Official Title: **A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-COMPARATOR, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RITUXIMAB VERSUS MMF IN PATIENTS WITH PEMPHIGUS VULGARIS**

NCT Number: NCT02383589

Document Date: Protocol Version 5: 19-December-2017

PROTOCOL

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PROTOCOL NUMBER:	WA29330
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-000382-41
IND NUMBER:	121595
TEST PRODUCT:	Rituximab (RO 0452294)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 24 July 2014
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	19-Dec-2017 21:10:57

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol WA29330 has been amended to address a health authority recommendation that data obtained via telemedicine (TM) is considered to be exploratory in nature and therefore the primary analysis for establishing efficacy is to be based on the intent-to-treat (ITT) population for patients who were not recruited via TM. The following changes have been made to the protocol to address this recommendation as follows:

- An additional minimum of 8 non-TM patients will be recruited into this study to maintain sufficient statistical power for the primary analysis, thereby increasing the overall enrolment from approximately 124 to approximately 132 patients with pemphigus vulgaris (Sections 3.1, 4.1, 4.2, and 9.4).
- The Statistical Considerations section (Section 6) has been updated, stipulating that all efficacy outcomes will be analyzed using the modified ITT (mITT) population and excluding patients who were enrolled via TM.
- The primary efficacy outcome measure has been revised to reflect the exclusion of TM patients (Section 3.4.1.1).
- As a result of the increase in enrollment, Section 6.1, Determination of Sample Size, has been revised.
- A new primary analysis population has been added, the mITT population, which includes patients in the ITT population, excluding the 10 patients enrolled via TM. This population will be used in the analyses of efficacy outcomes (Section 6.2.3).
- The analysis of the secondary efficacy endpoints has been updated and changed to the mITT population (Section 6.5.2).
- Exploratory analyses (Section 6.9) have been updated to include a statement on descriptive statistics for evaluation of the 10 patients recruited via TM.

In addition, the following change has been made:

- An exploratory objective and exploratory outcome measure to evaluate the proportion of patients experiencing treatment failure in each treatment arm have been added (Sections 2.3 and 3.4.3, respectively).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-COMPARATOR, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RITUXIMAB VERSUS MMF IN PATIENTS WITH PEMPHIGUS VULGARIS**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please return a copy of this form as instructed by your local study monitor and retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-COMPARATOR, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RITUXIMAB VERSUS MMF IN PATIENTS WITH PEMPHIGUS VULGARIS**
PROTOCOL NUMBER:	WA29330
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-000382-41
IND NUMBER:	121595
TEST PRODUCT:	Rituximab (RO 0452294)
PHASE:	III
INDICATION:	Moderate-to-severely active pemphigus vulgaris
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of rituximab compared with mycophenolate mofetil (MMF) in achieving sustained complete remission, evaluated by the Pemphigus Disease Area Index (PDAI; see Section 3.4.1.1), and assessed at Week 52 in patients with moderate-to-severely active pemphigus vulgaris (PV)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of rituximab compared with MMF, as measured by the time to disease flare, the duration of sustained complete remission, the total number of disease flares during the treatment period, and the time to initial sustained complete remission
- To assess corticosteroid exposure over 52 weeks
- To assess the effect of rituximab compared with MMF on health-related quality of life (HRQoL), as measured by the Dermatology Life Quality Index (DLQI)
- To assess the effect of rituximab compared with MMF on patients' impression of PV symptoms, as measured by the Patient Global Impression of Change (PGIC) questionnaire
- To assess the effect of rituximab compared with MMF on clinician impression of patients' PV symptoms, as measured by the Clinician Global Impression of Change (CGIC) questionnaire

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety of rituximab compared with MMF, with a focus on adverse events and safety laboratory values
- To evaluate corticosteroid-related adverse events in relation to corticosteroid exposure

Exploratory Objectives

The exploratory objectives for this study will include, but are not limited to, the following:

