prednisone/prednisolone for the treatment of pemphigus vulgaris are the only systemic steroids allowed during the study. Subjects who are receiving a different steroid for the treatment of pemphigus vulgaris will be switched to prednisone/prednisolone during the Screening Period. However, if the subject requires the continued use of another systemic steroid for the treatment of pemphigus vulgaris or the use of any systemic steroid for a concurrent medical condition, then the subject will not be eligible for the study.** **Multiple visits to the clinic are permitted during this Screening Period to assess disease status and to adjust the oral prednisone/prednisolone dose. All screening procedures should be completed within 12 weeks of informed consent being given.**	The use of systemic steroids other than prednisone/prednisolone will potentially confound the evaluation of the study endpoints. The treatment of another medical condition with prednisone/ prednisolone is not allowed during the study as steroid dose tapering is a required part of the study. A clarification has been added that subjects receiving another systemic steroid for the treatment of pemphigus vulgaris can switch to prednisone/prednisolone during the Screening Period. Details concerning the Screening Period have been moved from Section 3.1 and consolidated.
Section 3.1.2; Section 3.1.3	Section 3.1.2 Treatment Period NA	Section 3.1.2 **Core Study Period** **The Core Study Period includes the 56-week double-blind Treatment Period and the 4-week Follow-up Visit at Week 60. Subjects will visit the**	Sections reorganized for clarity. The 4-Week Follow-up visit at Week 60 (now Section 3.1.2.1) is part of the Core Study Period. The Individualized Follow-up Period (now

Section	Original Text	Changes	Rationale
		clinic at Baseline (Week 0); at Weeks 2, 4, 6, and 8; and then every 4 weeks from Week 8 through Week 60. Subjects will also have structured phone visits from Week 10 through Week 22 (see Appendix 14). Subjects should be instructed to contact the study site if a disease flare/relapse occurs between study visits.	Section 3.1.3) is described in a separate section. Details concerning visits during the Core Study Period have been moved from Section 3.1 and consolidated.
	Section ~~3.1.3~~ Follow-up ~~Period~~	Section **3.1.2.1** Follow-up Visit-**Week 60**	Revisions have been made to ensure consistency with the following new requirements: 1) the 1 year minimum for the Individualized Follow-up Period for subjects not enrolling into the extension study, and 2) subjects in sustained remission on minimal steroid therapy at the Week 60 Visit will enter the Individualized Follow-up Period. These subjects are eligible for the extension study if a disease flare/relapse is experienced during the first year of the OPV116910 Individualized Follow-up Period.
	Subjects will be followed~~-up~~…	Subjects will be followed…	
	The follow-up visit will include…	The **Week 60** follow-up visit will include…	
	~~If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study (OPV117059)~~ will remain in Individualized Follow-up until: • CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN) • ~~Other~~ criteria for study withdrawal~~/exit~~ are met ~~(see Section 4.4.3)~~. • Two years after the last dose of investigational product (~~whichever comes first~~).	**At the Week 60 visit, the subject's remission status will be confirmed to determine if the subject is potentially eligible for the extension study (OPV117059) or if the subject will enter the OPV116910 Individualized Follow-up Period (see Figure 3-2 and Section 3.1.3):** • **Subjects who are in sustained remission on minimal steroid therapy will transition from the OPV116910 Core Study Period into the OPV116910 Individualized Follow-up Period (Section 3.1.3).** • **Subjects who are not in remission or who are in remission on >10 mg/day prednisone/prednisolone may be eligible to transition directly from the OPV116910 Week 60 visit into the OPV117059 extension study.**	Subjects in sustained remission on minimal steroid therapy who become eligible for and enroll into the extension study may be in the Individualized Follow-up Period for less than 1 year. It is recommended that the transition to the extension study occurs prior to increasing the steroid dose to allow for the assessment of disease response to ofatumumab SC in the extension study.
	~~The Individualized Follow-up assessments should be scheduled approximately every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period.~~ ~~For subjects who participate in the extension study,~~ OPV116910 Week 60 study assessments will be completed before any study-related assessments are performed for the extension study.	**For subjects transitioning into the OPV117059 extension study, there will be a 4-week window between the Week 60 visit and the extension study Baseline visit (Week 0/ first dose in extension study). Within this 4-week window and prior to the subject's first dose in the**	Greater detail has been provided to assist in the determination of which subjects are potentially eligible for the extension study and which subjects will transition into the Individualized Follow-up Period and how the transition will occur.

Section	Original Text	Changes	Rationale
		OPV117059 extension study, informed consent must be collected, all screening assessments must be completed, and the subject's eligibility confirmed. It is recommended that appropriate site staff review the extension study informed consent with each subject before the OPV116910 Week 60 visit. OPV116910 Week 60 study assessments will be completed **and OPV117059 extension study informed consent will be obtained** before any study-related assessments are performed for the extension study. **Some of the assessments performed for the Week 60 visit will also be used for extension study screening. All remaining OPV117059 Screening/Baseline assessments will be performed at the OPV116910 Week 60 visit or within the 4-week window between the OPV116910 Week 60 visit and the OPV117059 Baseline (Week 0) visit (first dose in the extension study).** **Subjects screened for the OPV117059 extension study are considered to be in the OPV116910 Individualized Follow-up Period until eligibility for the extension study is confirmed and the subject receives the first dose of ofatumumab SC at the Baseline (Week 0) visit in OPV117059 (maximum of 4 weeks is permitted between screening assessments and the first dose at Baseline). Extension study screen failures will remain in the OPV116910 Individualized Follow-up Period** **Section 3.1.3 Individualized Follow-up Period** **Subjects who do not enroll into the extension study will enter the OPV116910 Individualized**	In the event of a disease flare/relapse between study visits, the subject may need to return to the clinic for an unscheduled visit so that the disease flare/relapse and steroid dose can be evaluated. Therefore, subjects should be instructed to contact the study site if a disease flare/relapse occurs between study visits.

