Division: World Wide Development

Retention Category: GRS019
Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for OPV116910: 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

Compound Number: GSK1841157 / NCT01920477

Effective Date: [29-MAR-2018] Based on Protocol dated 28-SEP-2015 amendment 6

Description: Ofatumumab is a novel human IgG1k lytic monoclonal antibody (mAb) 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

Author's Name, Title and Functional Area:

[redacted]

Approved by:

[redacted] **Date**

[redacted] **Date**

Modification History

Date	Version	Details
07-Apr-2017	Final Draft	Final Draft version
29-Mar-2018	Amendment	Updated to detail about PK/PD/PGx analysis • PK data: Only PK Plasma trough concentration data will be summarized and listed on PK population. • PD data: The PD Biomarker data (B-Cell panel and Neutrophil counts data only) will be summarized by Sex and time point. Other PD endpoints analysis as mentioned in section 2.2.6 Pharmacodynamic endpoints ('Time to repletion of CD19+ B-cell...' and 'B-cell depletion and repletion…') will not be performed. • PGx data: Pharmacogenetics results data not available and beyond the scope of this RAP. Hence no Pharmacogenetics analysis can be performed. 'Section 15 Pharmacogenetic data analyses' removed.

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ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
BLC	B-lymphocyte chemokine
BMI	body mass index
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
cm	centimeter
C_{max}	maximum of ofatumumab concentration
CMH	Cochran-Mantel-Haenszel (test)
dL	deciliter
[redacted]	[redacted]
DNA	deoxyribonucleic acid
Dsg	desmoglein
ECG	echocardiography
eCRF	electronic case report form
HAHA	human anti-human antibody
hsCRP	high sensitivity C-reactive protein
IDMC	independent data monitoring committee
IP	investigational product
ITT	Intent-to-Treat (population)
IV	intravenous
IVR	interactive voice response
kg	kilogram
kg/m^2	kilograms per meter-squared
LLN	lower limit of normal (reference range)
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
PCR	polymerase chain reaction
PD	pharmacodynamic
[redacted]	[redacted]
PGx	pharmacogenetics
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PP	Per Protocol (population)
PT	preferred term

PV	pemphigus vulgaris
RBC	red blood cells
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
SI	International System of Units
SOC	system organ class
SR	sustained remission
TLF	tables, listings and figures
[redacted]	[redacted]
UK	United Kingdom
US	United States
WBC	white blood cells

1. INTRODUCTION

At the time of SAP finalization, the sponsorship of the study was transferred from GSK to Novartis. All the core analyses were kept as per the original protocol analysis plan. However, because the study was terminated early with a limited sample size (total of 69 patients), the analyses plan was reduced or simplified. Due to the low sample size all subgroup analyses were removed and the multiplicity procedure omitted. All statistical tests will be performed at the two-sided 5% level.

Because advanced versions of the SAP and table/listing/figure documents already existed, the format of these documents where not changed to Novartis templates. All Table/ listings/ figures will follow Novartis conventions for outputs for a Novartis clinical study report.

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.

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 IgG4 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 to approximately 5% to 15% [Robinson 1997; Langan 2008]. An optimal steroid–sparing agent has not yet been identified, due in part to the paucity of randomized controlled studies conducted to date.

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 subjects 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 (Study OFA110867) and repeat-dose administration to subjects with RRMS (Study OMS112831).

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 suites), 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.

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. That is a separate study which will not be considered in this SAP. Whatever the data collected for study (OPV117059) will be handled separately.

1.5. Investigational Product

Initially, syringes containing 0.6 mL (60 mg) of concentration 100 mg/mL drug product was 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 according to detailed instructions. The 60 mg ofatumumab syringes was diluted using placebo syringes to achieve the 20 mg ofatumumab (concentration 50 mg/mL) dose.

When available, GSK supplied 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.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objective

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 PV.

2.1.2. Secondary Objectives – Efficacy and Pharmacodynamic

The secondary efficacy and pharmacodynamic (PD) objectives of the study include:

- 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.

2.1.3. Secondary Objectives – Pharmacokinetic

The secondary pharmacokinetic (PK) objective of the study is to assess the population pharmacokinetics of ofatumumab SC.

2.1.4. Secondary Objectives - Safety

- To evaluate the immunogenicity of ofatumumab SC.
- To evaluate the safety and tolerability of ofatumumab SC.

[redacted]

[redacted]

2.2. Study Endpoint(s)

In the discussion of study endpoints, please note the following:

- *Minimal steroid therapy* is defined as an oral prednisone/prednisolone dose of ≤10 mg/day.
- *Remission* is defined as the absence of new or nonhealing (established) lesions for ≥8 weeks (Note: Subjects with existing, healing lesions and no new lesions for ≥8 weeks may be considered in remission.).
- *Remission on minimal steroid therapy* is defined as the absence of new or nonhealing (established) lesions while on an oral prednisone/prednisolone dose of ≤10 mg/day for ≥8 weeks.
- *Sustained remission* (SR) is defined as the absence of new or nonhealing (established) lesions for ≥8 weeks that is sustained until Week 60.
- *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.
- *Disease Control* is defined as no new lesions for ≥2 weeks [Murrell 2008]

2.2.1. Co-Primary Efficacy Endpoints

Some of the analysis bullet points described in the original protocol is removed as requested by Novartis (section 2.2.2 - 2.2.6).

Two co-primary efficacy endpoints will be evaluated:

- Time to 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 (established) 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).

2.2.2. 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 (i.e. proportion of subjects achieving sustained remission).
- 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 appear within 1 month 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. For analysis purposes, "1 month" is assumed to be 30 days and "1 week" is assumed to be 7 days.
- 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.
- Cumulative dose of corticosteroids.

[redacted]

2.2.4. Safety Endpoints

- All AEs
- Frequency of serious adverse events (SAEs).
- Change from Baseline in vital signs.
- Change from Baseline in laboratory (hematology, chemistry, and urinalysis) parameters.
- Immunogenicity as measured by the incidence, titer, and type of human anti-human antibody (HAHA) immune response.

2.2.5. Pharmacokinetic Endpoints

- Plasma (trough) concentrations of ofatumumab.

2.2.6. 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 ≥ the lower limit of the normal (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

2.3. Statistical 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.

3. 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 Core Study Period consisting of a Screening Period (lasting up to 12 weeks), a 56-week Treatment Period, a 4-week Follow-up visit (Week 60). The Core Study Period is followed by an Individualized Follow-up Period which may last for up to 2 years (depending on time to B cell/IgG repletion). In the Core Study Period, 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. After Week 60, subjects who do not transition into the Extension Study (OPV117059) and have not achieved B Cell/IgG repletion, will return to the clinic every 12 weeks for individualized follow-up. It is anticipated that total duration of participation in this study will be approximately 72 weeks (1.4 years) for subjects who exit the study at Week 60, and up to 184 weeks (3.5 years) for subjects who enter the Individualized Follow-up Period.

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.

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). Individualized Follow-up visits will be scheduled every 12 weeks. Subjects who withdraw from treatment will also enter the Individualized Follow-up Period, unless the subject also withdraws consent.

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 PML will go through independent PML adjudication and an opinion will be provided to the sponsor.

3.1. Randomization, Stratification and Blinding

Subjects who meet all eligibility criteria will be randomized 1:1 to receive either ofatumumab SC at a dose of 20 mg or placebo; all doses of investigational product will be administered at the study site 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.

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.

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 (which includes the investigator, subinvestigators, other site trial staff, the subject, and Sponsor) will be blinded to the treatment allocated to individual subjects.