- To evaluate the efficacy of rituximab compared with MMF, as measured by the proportion of patients achieving complete or partial remission by 24 weeks and 52 weeks
- To explore the pharmacokinetics and pharmacodynamics of rituximab, and the pharmacodynamics of MMF, in patients with PV
- To evaluate the effect of rituximab as compared with MMF on the change in PDAI activity score
- To evaluate the effect of rituximab as compared with MMF on anti-desmoglein (anti-Dsg) autoantibody titers (anti-Dsg1 and anti-Dsg3) and other mechanistic studies of interest in patients with PV
- To assess the effect of rituximab compared with MMF on health utilities as measured by the European Quality of Life (EuroQol) 5-Dimension Questionnaire, 3-level version (EQ-5D-3L)
- To assess the effect of rituximab compared with MMF on HRQoL, as measured by the Skindex-29
- *To evaluate the efficacy of rituximab compared with MMF, as measured by the proportion of patients experiencing treatment failure from Week 12 to Week 52*

Study Design

Description of Study

This is a Phase III, randomized, double-blind, double-dummy, active-comparator, parallel-arm, multicenter study to evaluate the efficacy and safety of rituximab compared with MMF in patients with moderate-to-severely active PV requiring 60–120 mg/day oral (PO) prednisone or equivalent (1.0–1.5 mg/kg/day). Patients must have a confirmed diagnosis of PV within the previous 24 months (by skin or mucosal biopsy and immunohistochemistry) and evidence of moderate-to-severely active disease at screening (defined as at total PDAI activity score of ≥15).

This international study will be conducted at investigational sites throughout North America, Europe, the Middle East, and Latin America. It is expected that approximately 60 centers will participate. Approximately *132* patients will be randomized in a 1:1 ratio to receive either rituximab plus MMF placebo or rituximab placebo plus MMF. Randomization will be stratified by duration of illness (newly diagnosed [i.e., diagnosed within the 1 year prior to screening] vs. diagnosed greater than 1 year) and geographical region (North America [U.S./Canada] vs. rest of world).

The study will consist of three periods: a screening period of up to 28 days, a 52-week double-blind treatment period, and a 48-week safety follow-up (SFU) period that begins at the time of study treatment completion or discontinuation.

Rituximab (1000 mg or matching placebo) will be administered by intravenous (IV) infusion on Day 1 and Day 15, with repeat rituximab (or matching placebo) administration on Day 168 and Day 182 provided specific safety criteria have been met (see Section 4.6.4). MMF (500 mg or matching placebo) will be administered PO twice daily (every 12 hours [Q12H]), starting with a total dose of 1 g/day on Day 1. The MMF dose will be titrated to achieve a goal of 2 g/day in divided doses (1 g Q12H) by Week 2. Treatment with MMF (or matching placebo) will continue through Week 52.

All patients who withdraw from the treatment period or who complete the total 52-week treatment period must return for post–*Week 52* SFU assessments at 12, 24, 36, and 48 weeks after either the early withdrawal visit or study treatment completion, respectively. Thus, patients will be followed for approximately 1 year in the SFU period.

Telemedicine

For a small proportion of patients (approximately 10 patients *at one* investigational site), the Sponsor is proposing the use of telemedicine (TM) consultation visits between the patient and the Principal Investigator to make the trial more accessible to this population of patients with a rare disease. The local dermatologist, a research nurse, and other medical personnel in the patient's immediate vicinity will participate throughout the trial as needed. Data collected via TM will be in accordance with the American Telemedicine Association 2012 Guidelines for

Teledermatology (ATA 2012). The software platform to be used in the trial will allow efficient, high-quality data collection of all relevant clinical data (including the images of the skin and mucosa, prior medical records, notes, and laboratory tests) for easy and reliable review by the Principal Investigator. This type of assessment has become the standard for TM clinical care for the diagnosis and treatment of both mild and severe types of skin diseases. Images will be time-stamped and stored in a Health Insurance Portability and Accountability Act (HIPAA)-compliant advanced TM platform adapted for this specific trial use. Other safety and efficacy data sets will be transmitted through the TM platform to the Principal Investigator as well. The local dermatologist or other local primary care doctors may still provide standard-of-care services that do not require training on the protocol or investigational drug. All clinical trial-related medical decisions will be made by the Principal Investigator and or safety assessor.