Section	Original Text	Changes	Rationale
		Follow-up Period for a minimum of 1 year. The following types of subjects will enter the OPV116910 Individualized Follow-up Period: **a. Subjects who are in sustained remission (no new or non-healing lesions for ≥8 weeks that is sustained until Week 60) on minimal steroid therapy (≤10 mg/day) at the time of the Week 60 visit.** ***- If this type of subject experiences a disease flare/relapse during the first year of the OPV116910 Individualized Follow-up Period, then consenting subjects may be screened and enrolled into the OPV117059 extension study at the time of the initial flare/relapse.*** **(See Protocol-Specific Definitions for the definition of disease flare/relapse.) Subjects who enroll into the extension study may be in the Individualized Follow-up Period for less than one year.** **Note:** **i. It is recommended that the subject enters the extension study before the steroid dose is increased.** **ii. OPV116910 Individualized Follow-up Period Early Withdrawal visit assessments will be completed and OPV117059 extension study informed consent will be obtained before any study-related assessments are performed for the extension study. Some of the assessments performed for the OPV116910 Individualized Follow-up Period Early Withdrawal visit will be used for the extension**	

Section	Original Text	Changes	Rationale
		study screening assessments. All other extension study Screening/Baseline assessments will be performed at the time of disease flare/relapse in OPV116910 during the Individualized Follow-up Early Withdrawal visit. (Refer to the SPM for additional guidance.) **iii. Subjects are considered to be in the OPV116910 Individualized Follow-up Period until eligibility for the extension study is confirmed and the subject receives the first dose of ofatumumab SC at the Baseline (Week 0) visit in OPV117059.** **b. Subjects who withdraw from the OPV116910 Core Study Period.** **c. Subjects who do not consent to participation in the extension study.** **d. Extension study screen failures.** **After the first year of the OPV116910 Individualized Follow-up Period, subjects will remain in Individualized Follow-up for up to 1 more year until one of the following events occurs (whichever comes first):** • CD19+ B-cell counts or circulating IgG levels are ≥LLN or baseline levels (if <LLN) **(guidance will be provided within the [redacted] visit report, lab values will remain blinded)** • Criteria for withdrawal **from** the study are met • Two years after the last dose of investigational product. **Visits during the Individualized**	

Section	Original Text	Changes	Rationale
		Follow-up Period will be scheduled approximately every 12 weeks. Subjects should be instructed to contact the study site if a disease flare/relapse occurs between study visits.	
Section 3,1,2; Table 3-2	Subjects' daily oral steroid dose will be reduced by 1 dose level every 2 weeks (as illustrated in Table 3-2) until the onset of disease flare/relapse. For a subject who experiences disease flare/relapse, the prednisone/prednisolone dose will be increased by 1 to 4 levels per week until disease control is achieved (ie, no new lesions for 2 weeks); the prednisone/prednisolone taper will then be reinitiated after a 2-week period of disease control.	Subjects' daily oral steroid dose will be reduced by 1 dose level every 2 weeks (as illustrated in Table 3-2) until either the onset of disease flare/relapse **or a steroid dose of ≤10 mg/day has been achieved. When a steroid dose of ≤10 mg/day has been achieved, the prednisone/prednisolone dose may continue to be tapered (Table 3-2) or may be maintained at ≤10 mg/day according to the investigator's judgment.** For a subject who experiences disease flare/relapse, the prednisone/prednisolone dose will be increased by 1 to 4 levels per week until disease control is achieved (ie, no new lesions for ≥2 weeks); the prednisone/prednisolone taper will then be reinitiated after a 2-week period of disease control. **If the dose of prednisone/prednisolone is ≤10 mg/day at the time disease control is achieved, further steroid tapering attempts will be at the investigator's discretion.**	Clarification and consistency with the goal to eliminate or *reduce* the subject's steroid dose to ≤10 mg/day.
	Table 3-2	Table 3-2	
	Dose ~~for Post-~~Flare Taper	**Taper** Dose **after** Flare/**Relapse**	
	Footnote:	**Footnote**:	
	a. Prednisone/prednisolone is reduced by 1 dose level every 2 weeks, with the goal being elimination of prednisone/prednisolone.	**a.** Prednisone/prednisolone is reduced by 1 dose level every 2 weeks, with the goal being elimination of prednisone/prednisolone **or reduction of the dose to ≤10mg/day.**	
	c. ~~Once the dose is reduced to 10 mg, an attempt at reducing the steroid dose further need only be~~	c. In the event of a flare/relapse at a prednisone/prednisolone dose of ≤10 mg/day, the **steroid** dose will be	