The blinded study treatment assignments for individual subject will be maintained by a central interactive voice response (IVR) system. Emergency unblinding will be available via the central IVR system.

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.

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.

The blinded study treatment assignments for individual subjects will be unblinded to the blinded study teams at [redacted] Novartis once the database has been frozen once all subjects have completed the Week 60 Follow-up Visit or have discontinued from the treatment period. Investigators and study subjects will remain blinded to the study treatment assignments until conclusion of the Individualized Follow-up Period.

Randomization and unblinding information will be presented in a data listing.

3.2. Screening Period

A Screening Period of up to 12 weeks will allow subjects to achieve disease control (i.e., 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.

3.3. 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.

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 discussed in Section 10.6) 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 [Murrell 2008]). The prednisone/prednisolone taper will then be reinitiated after a 2-week period of disease control. Once the dose is reduced to 10 mg, an attempt at reducing the steroid taper further is made until the first flare/relapse occurs. After the first flare/relapse at or below 10 mg prednisone/prednisolone, further steroid tapering attempts will be made at the investigator's discretion based on the subject's clinical status.

3.4. Follow-up Period and Individualized Follow-up Period

Subjects are 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 will remain in Individualized Follow-up 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). 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, Week 60 study assessments will be completed before the first dose of ofatumumab SC in the extension study. Assessments from Wk 60 may be utilized to confirm subject eligibility for entry into the extension study.

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 polymerase chain reaction (PCR) monitoring at a minimum of every 12 weeks for 6 months after the last dose of study treatment.

3.5. Pharmacokinetic and Pharmacokinetic Substudy

The protocol planned to have a substudy to determine the pharmacokinetics and pharmacodynamics of ofatumumab SC in subjects with PV. The substudy was planned to be conducted at selected study centers and planned to enroll approximately 25 subjects. Subject participation in the substudy was optional and required subject informed consent. A subject was enrolled in the primary study irrespective of whether or not he/she choose to participate in the substudy.

4. PLANNED ANALYSES

4.1. Interim Analyses

There will be no interim analysis as planned in the protocol due to study early termination. This SAP serves only for the final analysis.

4.2. Final Analysis

The study was terminated early and the final analysis will be conducted on the available data.

5. SAMPLE SIZE CONSIDERATIONS

Due to early termination of the study, the sections on sample size assessment in the protocol (sample size assumptions, sample sensitivity, and blinded sample size re-

estimation) are not applicable. They will not be considered in the SAP for final analysis. A total of 69 patients were randomized to this study.

6. ANALYSIS POPULATIONS

6.1. Screening Failure Population

The number of subjects screened and the number of subjects who failed screening will be summarized.

The Screening Failure population will include all screened subjects who fail all the screen procedures or criteria. This will be the population used for the listing of screening failure reasons.

6.2. Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects regardless of whether or not they received a dose of investigational product (IP). This will be the primary population used for the efficacy analyses.

In the event of a discrepancy between the treatment assigned at randomization and the actual treatment received, subjects will be analyzed according to the treatment to which they were randomized.

6.3. Per Protocol (PP) Population

The PP population will consist of those members of the ITT population who have no major protocol deviations. Throughout the study, protocol deviations will be identified, tracked and reviewed by the clinical management team. Prior to unblinding, a list of rules will be developed to specify what classes of deviations will be considered to be major deviations, and thus, result in exclusion from the PP population.

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 co-primary efficacy endpoints and any key secondary efficacy endpoints described in Section 11.

In the event of a discrepancy between the treatment assigned at randomization and the actual treatment received, subjects will be analyzed according to the treatment they actually received for the majority of the 56-week Treatment Period.

6.4. Safety Population

The primary population for safety analyses will be the safety population, which will consist of all subjects who were randomized and were administered at least 1 dose of IP.

In the event of a discrepancy between the treatment assigned at randomization and the actual treatment received, subjects will be analyzed according to the treatment they actually received for the majority of the 56-week Treatment Period.

6.5. Pharmacokinetic Population

The PK population will include all subjects in the ITT population providing at least one analyzed PK sample.

In the event of a discrepancy between the treatment assigned at randomization and the actual treatment received, subjects will be analyzed according to the treatment which they actually received.

6.6. Pharmacogenetic Population

The Pharmacogenetic (PGx) 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.

In the event of a discrepancy between the treatment assigned at randomization and the actual treatment received, subjects will be analyzed according to the treatment they actually received for the majority of the 56-week Treatment Period.

7. TREATMENT COMPARISONS

7.1. Primary Comparisons of Interest

The primary comparisons of interest for this study are:

- ofatumumab SC versus placebo on time to SR on minimal steroid therapy and
- ofatumumab SC versus placebo on duration of remission on minimal steroid therapy.

7.2. Data Display Treatment and Other Sub-group Descriptors

Study treatments will be presented in all tables, listings and figures (TLFs) in the following order: Ofatumumab SC, Placebo.

All tables and figures presenting primary and secondary analysis results will include subgroup results for the stratification factors baseline prednisone/prednisolone dose [<60 mg, ≥60 mg] and disease duration [≤1 year, >1 year].

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All analyses will be conducted using SAS Version 9.2 or higher.

8.1. Multicentre Studies

Since too few subjects were randomized per sites, no region will be defined and region will not be used as stratification factor in any analysis.

8.2. Other Strata and Covariates

The study randomization is stratified by disease duration [≤1 year, >1 year] and baseline prednisone dose [<60 mg, ≥60 mg].

The randomization strata of disease duration and baseline prednisone dose will be included in the base model for the analysis of the co-primary efficacy endpoints. Due to smaller sample size in the analysis, we will remove one or both strata from the analysis model if the model does not converge.

In addition to the co-primary endpoints, baseline prednisone/prednisolone dose and disease duration will be used to stratify all secondary efficacy analyses.

8.3. Multiple Comparisons and Multiplicity

Because the study is terminated early, all endpoints will be tested at two-sided 5% level of significance and no adjustments will be made for multiplicity. Nominal p-values will be presented for each analysis.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

9.1.1. Premature Withdrawal

The reasons for subject withdrawal from the study will be recorded. Subjects who are withdrawn will not be replaced.

9.1.2. Missing Data

9.1.2.1. Co-primary Efficacy Endpoints

The co-primary efficacy endpoint of time to SR on minimal steroid therapy will be analyzed using the ITT. Subjects who discontinue from the study before the end of the study (Wk 60), or reach their last planned treatment visit without achieving SR on minimal steroid therapy, will be censored in the analysis at their last visit. 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.

9.1.2.2. Remission

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

9.1.2.3. Concomitant Medications

Partial dates will be imputed for medication start dates in order to determine if a medication is prior or concomitant. Imputed dates will be kept in the final derived datasets. The start and stop dates as reported in the electronic case report form (eCRF) will be presented in the data listings.

Partial or missing medication start dates will be handled as follows:

- If a day is missing, then the day will be set to the first day of the month.
- If a day and month is missing and the year is non-missing, then the date will be set to January 1st.
- If the stop date for a medication is on or after the date of the first dose of study medication and no start date is reported, it will be assumed that the medication was ongoing from prior to the start of IP.

Partial or missing medication stop dates for medications that are not ongoing will be handled as follows:

- If a day is missing, then the day will be set to the last day of the month.
- If a day and month are missing and the year is non-missing, then the date will be set to December 31st.
- If the start date for a medication is during the pre-therapy or on-therapy periods (defined in Section 9.3.2) and no stop date is reported, it will be assumed that the medication use was ongoing throughout the on-therapy and follow-up/individualized follow-up periods.