Number of Patients

Approximately 132 patients with active moderate-to-severely active PV will be recruited into this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 18–75 years
- Signed Informed Consent Form
- First confirmed diagnosis of PV within the previous 24 months, based on the presence of histological features of acantholysis via skin or mucosal biopsy and one of the following: tissue-bound immunoglobulin G (IgG) antibodies by direct immunofluorescence on the surface of affected epithelium or serological detection of serum Dsg3 autoantibodies against epithelial cell surface either by indirect immunofluorescence microscopy or by enzyme-linked immunosorbent assay
- Presence of moderate-to-severely active disease, defined as overall PDAI activity score of ≥15
- Receiving standard-of-care corticosteroids consisting of 60–120 mg/day PO prednisone or equivalent (1.0 – 1.5 mg/kg/day) and, in the judgment of the investigator, expected to benefit from the addition of immunosuppressive therapy
- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two effective methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 12 months after the last dose of study treatment

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Barrier methods must always be supplemented with the use of a spermicide.

  Examples of contraceptive methods with a failure rate of < 1% per year (highly effective contraceptive methods) include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.
- For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study treatment and agreement to refrain from donating sperm during this same period

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment

- Agreement to avoid excessive exposure to sunlight during study participation
- Able to comply with the study protocol, in the investigator's judgment

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Diagnosis of pemphigus foliaceus or evidence of paraneoplastic pemphigus or other non-PV autoimmune blistering disease
- History of a severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies, or known hypersensitivity to any component of rituximab
- Known hypersensitivity or contraindication to MMF, mycophenolic acid, polysorbate, or oral corticosteroids
- Lack of peripheral venous access
- Pregnant or lactating, or intending to become pregnant during the study

  Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have two negative results with a sensitivity of ≥25 mIU/mL: one from a serum pregnancy test at Day –8 to Day –10 of screening and another from a urine pregnancy test at Day 1 prior to randomization.
- Participated in another interventional clinical trial within 28 days prior to randomization
- Use of any investigational agent within 28 days or 5 elimination half-lives prior to randomization (whichever is the longer)
- Significant cardiovascular or pulmonary disease (including obstructive pulmonary disease)
- Evidence of any new or uncontrolled concomitant disease that, in the investigator's judgment, would preclude patient participation, including but not limited to nervous system, renal, hepatic, endocrine, malignant, or gastrointestinal disorders
- Any concomitant condition that required treatment with oral or systemic corticosteroids within 12 weeks prior to randomization
- Treatment with IV immunoglobulin (Ig), plasmapheresis, or other similar procedure within 8 weeks prior to randomization
- Treatment with immunosuppressive medications (e.g., azathioprine, MMF) within 1 week prior to randomization
- Treatment with cyclophosphamide within 12 weeks prior to randomization
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection and other severe Immunodeficiency blood disorders
- Known active infection of any kind (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to screening, or completion of oral anti-infectives within 2 weeks prior to randomization

  Entry into this study may be reconsidered once the infection has fully resolved.
- History of or current cancer, including solid tumors, hematologic malignancies, and carcinoma in situ (except basal cell carcinoma and squamous cell carcinoma of the skin that have been excised and cured)
- Currently active alcohol or drug abuse, or history of alcohol or drug abuse within 24 weeks prior to screening
- Major surgery within 4 weeks prior to randomization, excluding diagnostic surgery
- Treatment with rituximab or a B cell–targeted therapy (e.g., anti-CD20, anti-CD22, or anti-BLyS) within 12 months prior to randomization
- Treatment with a live or attenuated vaccine within 28 days prior to randomization

It is recommended that a patient's vaccination record and the need for immunization prior to study entry be carefully investigated.

- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase $>2.5\times$ the upper limit of normal (ULN)
- Absolute neutrophil count (ANC) $<1.5\times10^3/\mu L$
- Hemoglobin <8.0 g/dL
- Positive test results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) serology at screening

Length of Study

Based on study enrollment projections, this study is estimated to take approximately 4 years to complete, from first patient in to last patient's last visit (LPLV), when the final patient completes the 48-week SFU period.

End of Study

The end of the study is defined as the date when the LPLV occurs. LPLV is expected to occur approximately 2 years after the last patient is enrolled, assuming a 52-week treatment period and a 48-week SFU period for the last patient.

Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is as follows:

- Proportion of patients *(excluding TM patients)* who achieve a sustained complete remission without experiencing an event that constitutes treatment failure (as defined in Section 3.1.3), as measured at Week 52

  Sustained complete remission is defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for a total of at least 16 consecutive weeks, during the 52-week treatment period.

  Patients with transient new lesions for 1 week or less that heal without additional systemic corticosteroid therapy will not be considered to have experienced treatment failure.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Cumulative oral corticosteroid dose (prednisone or equivalent) over the treatment period
- Total number of disease flares during the treatment period
- Time to sustained complete remission
- Time to disease flare

  Disease flare is defined as the appearance of three or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved disease control.
- Change in HRQoL, as measured by the DLQI score from baseline to Week 52
- Duration of sustained complete remission
- Patients' impression of change in PV symptoms, as measured by the PGIC score during the treatment period
- Clinician impression of change in patients' PV symptoms, as measured by the CGIC score during the treatment period

Safety Outcome Measures

The safety outcome measures include, but are not limited to, the following:

- Nature, frequency, and severity of adverse events, including serious adverse events and adverse events leading to discontinuation

- Vital signs and clinical laboratory test results (including complete blood count and blood chemistry)
- Incidence of human anti–chimeric antibody (HACA)
- Circulating B cells, T cells, natural killer (NK) cells, plasma cells, and other leukocytes
- Plasma Ig levels (total Ig, IgG, IgM, and IgA)
- Corticosteroid-related adverse events in relation to corticosteroid exposure

Exploratory Outcome Measures

The exploratory outcome measures for this study will include, but are not limited to, the following:

- Proportion of patients achieving a complete remission by Week 24 and by Week 52

  Complete remission is defined as achieving wound healing with no new active lesions (i.e., PDAI activity score of 0) for at least 8 consecutive weeks during the 52-week treatment period.
- Proportion of patients achieving a partial remission by Week 24 and by Week 52

  Partial remission is defined as the presence of transient new lesions that heal within 1 week (while the patient is receiving minimal therapy, including topical corticosteroids). Minimal therapy is defined as ≤10 mg/day prednisone (or equivalent) for at least 8 consecutive weeks during the 52-week treatment period.
- Pharmacokinetics (PK)/pharmacodynamics (PD) of rituximab

  PK/PD parameters include, but are not limited to, serum levels of rituximab, peripheral CD19+ B-cell counts, HACA, and autoantibody concentrations.
- To explore the pharmacodynamics of MMF in patients with PV
- Change in total PDAI activity score during the treatment period
- Change from baseline in anti-Dsg1 and anti-Dsg3 autoantibodies
- Change in health utilities as assessed by the EQ-5D-3L score from baseline to Week 52
- Change in HRQoL as measured by the Skindex-29 from baseline to Week 52

Investigational Medicinal Products

Test Product–Rituximab

Patients randomized to the rituximab arm will receive treatment with 1000 mg IV rituximab (or matching placebo) on Day 1 and Day 15, with repeat rituximab (or matching placebo) administration on Day 168 and Day 182 provided specific safety criteria have been met (see Section 4.6.4).

Comparator–MMF

Patients randomized to the MMF arm will receive treatment with 500 mg MMF (or matching placebo) administered orally twice daily (Q12H) starting on Day 1. MMF dose will then be titrated to achieve a maximum dose goal of 2 g/day given as a divided oral dose (1 g Q12H) by Week 2. Slower titration will be allowed on the basis of tolerability. Treatment with MMF (or matching placebo) will continue through Week 52.