Section	Original Text	Changes	Rationale
	~~attempted until the first flare/relapse occurs.~~ In the event of a flare/relapse at a prednisone/prednisolone dose of ≤10 mg/day, the dose will be ~~temporarily~~ increased in order to re-establish disease control (no new lesions for >2 weeks); after disease control is maintained, further steroid tapering attempts to <10 mg will be the investigator's discretion.	increased in order to re-establish disease control (no new lesions for ≥2 weeks). After disease control is maintained, **the steroid taper will be reinitiated if the dose of prednisone is >10 mg/day. If the dose of prednisone/prednisolone is ≤10 mg/day at the time disease control is achieved,** further steroid tapering attempts will be at the investigator's discretion.	
Section 3.1.3; Section 6.3.10.2; Table 6-6	Section 3.1.3: ~~Note:~~ Subjects who ~~are~~ HBsAg negative, anti-HBc positive, and HBV DNA negative (or if in Japan and HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive) must continue HBV DNA PCR monitoring at a minimum of every 12 weeks for 6 months after the last dose of study treatment	Section 3.1.3: Subjects who **were** HBsAg negative, anti-HBc positive, and HBV DNA negative **at screening** (or, if in Japan **and South Korea**, and HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive) must continue HBV DNA PCR monitoring **in the Individualized Follow-up Period** at a minimum of every 12 weeks for 6 months after the last dose of study treatment.	Clarification and consistency with the 1-year minimum requirement for the Individualized Follow-up Period for subjects not enrolling into the extension study. Alignment with country-specific exclusion criteria for South Korea as described in Appendix 2.
	Section 6.3.10.2: ** In **Japan**, if a subject is HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive, …* Subjects who are HbsAg negative, anti-HBc positive, and HBV DNA negative may be included in the study, but must undergo HBV DNA PCR monitoring at a minimum of every 12 weeks during the Treatment Period and for 6 months after the last dose.	Section 6.3.10.2: * In Japan **and Korea**, if a subject is HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive, …… Subjects who are HbsAg negative, anti-HBc positive **(or, if in Japan and South Korea, and HBsAg negative, anti-HBc (HBcAb) negative, but HBsAb positive)**, and HBV DNA negative may be included in the study, but must undergo HBV DNA PCR monitoring at a minimum of every 12 weeks during the Treatment Period and **every 12 weeks during the Individualized Follow-up Period** for 6 months after the last dose **of study treatment**.	
	Table 6-6: Additional for **Japan**:	Table 6-6: Additional for Japan **and South Korea**:	

Section	Original Text	Changes	Rationale
Section 3.2	NA	**The first year of the Individualized Follow-up Period is expected to provide adequate time for B-cell repletion in the majority of subjects. The second year will continue to monitor for B-cell repletion in the remaining subjects. The duration of remission and time to flare/relapse after completing treatment will also be assessed.**	Rationale for changes to Individualized Follow-up Period.
Section 4.2, Inclusion criterion #3	3. At least 1 previous episode of a failed steroid taper (ie, disease flare/relapse) at a prednisone/prednisolone dose >10 mg/day, ~~with~~ a Pemphigus Severity of Clinical Disease score of moderate (2) or severe (3) (may be historical/retrospective assessment [see Appendix 6 ~~and SPM for guidance~~]), where severity of disease at flare/relapse necessitated an increase ~~of >~~20 mg/day. ~~*Note: prednisone/prednisolone dose should not be increased for the sole purpose of entry into this study.*~~	3. At least 1 previous episode of a failed steroid taper (ie, disease flare/relapse) at a prednisone/prednisolone dose >10 mg/day. **The following criteria must have been met as evidence of disease severity at the time of the failed steroid taper**: a. A Pemphigus Severity of Clinical Disease score of moderate (2) or severe (3) (may be historical/retrospective assessment [see Appendix 6]). b. **Required a treatment change at the time of the failed steroid taper of at least one of the following**: i. **A steroid** increase **to ≥**20 mg/day **OR** **ii. The addition of immunosuppressive/ immunomodulatory agent/treatment OR** **iii. A dose increase of immunosuppressive/ immunomodulatory agent/treatment** **Note: For subjects on immunosuppressive/ immunomodulatory agents, please review restrictions under Exclusion Criterion 4, Medication and Other Treatment Restrictions Prior to Randomization (Section 4.3).**	"…A steroid increase to **≥**20 mg/day…" These changes are corrections. Investigators have reported that, in their clinical practice, failed steroid tapers may be treated by the addition of an immunosuppressive/ immunomodulatory agent/treatment or increasing the dose of an existing immunosuppressive/ immunomodulatory agent/treatment. These treatment changes may be made instead of, or in addition to, an increased steroid dose to ≥20 mg/day. This change will improve the feasibility of the study. Further guidance will be provided in the SPM.

Section	Original Text	Changes	Rationale
Section 4.2, Inclusion criterion #5; Section 4.3, Exclusion criterion #4; Section 4.3, Exclusion criterion #8; Table 5-2	Section 4.2, Inclusion Criterion #5: (Note: subjects who are on every-other-day dosing regimens need to change to a daily dosing regimen for ≥2 weeks during the Screening Period in order to qualify.)	Section 4.2, Inclusion Criterion #5: (Note: subjects who are on every-other-day dosing regimens need to change to a daily dosing regimen for ≥2 weeks during the Screening Period in order to qualify. **Subjects who are receiving a different systemic steroid for the treatment of pemphigus vulgaris need to switch to prednisone/prednisolone during the Screening Period**.)	The use of systemic steroids other than prednisone/prednisolone within 2 weeks prior to randomization and during the study will potentially confound the evaluation of the study endpoints. Subjects receiving another systemic steroid for the treatment of pemphigus vulgaris will need to switch to prednisone/prednisolone during the Screening Period. The treatment of another medical condition with prednisone/prednisolone is not allowed during the study as steroid dose tapering is a required part of the study.
	Section 4.3, Exclusion Criterion #4: NA	Section 4.3, Exclusion Criterion #4 *(column added to table of Medication and other Treatment Restrictions Prior to Randomization):* **2 weeks** **Systemic steroids (except for prednisone/prednisolone)**	
	Section 4.3, Exclusion Criterion #8: 8. Significant concurrent, uncontrolled medical condition…	Section 4.3, Exclusions Criterion #8: 8. Significant concurrent, uncontrolled medical condition… **This includes subjects who require any systemic steroid treatment for a concurrent medical condition (other than pemphigus vulgaris).** **Note: Subjects who require treatment with prednisone/prednisolone for conditions other than pemphigus vulgaris are not eligible for the study due to the prednisone/prednisolone taper schedule during the Core Study Period.**	
	Table 5-2: NA	Table 5-2 (*row added*): *Medication or Therapy:* **Systemic steroids[a] (see Section 3.1.1, Section 4.2, and Section 4.3.)** **Note:** • **Prednisone/prednisolone for the treatment of pemphigus vulgaris is allowed.**	