9.1.2.4. Adverse Events

Partial dates will be imputed for adverse event start dates. Imputed dates will be kept in the final derived datasets. The start and stop dates as reported in the electronic case report form (eCRF) will be presented in the data listings.

Partial or missing AE start dates will be handled as follows:

- If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
- If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
  - If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

  - Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

- If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
  - If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
  - Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
- If the AE start date year value is equal to the treatment start date year value:
  - And if the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
  - Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
  - Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

Any AE with a missing start date will be considered a treatment emergent event, as defined in Section 9.3.2.

- Partial or missing AE stop dates will be handled as follows:
- If a day is missing, then the day will be set to the last day of the month.
- If a day and month are missing, then the date will be set to December 31st.
- However, if the imputation results in a date that is after the date of the last dose of study treatment, then the date of the last dose will be used as the imputed AE stop date.

Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

Imputed dates will be kept in the final derived datasets. The start and stop dates as reported in the eCRF will be presented in the data listings.

9.1.2.5. Historical Information

For a stand-alone date of historical information (i.e. date of PV symptom onset, date of PV diagnosis, date of most recent failed steroid taper), a date with a missing day and month will be imputed as June 30th of the year. If the month is present but the day of the month is missing, then the day of the month will be imputed to be the 15th of the month.

9.1.3. Laboratory data

Some subjects may have the lab results values below the instrument detectable range like values with ‘<x.x' or '<x’. For such cases, the numeric values will be set as being half of

the instrument detect range. i.e., If the lab result value is “<14” then the numeric result value will be set to 7.

In some cases subjects may have the values above the instrument detectable range; like '>x.x'. In such cases the character value will just be set to numeric value after removing the ‘>’ prefix. i.e., If the lab result value is “>100” then the numeric result value will be set to 100.

9.2. Derived and Transformed Data

9.2.1. Change from Baseline

The baseline value for an assessment is defined as the last non-missing value before the start of treatment. Change from Baseline is defined as the post-baseline value minus the baseline value for the given assessment. If either the baseline or post-baseline value is missing then the change from baseline value will also be missing.

9.2.2. Race

Using nine standard race categories in the eCRF, subjects are asked to provide all geographic ancestry (i.e. race) to which they identify.

These race categories include:

1. African American /African Heritage
2. American Indian or Alaska Native
3. Asian – Central/South Asian Heritage
4. Asian – East Asian Heritage
5. Asian – Japanese Heritage
6. Asian – South East Asian Heritage
7. Native Hawaiian or other Pacific Islander
8. White – Arabic/North African Heritage
9. White – White/Caucasian/European Heritage

Race will be summarized in the demography table for ITT population.

9.2.3. Time Since Pemphigus Vulgaris Symptom Onset and Diagnosis

The time (in years) since PV symptom onset is defined as: (date of randomization – date of PV symptom onset)/365.25.

The time (in years) since PV diagnosis is defined as: (date of randomization – date of PV diagnosis)/365.25.

PV history will be summarized in a table as per section 10.8.

9.2.4. Time Since Most Recent Failed Steroid Taper

The time (in years) since the most recent failed steroid taper that resulted in a disease flare/relapse at a prednisone/prednisolone dose >10 mg/day is defined as: (date of randomization – date of most recent failed steroid taper)/365.25.

9.2.5. Time to Remission on Minimal Steroid Therapy

Time to remission on minimal steroid therapy (in days) is defined as: ([date 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] – [date of randomization]) + 1 day. For subjects who experience more than one period of remission on minimal steroid therapy (i.e. a subject went into remission, then relapsed, and then went into remission again) time to remission on minimal steroid therapy is derived using a subject's first period of remission.

9.2.6. Time to Initial Flare/Relapse

Time to initial flare/relapse (in days) is defined as: [(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 - date of randomization] + 1 day.

9.3. Assessment Windows

9.3.1. Study Day

When study day is used for display or in comparisons, the following algorithm will be used:

- study day = date of assessment - date of first dose + 1, if date of assessment ≥ first dose date
- study day = date of assessment - date of first dose, if date of assessment < first dose date.

Note that the date of first dose is Day 1 and the day before the date of first dose is Day -1 (there is no Day 0).

9.3.2. Therapy Periods

For classifying AEs, infections, injection site reactions, cardiac events, liver events, medications, and non-drug therapies, the therapy periods will be defined as:

- **Pre-therapy:** If the onset date of the event is before the start date of study medication, the event will be considered pre-therapy. If the onset date of the event is on the start date of study medication, the event will be considered as on-therapy.
- **On-therapy (Treatment-emergent):** If the onset date of the event is on or after the start date of study medication and on or before 4 weeks after the date of last dose, the event will be considered on-therapy.

- **Follow-up:** For all subjects who do not enter the Individualized Follow-up Period, if the onset date of the event is after 4 weeks after the date of last dose, the event will be considered a follow-up event.

- **Individualized Follow-up:** For all subjects identified as entering the Individualized Follow-up period, events with an onset date after 4 weeks after the date of last dose will be considered individualized follow-up events.

9.3.3. Visit Slotting Algorithm

For all safety and efficacy parameters to be summarized or analyzed by visit, data records will be slotted to one of the protocol specified visits using the following algorithm

a) Determine the therapy period and study day for all records using the algorithms from Section 9.3.1 and Section 9.3.2.

b) For all records (including unscheduled visit records, early withdrawal records and repeat visit records), use the therapy period and study day determined above with the slotting intervals in the analysis visit window table below to slot the record to the appropriate analysis visit.

   - For records determined to be during the pre-therapy period, the analysis visits will be based on the nominal visits recorded in the eCRF. The Baseline analysis visit will be assigned based on the study day slotting intervals as shown in the table below.

   - For records determined to be during the on-therapy period, use the study day with the slotting intervals in the table below to assign the records to the appropriate on-therapy analysis visit.

   - For records determined to be during the follow-up period, use the study day with the slotting intervals in the table below to assign the records to the appropriate follow-up period analysis visit.

   - For records determined to be during the individualized follow-up period, use the study day with the slotting intervals in the table below to assign the records to the appropriate individualized follow-up period analysis visit.

Table 9-1 Analysis Visit Windows

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Screening	-84 to -4	Not applicable
Baseline (Week 0)	1	-3 to 1 days
Week 2	15	2 to 22 days
Week 4	29	23 to 36 days
Week 6	43	37 to 50 days
Week 8	57	51 to 64 days
Week 10	71	65 to 78 days
Week 12	85	79 to 92 days
Week 14	99	93 to 106 days
Week 16	113	107 to 120 days
Week 18	127	121 to 134 days

Scheduled Visit	Target Study Day of Visit	Slotting Intervals
Week 20	141	135 to 148 days
Week 22	155	149 to 162 days
Week 24	169	163 to 176 days
Week 28	190	177 to 204 days
Week 32	218	205 to 232 days
Week 36	246	233 to 260 days
Week 40	274	261 to 288 days
Week 44	302	289 to 316 days
Week 48	330	317 to 344 days
Week 52	358	345 to 372 days
Week 56 *	386	373 to 400 days
Week 60** (End of Core Study Period) Subject has completed.	414	401 to 428 days

* Week 56 is the end of treatment visit for those subjects completing the study per protocol. For subjects who withdraw early from active treatment, the end of treatment visit will be assigned to an analysis visit based on the visit slotting algorithm using study day and therapy period.
** Week 60 is the follow-up visit for those subjects completing the study per protocol. Subjects completing the study and meeting all entry criteria will be offered the option to participate in an extension study, which will start after completion of the Week 60 visit.