Section	Original Text	Changes	Rationale
		Washout Before Randomization: **2 weeks** Footnote: **a. Subjects who require treatment with prednisone/prednisolone or another systemic steroid for conditions other than pemphigus vulgaris are not eligible for the study. Subjects will be switched from other systemic steroids used for the treatment of pemphigus vulgaris to prednisone/prednisolone during the Screening Period. However, subjects who require the continued use of systemic steroids other than prednisone/prednisolone for the treatment of pemphigus vulgaris are not eligible for the study.**	
Section 4.3, Table for criterion #4	**8 weeks[a]** **18 months** Rituximab or other ~~anti- CD20 treatments~~	**8 weeks** **18 months** Rituximab or other **drugs affecting the number and function of B-cells**	Erroneous hyperscripted "a" deleted. Clarification.
Section 4.3, criterion #6	NA	• **** In South Korea, refer to Appendix 2 for additional country-specific screening procedures and exclusion criteria for TB and hepatitis.****	Added reference to Appendix 2 for additional country-specific procedures and exclusion criteria for South Korea.

Section	Original Text	Changes	Rationale
Section 4.4.3	NA	**If a subject experiences flares/relapses and the investigator determines it is in the best interest of the subject to initiate alternative disease modifying treatment that may affect B-cells, treatment with investigational product will be discontinued (if the subject is in the treatment phase) and the subject will be withdrawn from the study (ie, will not transition into Individualized Follow-up Period).** **A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for a subject not completing the study will be recorded in the case report form (CRF). If applicable, the investigator must document the reason for withdrawal of consent (if specified by the subject).** **If a subject withdraws from the study, the subject should complete an early withdrawal visit.**	Clarification that the subject may withdraw from the study at any time at his/her own request or at the discretion of the investigator.
Section 5.1.1	~~Ofatumumab SC (GSK1841157; human mAb ofatumumab injection for subcutaneous use) will be supplied by GSK as a liquid concentrate in a prefilled glass syringe with staked needle, stopper, and plunger, with a needle safety device. Initially, syringes containing 0.6 mL (60 mg) of concentration 100 mg/mL drug product will be provided.~~ ~~Placebo in prefilled glass syringes to match the ofatumumab syringes, will be made and supplied by GSK, using normal saline (sterile, pyrogen-free 0.9% NaCl) and filled to 0.6 mL in a prefilled glass~~	GSK will supply ofatumumab SC (**GSK1841157**; **human mAb ofatumumab injection for subcutaneous use**) in prefilled glass syringes containing 0.4 mL (20 mg) of concentration 50 mg/mL drug product and matching placebo prefilled glass syringes containing 0.4 mL of normal saline. Contents of the label will be in accordance with all applicable regulatory requirements.	The dilution method is no longer being used. Therefore, text pertaining to the dilution method has been deleted.

Section	Original Text	Changes	Rationale
	~~syringe with staked needle, stopper, and plunger, with a needle safety device.~~ Contents of the label will be in accordance with all applicable regulatory requirements… ~~For study centers initiated using the dilution method for study treatment preparation, an unblinded pharmacist (or appropriately-qualified designee) at the study center will prepare each dose via a dilution process according to the detailed instructions in the pharmacy manual. Briefly, the contents of 2 prefilled (0.6 mL) syringes (either 1 ofatumumab 60 mg syringe plus 1 placebo syringe or 2 placebo syringes) will be injected into a sterile vial and 0.4 mL of the resulting solution will be drawn into a new syringe to achieve the 20 mg ofatumumab (concentration 50 mg/mL) or placebo dose. Solutions obtained from the dilution method will be filtered through Kendall 5 micron filter needles prior to injection. The in-use time after the drug product is drawn into the syringe for administration should not exceed 2 hours; however, it is recommended that the drug product be administered immediately.~~ ~~In countries (including Japan) and/or study centers not using the dilution method to prepare study injections, Kendall 5 micron filter needles will not be used and there is no need to designate an unblended pharmacist (or appropriately-qualified designee) for drug preparation.~~ ~~When available,~~ GSK will supply ofatumumab SC in prefilled glass syringes containing 0.4 mL (20 mg) of concentration 50 mg/mL drug product and matching placebo prefilled glass syringes containing 0.4 mL of		

Section	Original Text	Changes	Rationale
	normal saline.		
Section 5.1.1	The injection site may be adjusted at investigator's discretion ~~if there are extensive abdominal lesions present~~.	The injection site may be adjusted at **the** investigator's discretion **based on medical judgment**.	There may be medical reasons other than extensive abdominal lesions that would necessitate an alternate injection site.
Section 5.1.1; Section 5.4	Section 5.1.1: ~~Detailed instructions related to the destruction of unused materials are provided in the pharmacy manual.~~	Section 5.1.1: NA	Details regarding product accountability and final disposition of unused study treatment are now located in the SPM. Additionally, the Material Safety Data Sheet will be located in the SPM.
	A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff in the ~~pharmacy manual~~.	A Material Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff in the **SPM**.	
	Section 5.4: ~~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 administered to study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.~~	Section 5.4: **The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). Further guidance and information for final disposition of unused study treatment are provided in the SPM.**	
	~~The designated pharmacist must keep drug inventory and accountability logs. The inventory will include details of ofatumumab SC and placebo received and dispensed (administered) to subjects, batch, and ID numbers. All unused prefilled syringes (supplied by GSK) must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site may destroy the syringes, unless otherwise instructed. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of ofatumumab SC and placebo~~		