For parameters that were not scheduled to be collected at all visits, yet values are available, the visit intervals defined in the table above will be used to slot records. As previously noted for the baseline record, the last non-missing value before the start of treatment will be used for analysis. For post-baseline records, for parameters collected multiple times within a slotting interval, the assessment taken closest to the target study day will be used for analysis/summarization.

10. STUDY POPULATION

10.1. Disposition of Subjects

The number of subjects screened and the number of screen failures with primary reason for screening withdrawal will be summarized for each treatment group and percentages will be based on the number of screened subjects. The subjects within each population (ITT, Per Protocol, Safety, PK and PGx) will be summarized in a separate table for each treatment group and percentages will be based on the number of subjects in the ITT population.

For the core study period (i.e. through the Week 60 visit or early discontinuation), a summary of the number and percentage of subjects randomized, treated, completed core study, discontinued from core study, primary reasons for reason for withdrawal from core period, reason for discontinuation due to protocol-defined stopping criteria and subjects who entered open-label extension will be summarized for each treatment group. Percentages will be based on the number of subjects in the ITT population.

A subject will be determined to have completed the core study period if they receive treatment with study medication through Week 56 and complete the Wk 60 Follow-up visit. Percentages will be based on the number of subjects in the ITT population.

The number and percentage of subjects who entered the Individualized Follow-up Period, completed the Individualized Follow-up Period and criterion upon which completion was based, discontinued from the Individualized Follow-up Period and the reason for discontinuation will be summarized for each treatment group. Percentages will be based on the number of subjects in the ITT population.

A summary of subjects randomized by analysis region, country, and site will also be provided by treatment group for the ITT population.

Screening failure details will be presented in a data listing for all subjects who were screening failures. Subject disposition data for the core study period and for the Individualized Follow-up Period and subject completion of Individualized Follow-up Period visits will be presented in data listings for the ITT population.

10.2. Protocol Deviations

Subjects who fail to fulfill any of the inclusion/exclusion criteria will be tabulated for each treatment group and listed for each subject in the ITT population.

Protocol deviations will be tracked by the clinical team on an on-going basis through the completion the individualized follow-up period (or early withdrawal from the study) for all subjects and will be listed by subject. The number and percentage of subjects with any protocol deviation and the number and percentage of subjects experiencing each protocol deviation category will be summarized for the ITT population.

Specific criteria for what constitutes a major protocol deviation (i.e. causing exclusion from the Per Protocol population) will be identified by the study team prior to study unblinding. The following criteria may be considered:

- Not meeting key inclusion/exclusion criteria
- Withdrawal criteria met but subject not withdrawn
- Taking prohibited concomitant medications
- Not being compliant with the study medication dosing schedule

Please refer to Section 6.3 for a discussion of protocol deviations as they pertain to the PP population.

The analysis sets and severity codes used in the trial programming are listed in below Table, which includes the analysis set codes 1-5 and the severity codes 0, 1, 5, 8 and 49 for the double-blind treatment period.

Table 10-1 The analysis populations and severity codes

Analysis set codes	**Deviation Severity Codes**		
1 = Screening Population 2 = Intent-to treat Population 3 = Per protocol Population 4 = Safety Population	0 = Exclude patient from all efficacy analyses 1 = Exclude patient from per-protocol analysis 8 = Exclude patient from all analyses		
	Deviation Severity Codes		
Analysis set (code)	**0**	**1**	**8**
Screening Population (1)	*Yes*	*Yes*	*No*
Intent-to-Treat population (2)	*No*	*Yes*	*No*
Per Protocol Population (3)	*No*	*No*	*No*
Safety Population (4)	*Yes*	*Yes*	*No*

Note: 'Yes' means include in the analysis population, 'No' means exclude from the analysis population.

The number and percentage of subjects with any major protocol deviation and the number and percentage of subjects experiencing each major protocol deviation category will be summarized for the ITT population. Major protocol deviations with deviation category and severity codes will be identified in the protocol deviations listing presented by subject for the ITT population.

10.3. Demographic and Baseline Characteristics

A summary of demographics and baseline information will be presented for each treatment group and for all subjects for the ITT population.

The demographic characteristics consist of age at randomization (years), sex, race, ethnicity, geographic ancestry and fertility status. A subject's age in years is calculated as (randomization date – date of birth)/365.25. A subject's race is determined as described in Section 9.2.2.

The baseline characteristics consist of baseline height (cm), baseline weight (kg), baseline body mass index (BMI) (kg/m^2), disease duration, and baseline prednisone dose. Body mass index, calculated as (body weight in kilograms) / (height in meters)^2 is collected in the eCRF.

Age at randomization (years), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of subjects by age category (<65, ≥65 years) and (<Median, ≥Median), sex (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino), disease duration (≤1 year, >1 year), and baseline prednisone dose (<60 mg, ≥60 mg) will also be reported. Percentages will be based on the total number of subjects in the population being summarized.

Subject demographic and baseline characteristics, including geographic ancestry (from which race is derived), will be presented in a listing for all subjects in the population

being summarized. The number and percentage of subjects for each collected race category will be presented along with the demographic characteristics for each treatment group and for all subjects for the population being summarized.

A summary of substance (tobacco) use (both categorical and quantitative), collected at Screening, will be presented as well as a by-subject listing of data on tobacco use for all subjects in the ITT population. A subject's smoking pack-years is calculated as (number of cigarettes smoked per day/20) * (number of years smoked).

Smoking status updates reported at Baseline, Week 24 and Week 60/Early Withdrawal will be summarized by visit for all subjects in the ITT population and will be presented in a data listing.

For subjects who experience a liver event, alcohol use (categorical) and the volume of consumption (quantitative) will be summarized and presented in a data listing with the liver event data for the ITT population. In the United States (US): 1 unit of alcohol = 1.5 oz hard liquor, 1 beer, 4 oz wine (or metric equivalent). In the United Kingdom (UK): 1 unit of alcohol = 1 measure of spirits, 1/2 pint beer, 1 small glass of wine (125mL) (or metric equivalent).

10.4. Concomitant Medications

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 specified in the protocol.

Concomitant medications terms will be coded using an internal validated medication dictionary, GSKDrug and will be reported by Anatomical Therapeutic Chemical (ATC) class and medication. GSKDrug Version 1.2 or higher, that covers all approved drugs in studies where Japan is participating, will be referenced.

As discussed in Section 9.3.2, all medications will be assigned to a therapy period and a medication will be counted in each period during which it is used.

All concomitant medications will be presented in a data listing for the ITT population. This listing will indicate in which study period(s) the concomitant medications were taken. A separate data listing will be provided for use of steroids medications only.

10.5. Acetaminophen and Antihistamine Use

As noted above, medication terms will be coded using an internal validated medication dictionary, GSKDrug. Pre-dose acetaminophen and antihistamine use is specifically noted in the eCRF. Post-dose use subsequent to the baseline visit that is not administered at the study site is collected in the eCRF with all other concomitant medications. Post-dose use at the baseline visit that is administered at the study site will be listed for the ITT population.

Pre-dose acetaminophen and antihistamine use will be presented in a data listing for the ITT population.

10.6. Steroid Taper

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 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 (i.e, no new lesions for ≥2 weeks); the prednisone/prednisolone taper will then be reinitiated after a 2-week period of disease control.

Table 10-2 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 [c]	15	17.5	20	25	
10 [c]	7.5	12.5	15	17.5	20	
7.5	5	10 [c]	12.5	15	17.5	
5	2.5	7.5	10 [c]	12.5	15	
2.5	0	5	7.5	10 [c]	12.5	
0	0	2.5	5	7.5	10 [c]	

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 reestablish 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.