Section	Original Text	Changes	Rationale
	~~received and dispensed must be reconciled.~~		
Section 5.2	The subjects and the investigative staff~~, except the unblinded pharmacist,~~ will be blinded to the treatment assignment.	All study staff (including the investigator, subinvestigators, other site staff, the subject, and Sponsor) will be blinded to the treatment allocated to individual subjects.	The dilution method is no longer being used so there is no longer a need for an unblinded pharmacist.
Section 5.3	~~Each site that prepares study injections using the dilution method must designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation.~~ All ~~other~~ study staff (including the investigator, subinvestigators, other site staff, the subject, and Sponsor) will be blinded to the treatment allocated to individual subjects. ~~In countries (including Japan) and/or study centers not using the dilution method to prepare study injections, there is no need to designate an unblinded pharmacist (or appropriately-qualified designee) for drug preparation.~~	All study staff (including the investigator, subinvestigators, other site staff, the subject, and Sponsor) will be blinded to the treatment allocated to individual subjects.	The dilution method is no longer being used so there is no longer a need for an unblinded pharmacist.
	~~After~~ the ~~Week 60 visit and each~~ Individualized Follow-up visit, the central laboratory (or designee) will notify the investigator whether or not a subject needs to remain in follow-up….	**At** the **end of the first year of OPV116910** Individualized Follow-up **and after each subsequent** visit **during the second year of Individualized Follow-up,** the central laboratory (or designee) will notify the investigator whether or not a subject needs to remain in follow-up…	For consistency with the changes to the Individualized Follow-up Period. Subjects who do not enter the extension study will enter the Individualized Follow-up Period for a minimum of 1 year. After the first year, the central lab will notify the investigator whether or not the subject needs to remain in the Individualized Follow-up Period (lab values will remain blinded).
Table 5-2	• alemtuzumab (Campath)	• alentuzumab (Campath; **MabCampath**)	Updated information

Section	Original Text	Changes	Rationale
Section 5.6.2; Section 11.2.1 (Appendix 2 Country-specific requirements: Japan)	Section 5.6.2: * *In* ***Japan****, ~~alemtuzumab (Campath) and~~ anti-CD4 treatments ~~are not approved~~.* Section 11.2.1 (Appendix 2): **Section 5.6.2 Prohibited Medications and Non-Drug Therapies** ~~In Japan, alemtuzumab (Campath) and anti-CD4 treatments are not approved. Immunoglobulin therapy is prohibited as an immunosuppressive agent.~~	* *In* ***Japan, market authorization has not been granted for*** *anti-CD4 treatments* ***for the treatment of pemphigus vulgaris****.*	Alemtuzumab is now approved in Japan. Statement regarding anti-CD4 treatments has been clarified. A separate statement regarding immunoglobulin therapy was not required as it is a prohibited medication in Table 5-2.
Section 5.7	Subjects completing the study and meeting entry criteria will be offered the option to participate in an extension study (OPV117059), which will start ~~after completion of~~ the Week 60 visit.	Subjects completing the study and meeting entry criteria will be offered the option to participate in an extension study (OPV117059), which will start **within 4 weeks of completing** the Week 60 visit **(see Section 3.1.2.1). Subjects who are in sustained remission on minimal steroid therapy at the Week 60 visit are eligible for the extension study only if a *disease flare/relapse is experienced during the first year* of the OPV116910 Individualized Follow-up Period, and they consent to participation in the extension study (see Section 3.1.3).**	Clarification of the period of time allowed between the Week 60 visit and the start of the extension study. To achieve consistency with the protocol change that subjects in sustained remission on minimal steroid therapy at the Week 60 Visit will enter the Individualized Follow-up Period.
Section 6	Table 6-1 present~~s~~…	Table 6-1 **and Table 6-2** present…	Clarification
Section 6	If a visit cannot be scheduled on the appropriate date, the visit should be re-scheduled as close as possible to the planned date, ideally within ±3 days.	If a visit cannot be scheduled on the appropriate date, the visit should be re-scheduled as close as possible to the planned date, ideally within ±3 days **during the Core Study Period (for visits from Week 2 through Week 60) and within ±7 days during the Individualized Follow-up Period.**	Clarification

Section	Original Text	Changes	Rationale
Table 6-1	b. If subject is not entering the extension study ~~and CD19+ B-cell counts and circulating IgG levels are <LLN at Week 60 (or early withdrawal visit)~~, the subject will transition into Individualized Follow-up (see Table 6 2). ~~Subjects requiring additional HBV testing will also return for follow up visits for 6 months after the last dose.~~	b. If the subject is not entering the extension study, the subject will transition into Individualized Follow-up **for a minimum of 1 year** (see Table 6-2). Footnote (*sentence added*): **f. HBV DNA—at Screening and every 12 weeks during the Treatment Period for applicable subjects (see Section 6.3.10.2).**	Consistency with the new requirement for a minimum 1-year Individualized Follow-up Period for subjects not enrolling into the extension study. Reminder added to footnote "f" for HBV DNA testing for applicable subjects. HBV DNA testing for 6 months after the last dose of study treatment, if applicable, will be performed during the Individualized Follow-up Period.
Table 6-1	NA	**Photography**[i] (*Time and Events Table shows that this is performed at the Baseline, Week 4, 8, and 12 clinic visits.)* Footnote: **j. Only sites preidentified to perform clinical photography. Subject participation is voluntary. Informed consent must be obtained before taking photographs for the study. The same area should be photographed at each visit.**	Clinical photography will be performed at selected study sites for use in future publications and/or presentations.
Table 6-1	~~Note: Visits from Week 2 through Week 60 to be scheduled within ±3 days of the specified time point. Visits during Individualized Follow up to be scheduled within ±7 days.~~	*Second row:* Treatment Period (56 Weeks) **(Visits ±3 days)**	The information has been rearranged. The visit window for the Treatment Period is now at the top of the table. The visit window for the Individualized Follow-up Period is in Table 6-2.