A steroid administration log capturing the tapering of the medication will be collected in the eCRF.

A by-visit summary of oral prednisone/prednisolone dose and a summary of each subject's cumulative oral prednisone/prednisolone dose will be presented using descriptive statistics for each treatment group. Additionally, since a subject's steroid dose at each visit is dependent upon his/her stable dose achieved during Screening, descriptive statistics will be presented for the oral prednisone/prednisolone dose at each visit for each stable dose level of oral prednisone/prednisolone achieved during Screening for each treatment group.

Tables summarizing oral prednisone/prednisolone dose will be presented for the ITT population.

The information collected in the steroid taper log will be presented in a data listing for the ITT population.

10.7. Medical History

Any significant medical conditions affecting the subject in the past 5 years and whether the condition occurred in the past or is a current condition will be recorded in the eCRF.

Medical history information will be presented in a data listing for the ITT population.

10.8. Pemphigus Vulgaris History

Details of the subject's PV history will be collected in the eCRF. The time (in years) since PV symptom onset, the time (in years) since PV diagnosis, the number of flares/relapses since diagnosis and the time (in years) since the subject's most recent failed steroid taper that resulted in a disease flare/relapse at a prednisone/prednisolone dose >10 mg/day will be summarized using descriptive statistics for each treatment group for the ITT population. The time since PV symptom onset and PV diagnosis are defined in Section 9.2.3. The time since the most recent failed steroid taper is defined in Section 9.2.4.

PV history information will be presented in a data listing for the ITT population.

11. EFFICACY ANALYSES

Baseline prednisone/prednisolone dose and disease duration will be used to stratify all primary and secondary analyses.

Summary statistics will be provided for the primary and key secondary variables

As noted in Section 8.2, covariate analyses will be performed on the co-primary efficacy 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. 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.

The primary analysis for the co-primary endpoints will use the ITT population. The ITT population will also be used for all secondary and other efficacy analyses.

If the PP population comprises between 50% and 95%, inclusive, of the ITT population, it will be used for a confirmatory analysis of the co-primary endpoints and the key secondary efficacy endpoints identified above.

The primary efficacy and key secondary efficacy endpoint parameters will be presented in a data listing for the ITT population.

11.1. Primary Efficacy Analyses

11.1.1. Time to SR on Minimal Steroid Therapy by Week 60

The co-primary efficacy endpoint of time to SR on minimal steroid therapy by Week 60 (as defined in Section 2.2.1) 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) and who have not achieved remission upon discontinuation will be censored at the time they discontinued. Subjects who reach Week 60 without remission will be censored at the date of their last visit.

For subjects achieving remission, time to SR on minimal steroid therapy will be derived as: [(the date on which 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) – (the date of randomization)] + 1 day.

A summary table presenting the Kaplan-Meier estimates for the time to SR and 95% CI at Week 4, week 8, Week 12 etc. for each of the treatment groups and p-value for the treatment difference, using the 2-sided log-rank test indicated above will be presented for the ITT population and PP population (if criteria are met as discussed in Section 11).

For the covariate analysis, a summary table computing hazard ratio and 95% CI for the hazard ratio and the p-value using the Cox proportional hazards model discussed in Section 8.2, will be presented for the full model for the ITT population.

A Kaplan-Meier plot of time to SR on minimal steroid therapy will be constructed for each treatment group for the ITT population.

11.1.2. Duration of Remission on Minimal Steroid Therapy by Week 60

The co-primary endpoint of duration of remission on minimal steroid therapy will be analyzed using a rank ANCOVA [Stokes 2000], with treatment as a main effect, and baseline prednisone/prednisolone dose and disease duration strata as covariates. If a subject discontinues the study prior to Week 60, the subject will be considered as not in remission from the date of the last known study visit until Week 60.

For subjects who complete the study without experiencing any periods of remission, duration of remission on minimal steroid therapy will be 0 days.

One Period of Remission

For subjects who experience one period of remission on minimal steroid therapy that:

- Is continuing at the Week 60 study visit (or early discontinuation):

- Duration of remission on minimal steroid therapy will be derived as: [(the date of the Week 60 study visit/date of last known visit) - (the date on which an absence of new or nonhealing lesions occurs while the subject is on a prednisone/prednisolone dose of ≤10 mg/day for ≥8 weeks)] + 1 day.

- Relapses/flares prior to the Week 60 study visit (or early discontinuation):
  - Duration of remission on minimal steroid therapy will be derived as: [(the date on which flare/relapse occurs) - (the date on which an absence of new or nonhealing lesions is found while the subject is on a prednisone/prednisolone dose of ≤10 mg/day for ≥8 weeks)].

Note that for periods of remission that end with relapse/flare, "+ 1 day" is not included in the calculation since the end date is the date on which relapse/flare occurs so the subject is not considered to be in remission on that day.

More Than One Period of Remission

For subjects who experience more than one period of remission on minimal steroid therapy (i.e. 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 sum of all periods of remission while on minimal steroid therapy up to Week 60.

Individual periods of remission will be defined as specified above for subjects experiencing one period of remission. Duration of remission will be derived as the sum of all individual periods of remission.

A summary table computing the raw duration and p-value for the treatment difference, using the rank ANCOVA indicated above, will be presented for the ITT population and PP population (if criteria are met as discussed in Section 11).

11.1.3. Consistency Criterion for Co-Primary Endpoint Significance

The protocol planned to check the consistency criterion for the analysis of co-primary endpoints to protect the overall type-I error at 0.05 (one-sided 0.025) using the procedure by Alosh and Huque [Alosh 2010]. But now since the study is terminated, the efficacy endpoints tables will only be presented with the p-value at a two-sided 0.05 level of significance without any further adjustments for multiplicity.

11.2. Secondary Efficacy Analyses

11.2.1. Proportion of Subjects Achieving Remission on Minimal Steroid Therapy at Week 60

A subject's daily dose of prednisone/prednisolone will be obtained from the steroid taper log that is completed at all in-clinic and telephone study visits between Weeks 2 and 60.

The absence of new or nonhealing lesions will be determined from the lesion evaluation performed at all post-baseline in-clinic study visits.

The proportion of subjects achieving 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. In this analysis, subjects who discontinued prior to Week 60 will be considered as not having remission at Week 60.

A summary table presenting the proportion of subjects achieving remission on minimal steroid therapy and the proportion of subjects not achieving remission on minimal steroid therapy for each of the treatment groups and the p-value for the treatment difference, using the CMH test indicated above, will be presented for the ITT population.

11.2.2. Time to Remission While on Minimal Steroid Therapy by Week 60

A subject's daily dose of prednisone/prednisolone will be obtained from the steroid taper log and the determination of the absence of new or nonhealing lesions will be obtained from the lesion evaluations performed at all post-baseline in-clinic study visits.

Time to remission on minimal steroid therapy, as defined in Section 9.2.5, will be analyzed using a log-rank test stratified by baseline prednisone/prednisolone dose and disease duration. 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.

A summary table presenting the Kaplan-Meier estimates for time to remission on minimal steroid therapy and 95% CI at Week 4, week 8, Week 12 etc. for each of the treatment groups and p-value for the treatment difference, using the 2-sided log-rank test described above, will be presented for the ITT population.

A Kaplan-Meier plot of time to remission on minimal steroid therapy will be constructed for each treatment group.