Section	Original Text	Changes	Rationale
Table 6-2	~~Clinic visits every 12 weeks[a] (eg, up to 8 visits total at approximately Weeks 72, 84, 96, 108, 120, 132, 144, & 156)~~ *Footnote:* a. Subjects entering the individualized follow-up period will continue to be monitored every 12 weeks, until CD19+ B-lymphocyte counts or IgG recover to LLN or to the ~~subject's~~ Baseline value (if <LLN) or if criteria for study withdrawal are met or for a ~~maximum of~~ 2 years after the last dose of ~~ofatumumab SC~~.	*Table updated to show assessments for each visit during the 2-year Individualized Follow-up Period.* Footnote: a. Subjects entering the Individualized Follow-up Period will continue to be monitored every 12 weeks **for a minimum of 1 year. (The following group of subjects may be in the Individualized Follow-up Period for <1 year: subjects who were in sustained remission on minimal steroid therapy at the Week 60 visit who enter the extension study after experiencing a disease/flare relapse during the 1st year of the Individualized Follow-up Period.) After the 1st year, subjects will remain in the Individualized Follow-up for up to 1 more year** until CD19+ B-cell counts or circulating IgG recover to ≥LLN or to the baseline values (if <LLN) or if criteria for study withdrawal are met or for 2 years after the last dose of **investigational product (whichever comes first).**	For clarity and consistency with the required 1-year minimum Individualized Follow-up Period for subjects not enrolling into the extension study.

Section	Original Text	Changes	Rationale
Table 6-2	~~Serious adverse events and adverse events of special interest~~	**Adverse Events (including SAEs and AEs of special interest)[b]** *(X for weeks 72, 84, 96, 108, Early WD)* **SAEs and AEs of Special Interest[b]** *(X for weeks 120, 132, 144, 156, Early WD)* ***Footnote:*** **b. AEs (including AEs of special interest) and SAEs will be collected during the first year of the Individualized Follow-up Period. Only SAEs and AEs of special interest will be collected during the second year of the Individualized Follow-up Period. SAEs assessed as related to study participation will be collected from the time a subject consents to participate in the study up to and including any follow-up contact.**	All AEs will be collected during the 1st year of the Individualized Follow-up Period in order to collect additional safety information in subjects who have discontinued or completed treatment with investigational product. During the 2nd year of Individualized Follow-up, SAEs and AEs of special interest will be collected.
Table 6-2	NA	**PV lesion mapping** *(Time and Events Table shows that this is required at each visit.)*	PV lesion mapping will be performed at every visit during the Individualized Follow-up Period to assess
[redacted]			
Table 6-2	Clinical chemistry ~~– only required for subjects meeting liver chemistry stopping/monitoring criteria~~	*Clinical chemistry* *(Time and Events Table shows that this is required at each visit.)*	Added to collect additional safety data during the Individualized Follow-up Period.
[redacted]			
Table 6-2	NA	**Human anti human antibody (HAHA)** *(Time and Events Table shows that this is required at Week 72 and Early Withdrawal.)*	Added to evaluate immunogenicity after discontinuation or completion of investigational product.

Section	Original Text	Changes	Rationale
Table 6-2	NA	*Footnotes:* Abbreviations: **AE=Adverse Event; PV=pemphigus vulgaris; SAE=Serious Adverse Event; WD=withdrawal**	Abbreviations added due to table visit and assessment changes.
		Note: Visits during Individualized Follow up to be scheduled within ±7 days.	Clarification regarding the visit window.
Section 6.1	NA	**** In South Korea, refer to Appendix 2 for additional screening assessments for TB.****	Added reference to Appendix 2 for additional country-specific assessments for South Korea.
Section 6.2.2	A flare/relapse is defined as new lesions that do not heal spontaneously within 1 week, or when there is an extension of lesions that were present at the randomization visit.	A flare/relapse is defined as **the appearance of ≥3** new lesions **within 1 month** that do not heal spontaneously within 1 week, or when there is an extension of lesions that were present at the randomization visit.	Correction for consistency between sections.
[redacted]			
Section 6.3.2.3	• Hepatitis B virus reactivation (see Section 6.3.10.2).	• Hepatitis B virus **infection or** reactivation (see Section 6.3.10.2).	Clarification
Section 6.3.5	…will require a specific death data collection tool to be completed.	…will require a specific death data collection tool to be completed **(eCRF page)**.	Clarification
Section 6.3.6	Pregnancy information will be collected from the start of study treatment ~~through the follow-up contact.~~	Pregnancy information will be collected from the start of study treatment **and until the end of the study**.	Clarification and consistency with the time period for collecting AEs, AEs of special interest, and SAEs.

Section	Original Text	Changes	Rationale
Section 6.3.7	SAEs and AEs of special interest will continue to be collected during the Individualized Follow-up Period.	**For subjects who enter the Individualized Follow-up Period, all AEs will continue to be collected during the first year of the Individualized Follow-up Period. During the second year of the Individualized Follow-up Period, only** SAEs and AEs of special interest will be collected. **For subjects transitioning into extension study OPV117059, AEs and SAEs that occur prior to the first dose of ofatumumab SC in OPV117059 will be collected in the OPV116910 eCRF.**	All AEs will be collected during the 1st year of the Individualized Follow-up Period in order to collect additional safety information in subjects who have discontinued or completed treatment with investigational product. Clarification regarding the collection of AEs for subjects who will be transitioning into the extension study.
Section 6.3.9.1	NA	**Section 6.3.9.1 Regulatory Reporting Requirements for SAEs**	Subheading has been added for clarity and ease in locating information.
Section 6.3.10.1	…in accordance with the [redacted] investigator manual and Protocol Time and Events Schedule (Table 6-1).	…in accordance with the [redacted] investigator manual and Protocol Time and Events Schedule (Table 6-1 **and Table 6-2**).	Clarification
Table 6-5	NA	**Serum hCG pregnancy testing (women of reproductive potential)[b]** *Abbreviation:* **hCG=human chorionic gonadotropin**	Correction
Table 6-5	**Note**: Refer to the Time and Events Schedule (Table 6-1)…	**Note**: Refer to the Time and Events Schedule (Table 6-1 **and Table 6-2**)…	Clarification
Table 6-5	a. ~~.After the Week 60 visit and all~~ Individualized Follow-up ~~visits~~, the central laboratory (or designee) will notify the investigator whether or not a subject needs to remain in Follow-up,…	a. …**At the end of the first year of Individualized Follow-up and after each subsequent visit during the second year of** Individualized Follow-up, the central laboratory (or designee) will notify the investigator whether or not a subject needs to remain in Follow-up…	For consistency with the changes to the Individualized Follow-up Period. Subjects who do not enter the extension study will enter the Individualized Follow-up Period for a minimum of 1 year. After the first year, the central laboratory will notify the investigator whether or not the subject needs to remain in the Individualized Follow-up Period (laboratory values will remain blinded).