11.2.3. Time to Initial Flare/Relapse by Week 60

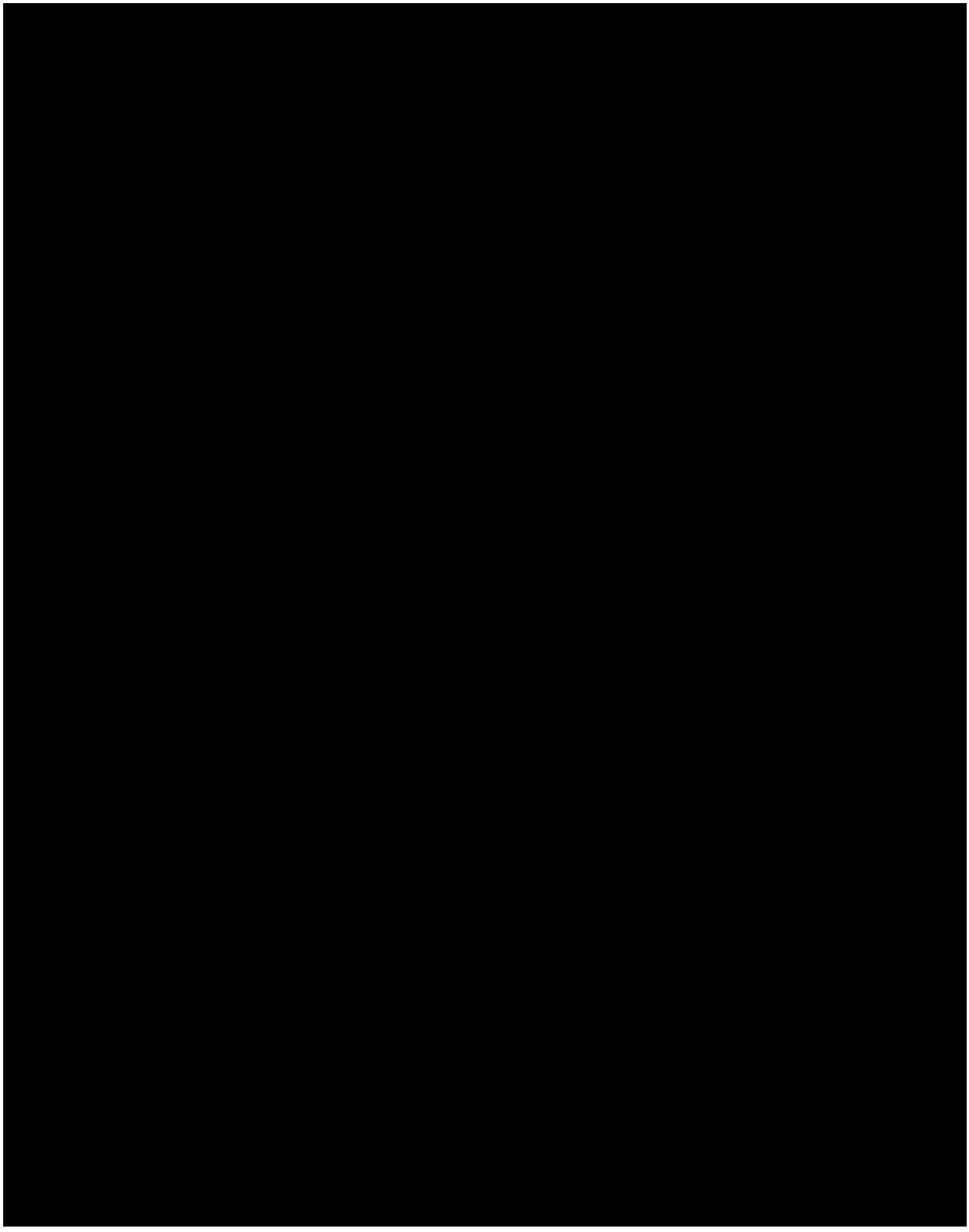
Lesion evaluation will be performed at all in-clinic study visits, including whether the subject is currently experiencing flare/relapse and, in the event that the subject has self-reported a flare/relapse since the last scheduled visit, the date of the first onset of flare was reported by the subject is collected.

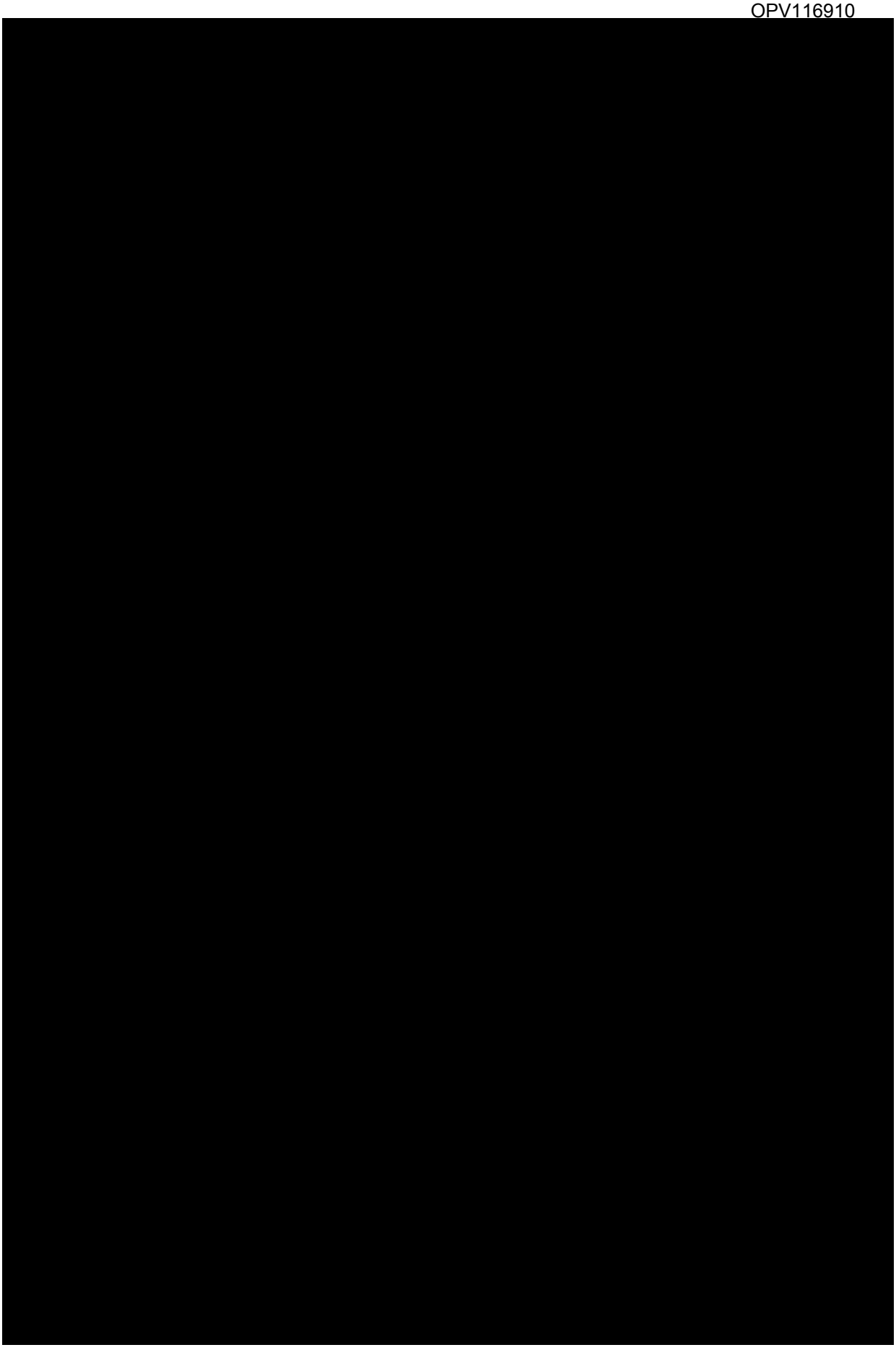
Time to initial flare/relapse, as defined in Section 9.2.6, will be analyzed using a log-rank test stratified by baseline prednisone/prednisolone dose and disease duration. Subjects who discontinue prematurely (prior to Week 60) will be censored at the time they discontinued. Subjects who reach Week 60 without flare/relapse will be censored at their last visit.

A summary table presenting the Kaplan-Meier estimates for time to initial flare/relapse and 95% CI at Week 4, week 8, Week 12 etc for each of the treatment groups and p-value for the treatment difference, using the log-rank test described above, will be presented for the ITT population.

For the covariate analysis, a summary table computing hazard ratio and 95% CI for the hazard ratio and the p-value using the Cox proportional hazards model discussed in Section 8.2, will be presented for the full model for the ITT population.

A Kaplan-Meier plot of time to initial flare/relapse will be constructed for each treatment group.





12. SAFETY ANALYSES

All safety analyses will be performed for the Safety population as defined in Section 6.4. These data will not undergo any inferential statistical analysis. All safety analyses described below will be performed on data collected through the Week 60 study visit for the primary safety. The safety data from individualized follow-up period will be listed for any data available.

Section 9.2.1 details the algorithm for deriving baseline values. In the event that a baseline value for an assessment cannot be derived for a subject, the subject will be excluded from the change from Baseline analysis for that assessment; however, the subject's data will still be included in visit assessment summaries and analyses.

12.1. Extent of Exposure

Each subject is expected to receive 17 injections of study drug over the 56-week treatment period (two injections for a total of 40 mg at Weeks 0 and 4; 1 injection of 20 mg at all remaining treatment period study visits). Descriptive statistics will be used to summarize a subject's exposure (i.e. the number of injections each subject received) for each treatment group.

Percentage subject compliance will be defined as the number of injections received/17 planned injections. Percentage compliance will be summarized using descriptive statistics for each treatment group. The number and percentage of subjects receiving 100%, ≥ 80% - <100%, ≥ 60% - <80%, ≥ 40% - <60%, ≥ 20% - <40% and <20%.

Each subject's treatment exposure and compliance will be presented in a data listing.

12.2. Adverse Events

AEs will be collected from the start of study treatment (treatment emergent AEs) through the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.

AEs will be categorized by their occurrence in regard to therapeutic period (pre-therapy, on-therapy, follow-up or individualized follow-up) as defined in Section 9.3.2. Any events that occur prior to initiation of investigational product will be reported as medical history. If, however, a prior event is reported on the AE page of the eCRF it will be reported as 'pre-therapy' AE. Pre-therapy AEs will be presented only in data listings and will not be summarized.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized based on system organ class (SOC) and PT. Summaries by treatment group of the number and percentage of subjects with an AE will be presented in alphabetical order by SOC. Within the SOC level, the PTs will be presented in descending order of incidences. A PT will not be presented if no AEs occur within the level.

An overview summary of the number and percentage of subjects with any AE and the total number of AEs recorded during the randomized treatment period will be presented by treatment group. For the AEs recorded in the follow-up (FU) period if there are not enough events to summarize (i.e. <10 events) then the data of those AEs will be listed only otherwise it will be summarized. If any AEs recorded in the individualized follow-up period it will be listed only.

For AE listings, AE duration will be defined as (the date of resolution of the AE – the onset date of the AE) + 1 day. If no date of resolution is provided, AE duration will be presented as 'Continuing'.

12.2.1. Counting Rules for AEs

In the summary tables, the following rules apply when counting AEs:

1. If a subject experiences the same AE (i.e. same PT) more than once during a study period, they are only counted once under the count for the PT.
2. If a subject experiences more than one AE (i.e. differing PTs) in a particular SOC, they will only be included once in the count for the SOC, but will appear in the count for each appropriate PT within the SOC (unless it is the same PT, see Point 1. above). As a result, the sum of the numbers of subjects with each event (i.e. PT) within a SOC may exceed the number of subjects with events within that SOC. Similarly, the sum of the SOC totals may exceed the total number of subjects with at least one event.

12.2.2. Overall Adverse Events

Summaries of the number and percentage of subjects with TEAEs and the total number of TEAEs will be provided by treatment group at the SOC and PT level for on-therapy period. For the AEs recorded in the follow-up (FU) period if there are not enough events to summarize then the data of those AEs will be listed only otherwise it will be summarized for the follow-up period. If any AEs recorded in the individualized follow-up period it will be listed only.

A by-subject listing of all AEs will also be presented.

12.3. Deaths and Serious Adverse Events

All SAEs will be summarized in a manner similar to that described above for the overall AE summary by treatment group. By-subject listings of all non-fatal SAEs and all deaths will be presented.

12.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events Incidents

12.4.1. Post-injection Systemic Reactions

Systemic reactions will be collected on the 'Injection Site Reaction' page of the CRF over the same time period as stated above for AEs. Symptoms will also be recorded on the AE form and identified by MedDRA preferred term (PT). A summary of the number and percentage of subjects with a post-injection systemic reaction and the number of reactions, the symptoms associated with the reaction (e.g. fever and chills), whether a subject had any medications administered for a reaction and whether a subject had an event meeting anaphylaxis criteria will be presented by treatment group for the on-therapy period.

Systemic Injection reactions are defined as those with AETERM in ('ABDOMINAL PAIN', 'CHILLS' 'FEVER', 'HEADACHE', 'NAUSIA', etc..) all the systemic symptoms as per listed in the 'Post-injection Systemic reactions' page of the CRF.

A by-subject listing of post-injection systemic reactions will be presented.

12.4.2. Local Reactions

Local reactions will be collected on the 'Injection Site Reaction' page of the CRF over the same time period as stated above for AEs. Symptoms will also be recorded on the AE form and identified by MedDRA preferred term (PT). A summary of the number and percentage of subjects with a local reaction and the number of reactions, the symptoms associated with the reaction (e.g. erythema and swelling), whether a subject had any medications administered for a reaction will be presented by treatment group for the on-therapy period.

Systemic Injection reactions are defined as those with AETERM in ('ERYTHEMA', 'BLEEDING' 'ITCHING', 'EDEMA', 'PAIN', 'SWELLING' etc..) all the local symptoms as per listed in the 'Post-injection local reactions' page of the CRF.

A by-subject listing of local reactions will be presented.

12.5. Pregnancies (as applicable)

A listing of subject pregnancies (if any) will be presented.

12.6. Clinical Laboratory Evaluations

Hematology, chemistry and urinalysis evaluations will be performed. Established or generally acknowledged methods, normal ranges, and quality control procedures will be supplied by [redacted] for the study records. All laboratory results will be presented in the International System of Units (SI).

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, BAFF, anti-Dsg autoantibodies, and HAHA.

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 or if the subject may be discharged from the study (based on B-lymphocyte counts and IgG levels, but the actual laboratory values will not be provided).

Hematology parameters collected will include platelet count, red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, WBC differential (neutrophils, lymphocytes, monocytes, bands, eosinophils, basophils), nucleated RBCs, CD19+B-lymphocyte counts, CD3, CD4, CD8 and CD4:CD8 ratio. Chemistry parameters collected will include total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, blood urea nitrogen (BUN), creatinine, creatinine clearance (calculated), sodium, potassium, chloride, calcium, bicarbonate (carbon dioxide content) and glucose. Urinalysis parameters collected will include appearance, specific gravity, pH, protein, glucose, ketones, leukocyte esterase (leukocytes), hemoglobin (RBCs), microscopy (RBC/HPF, WBC/HPF, epithelial cells, trichomonas, bacteria, yeast, crystals, ammonia urates, mucous threads, amorphous sediment, casts, microalbumin, creatinine and microalbumin:creatinine ratio.