Section	Original Text	Changes	Rationale
Section 6.8	NA	**6.8 Additional Assessments-Photography** **Clinical photography will be performed at selected study sites for publication and/or presentation purposes. Photographs will not be used in the evaluation of efficacy endpoints for the study. Subject participation in the photography portion of the study is voluntary. Separate subject informed consent and photographic release will be required. Photographs of a representative area containing pemphigus vulgaris lesions will be selected by the investigator or designee. The same area will be photographed at the clinic visits specified in Table 6-1. Additional details regarding clinical photography will be described in the SPM.**	Clinical photography will be performed at selected study sites for use in future publications and/or presentations.
Section 8.3.6.9	The analysis of safety data will use the Safety population. These data will not undergo any formal statistical analysis.	The analysis of safety data will use the Safety population. These data will not undergo any formal statistical analysis. **All safety endpoints will be presented by treatment phase and duration of follow-up, including the Individualized Follow-up Period. Safety summaries will be presented separately for the Core Study Period and Individualized Follow-up Periods. Core Study Period safety will be evaluated up to 4 weeks after the Week 60 visit or the first dose of ofatumumab in the OPV117059 extension study (for subjects who go into the extension study) whichever comes first, and AEs prior to that time will be included in the Core Study Period reports.**	Clarification of the presentation of safety data by study phase. Safety data for the Core Study Period will be evaluated up to 4 weeks after the Week 60 because subjects are allowed a 4-week window between the Week 60 visit and the Baseline visit (Week 0/first dose) in the extension study.

Section	Original Text	Changes	Rationale
Section 10	NA	**GlaxoSmithKline Document Number GM2008/00147/10. GSK1841157 Investigator's Brochure (IB). Version 08. 05 March 2015.** *Other slight revisions made to references as either corrections or clarifications.*	Clarification
Section 11.2.1 (Appendix 2- Country-specific requirements: Japan)	The following country-specific information and study conduct considerations for OPV116910 Protocol Amendment 5…	The following country-specific information and study conduct considerations for OPV116910 Protocol Amendment 5 **and Protocol Amendment 6…**	Updated information
	Section 9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process	**Section 9.2 Regulatory and Ethical Considerations, Including the Informed Consent Process**	
	The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No. 28 dated 27 March 1997)" and Article 14-3 and 80-2 of the ~~Pharmaceutical Affairs Law.~~	The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No. 28 dated 27 March 1997)" and Article 14-3 and 80-2 of the **Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.**	
	GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the ~~Pharmaceutical Affairs Law~~ before conclusion…	GSK will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the **Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics** before conclusion…	

Section	Original Text	Changes	Rationale
Section 11.2.2, (Appendix 2 – South Korea; with cross-references from applicable sections within body of protocol)	NA	Addition of county-specific requirements for South Korea: additional screening procedures and exclusion criteria specifications.	Protocol modifications and supplementary details requested during review by the Ministry of Food and Drug Safety.
Section 11.6 (Appendix 6-Pemphigus severity of clinical disease score)	*Column: Oral Scoring Rows: 2, Moderate activity, and 3, Severe activity:* …desquamative gingivitis…	*Column: Oral Scoring Rows: 2, Moderate activity, and 3, Severe activity:* …desquamative **(erosive)** gingivitis…	Clarification to facilitate translations.
Section 11.15 (Appendix 15-Protocol changes)	NA	**List of all changes in Protocol Amendment 6.**	

Protocol Amendment 7: 25 April 2016

Applicable to all countries and study centers.
At the time of this amendment, 35 subjects had been randomized in the study.

** OPV116910 Amendment 6 was not implemented at any study center. As a result, conduct of the study for all study centers transitioned from Amendment 5 directly to Amendment 7 (ie, nonconsecutive numbering) **

Section	Original Text	Changes	Rationale
Title page	NA	Protocol amendment number, date, and revision chronology.	Amendment 7
Protocol-specific definitions; Protocol summary, Study design; Section 3.1	If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until ~~either~~ the CD19+ B-cell counts ~~or~~ circulating IgG levels are ≥LLN or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first).	If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study will remain in an Individualized Follow-up Period until **both** the CD19+ B-cell counts **and** circulating IgG levels are ≥LLN or baseline levels (if <LLN) or until 2 years after the last dose of investigational product (whichever comes first).	Based on discussion with investigators, criteria for maintaining subjects in the Individualized Follow-up Period were modified to allow for improved safety monitoring following last dose of investigational product, while facilitating the exit of subjects from the study in order to progress to alternative treatment if needed.
Section 3.1, Figure 3-2	Meet any of these criteria: • CD19+ B-cells ~~or~~ IgG ≥LLN or baseline? • Meet other criteria for study withdrawal/exit? • 2 years after the last dose? AND HBV monitoring complete (if applicable)?	Meet any of these criteria: • CD19+ B-cells **and** IgG ≥LLN or baseline? • Meet other criteria for study withdrawal/exit? • 2 years after the last dose? AND HBV monitoring complete (if applicable)?	
Section 3.1.3	If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study (OPV117059) will remain in Individualized Follow-up until: • CD19+ B-cell counts ~~or~~ circulating IgG levels are ≥LLN or baseline levels (if <LLN)	If B-cell counts have not recovered by the Week 60 visit, subjects not entering the extension study (OPV117059) will remain in Individualized Follow-up until: • CD19+ B-cell counts **and** circulating IgG levels are ≥LLN or baseline levels (if <LLN)	