All hematology, chemistry and urinalysis laboratory parameters with a quantitative result will be summarized, for each treatment group, at every assessed time point using descriptive statistics. In addition, change from Baseline in these quantitative tests will be summarized by treatment group and at every assessed post-baseline time point.

All laboratory assessments will be summarized for the Safety population and will be presented in a data listing.

12.6.1. Immunogenicity

A by-visit summary will present descriptive statistics for the actual and change from Baseline results by visit and treatment group for IgG, IgA, IgM, HAHA, high sensitivity C-reactive protein (hsCRP), and B-lymphocyte chemokine (BLC). Additionally, descriptive statistics will be used to summarize each subject's largest decrease from Baseline. The number and percentage of subjects below the LLN at each visit, below the LLN at any time during the on-therapy period and below the LLN during the first 12 weeks of treatment will be presented by treatment group

All immunogenicity data will be presented in a data listing.

12.6.2. Hepatitis

Hepatitis B (HBV surface antigen, HBV surface antibody, HBV core antibody (anti-HBc) and HBV DNA PCR) and Hepatitis C antibody will be measured at the Screening and Week 60/early withdrawal visits. All hepatitis sampling data will be presented in a data listing.

The end of HBV DNA monitoring sample information, including date of last HBV sample and whether the subject failed to complete HPV DNA PCR monitoring for 6 months after the last dose of IP will be presented in a data listing.

12.6.3. Other Laboratory Parameters

Pneumococcal antibody assay (*Streptococcus pneumoniae* IgG antibody assay) and toxoid antibody assay (Tetanus toxoid IgG antibody assay) will be collected at the Screening and Week 60/early withdrawal visits.

All pneumococcal and toxoid antibody assay data will be presented in a data listing.

12.7. Other Safety Measures

All other safety analyses will be performed on the Safety population.

12.7.1. Vital Signs

Vital sign parameters collected at each study visit include: systolic and diastolic blood pressure (mmHg), heart rate (bpm) and temperature (degrees C). Height (cm), weight (kg) and BMI (kg/m^2) are collected at the Screening visit only. At all visits beginning with the baseline visit, vital signs will be assessed both prior to and after dosing with study treatment. As described in Section 9.2.1, the baseline value for an assessment is defined as the last non-missing value before the start of treatment.

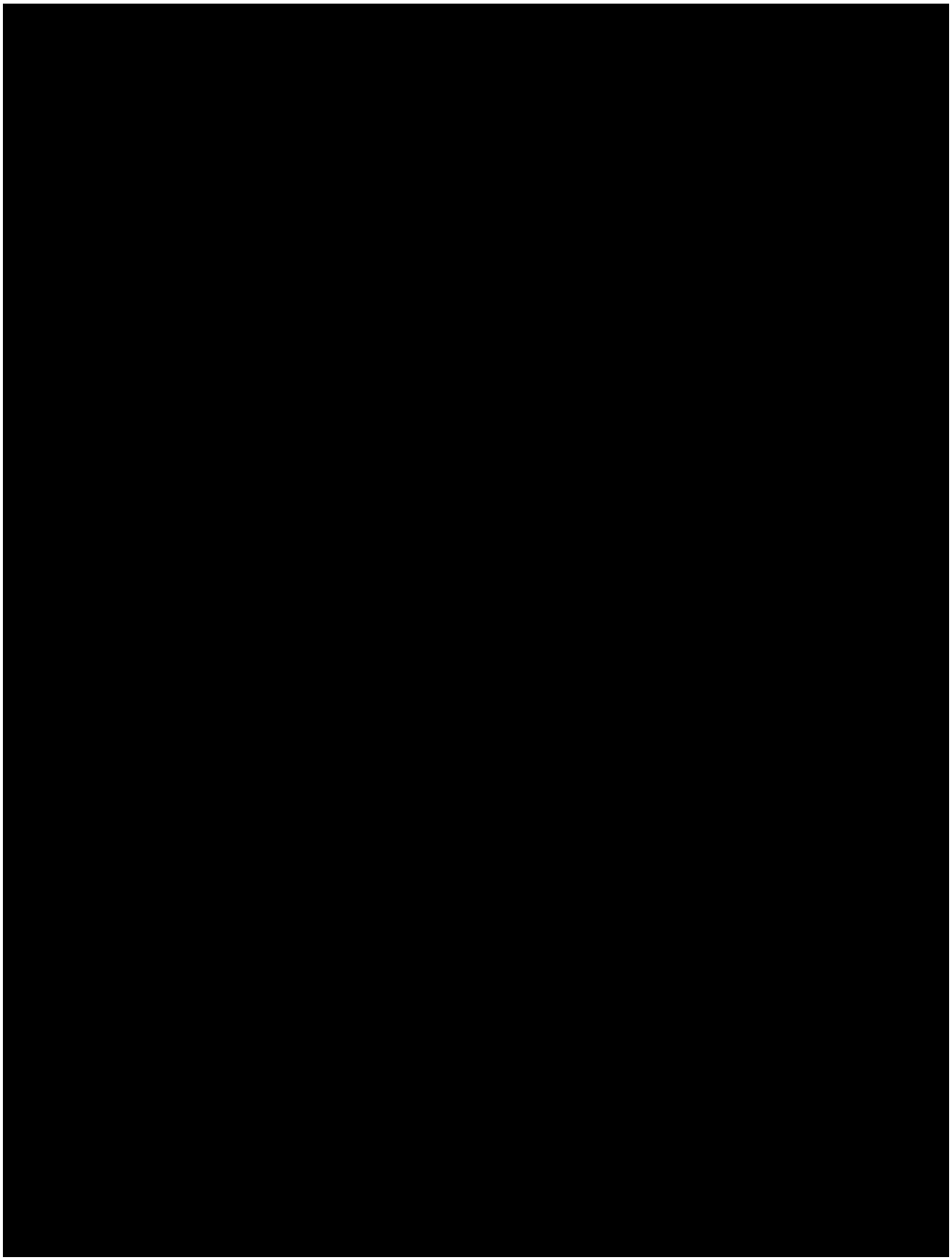
Each vital sign parameter will be summarized at every assessed time point and change from Baseline in each parameter will be summarized at each post-baseline time point using descriptive statistics for each treatment group

All vital sign data will be presented in a data listing.

12.7.2. Twelve-Lead Electrocardiogram (ECG)

All ECG data collected at Screening and Week 60/Early Withdrawal will be presented in a data listing.

[redacted]



[redacted]

14. CLINICAL PHARMACOLOGY DATA ANALYSES

All PK and PD analyses will be performed by Novartis [redacted] for all subjects in the PK population. Only PK plasma trough concentration results will be summarized and the PK sampling data will be presented in data listings for all subjects in the PK population.

14.1. Pharmacokinetic Analyses

The ofatumumab plasma trough concentration data obtained from the PK core study will be summarized in and table and also will be presented in a data listing for the PK population.

14.2. Pharmacodynamic Analyses

Peripheral blood B-lymphocyte counts will be used as a PD marker. These data will be tabulated by sex at each time point and will be summarized using descriptive statistics. Similar summaries will be provided for neutrophil counts, which are considered a negative control. All the available PD data will be listed.

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