Section	Original Text	Changes	Rationale
Section 6, Table 6-2	a. Subjects entering the individualized follow-up period continue to be monitored every 12 weeks, until CD19+ B-lymphocyte counts or IgG recover to LLN ~~or~~ to the subject's Baseline value (if <LLN) or if criteria for study withdrawal are met or for a maximum of 2 years after the last dose of ofatumumab SC.	a. Subjects entering the Individualized Follow-up Period continue to be monitored every 12 weeks, until CD19+ B-lymphocyte counts **and** IgG recover to ≥LLN or to the subject's Baseline value (if <LLN) or if criteria for study withdrawal are met or for a maximum of 2 years after the last dose of ofatumumab SC.	Based on discussion with investigators, criteria for maintaining subjects in the Individualized Follow-up Period were modified to allow for improved safety monitoring following last dose of investigational product, while facilitating the exit of subjects from the study in order to progress to alternative treatment if needed.
Section 5.3	Sponsor unblinding for analyses will occur after all subjects have completed the Week 60 visit ~~or~~ been withdrawn from the treatment period (see Section 8.3.4).	Sponsor unblinding for analyses will occur after all subjects have completed the Week 60 visit, been withdrawn from the treatment period, **or the study has been terminated**.	Given the study had been terminated, the Sponsor unblinded subjects' randomized treatment assignments to provide information for the investigators' continued monitoring of their subjects.

Protocol Amendment 8: 05 Sep 2016

Applicable to all countries and study centers.
At the time of this amendment, 35 subjects had been randomized in the study.

Section	Original Text	Changes	Rationale
General	NA	From Section 1 through Section 9.9, did not abbreviate a term if it is used only once. Defined an abbreviation at the point of first use in the text. Defined abbreviations used in a table in a table footnote.	Treated Section 1 through Section 9.9 as the main body of the document when verifying abbreviation usage.
Title page	NA	Protocol amendment number, date, and revision chronology.	Amendment 8
Throughout	NA	All mentions of GlaxoSmithKline / GSK changed to Novartis. Legal registered and contact addresses updated.	Transition of protocol Sponsor
Title page; Sponsor information page; Protocol summary	NA	Novartis Study IDs added as follows: Core Study: OPV116910 (also known as COMB157J2301)	Transition of protocol Sponsor; Novartis study ID format required for Novartis administrative purposes. Novartis study IDs added at first usage in both protocol summary and main text; GSK ID only used at subsequent instances.
Study design; Section 3.1; Section 3.1.3	NA	Novartis Study IDs added as follows: Extension Study: OPV117059 (also known as COMB157J2301E1)	Transition of protocol Sponsor; Novartis study ID format required for Novartis administrative purposes. Novartis study IDs added at first usage in both protocol summary and main text; GSK ID only used at subsequent instances.

Section	Original Text	Changes	Rationale
Protocol-specific definitions; Protocol summary, Study design; Section 3.1; Figure 3-2, Section 3.1.3, Section 6, Table 6-2; Section 5.3	NA	Protocol Amendment 7 was incorporated in the full protocol document as part of the Amendment 8 updates because previously only a summary of changes version was available.	
Protocol Summary, Study Design; Section 3.1; Section 5.7	Subjects completing the study ~~and meeting entry criteria will~~ be ~~offered the option~~ to participate in an extension study (OPV117059), ~~which will start after completion of the Week 60 visit~~.	**As the ofatumumab development program in the indication PV has been terminated,** subjects completing the study **will no longer be eligible** to participate in the extension study (OPV117059). **Subjects who were enrolled in the extension study prior to program termination may remain in the extension study until exit criteria are met.**	Text was updated based on the ofatumumab development program in the indication PV having been terminated.
Section 6.3.6	To ensure subject safety, each pregnancy must be reported to ~~GSK~~ within ~~2 weeks~~ of learning of its occurrence.	To ensure subject safety, each pregnancy must be reported to **Novartis** within **24 hours** of learning of its occurrence.	Transition of protocol Sponsor
Section 6.3.9, Table 6-4	**Type of Event** / **Time Frame** Pregnancy / ~~2 weeks~~	**Type of Event** / **Time Frame** Pregnancy / **24 hours**	
Section 7	Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, ~~GSKDrug~~.	Adverse events and concomitant medications terms will be coded using the **Medical Dictionary for Regulatory Activities (**MedDRA**), the World Health Organization Drug Dictionary**, and an internal validated medication dictionary.	Updated to provide expanded MedDRA term at first use and to include the World Health Organization Drug Dictionary and to remove the GSKDrug specification.
Section 10	NA	Ofatumumab/OMB157/GSK1841157 Investigator's Brochure (IB). Version 09. Document number 090095a888b3fd50. 12 April 2016	Reference for ofatumumab Investigator's Brochure added to protocol body references in Section 10. Cross-references to the Investigator's Brochure hyperlinked in protocol body to the citation in the list of references in Section 10.

Section	Original Text	Changes	Rationale
Throughout	Investigator's Brochure	Investigator's Brochure **[Ofatumumab/OMB157/GSK1841157 Investigator's Brochure, 2016]**	Further detail and year added to Investigator Brochure references for clarity and consistency with format of other references.