Non-Investigational Medicinal Products

In order to reduce the frequency and severity of infusion-related reactions, all patients will receive methylprednisolone 100 mg or saline solution prior to infusion of rituximab or rituximab placebo, respectively. This premedication will be administered by slow IV infusion, and administration should be completed at least 30 minutes prior to infusion of rituximab or rituximab placebo.

All patients should be premedicated with paracetamol/acetaminophen (1 g PO) and an antihistamine (diphenhydramine HCl 50 mg PO [or IV equivalent] or equivalent dose of a similar agent, or in accordance with local approved labeling) 30 to 60 minutes prior to the start of the infusion of rituximab or rituximab placebo.

Statistical Methods

Primary Analysis

The proportion of patients (*excluding TM patients*) achieving a sustained complete remission (as defined in Section 3.4.1.1) in the rituximab and MMF arms will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables. Results will be summarized descriptively by treatment arm and expressed as proportions, corresponding adjusted 95% confidence intervals of the difference between response rates, and p-values.

Patients who meet the pre-specified definitions of treatment failure before entering sustained complete remission (as defined in Section 3.1.3) will be deemed non-responders in the primary analysis.

Determination of Sample Size

The primary efficacy endpoint of this study is the proportion of patients *(excluding TM patients)* achieving a sustained complete remission, as assessed at Week 52, that has been maintained for ≥16 consecutive weeks during the 52-week treatment period. With use of limited data available in the literature from randomized clinical trials of MMF and investigator-initiated trials of rituximab, it is estimated that approximately 40% of patients with PV receiving MMF will achieve a sustained complete remission. It is estimated that patients receiving rituximab will induce a sustained complete remission rate of 65%. On the basis of these assumptions, a total of *122* patients randomized to the rituximab arm or the MMF arm in a 1:1 ratio (*61* patients in the rituximab arm and *61* patients in the MMF arm) will yield *approximately* 80% power in a two-sided test at the 5% significance level. *To account for the 10 TM patients excluded from the primary efficacy analysis, approximately 132 patients will be randomized in total*.

No adjustment will be made to account for dropouts.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CGIC	Clinician Global Impression of Change
CL	clearance
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
Dsg1	desmoglein-1
Dsg3	desmoglein-3
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-3L	EuroQol 5-Dimension Questionnaire, 3-level version
EuroQol	European Quality of Life
FACS	fluorescence-activated cell sorting
FDA	(U.S.) Food and Drug Administration
GPA	granulomatosis polyangiitis
HACA	human anti–chimeric antibody
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International *Council for* Harmonisation
iDMC	independent Data Monitoring Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent to treat
IV	intravenous
IV Ig	intravenous immunoglobulin
IxRS	interactive/web voice response system
KLH	keyhole limpet hemocyanin
LDH	lactate dehydrogenase
LPLV	last patient, last visit
mITT	*modified intent-to-treat (population)*
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer (cell)
PD	pharmacodynamic
PDAI	Pemphigus Disease Area Index
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PRCA	pure red cell aplasia
PRO	patient-reported outcome
PV	pemphigus vulgaris
Q12H	every 12 hours
RA	rheumatoid arthritis
RBC	red blood cell
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SFU	safety follow-up
SJS	Stevens-Johnson syndrome
SMT	Study Management Team
TEN	toxic epidermal necrolysis
TM	telemedicine
ULN	upper limit of normal
VAS	visual analog scale
V_c	central compartment volume of distribution

Abbreviation	Definition
V_p	peripheral compartment volume of distribution
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON PEMPHIGUS VULGARIS

Pemphigus is a rare, severe autoimmune disease—one of a group of unique, related blistering disorders that includes pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus. They are histologically characterized by suprabasilar acantholysis and immunopathologically characterized by autoantibodies to desmosomal cadherins. In PV (characterized by skin and mucosal lesions), the autoantibodies are to desmoglein 1 (Dsg1) or desmoglein-3 (Dsg3). In pemphigus foliaceus (which typically does not affect the mucosa), the autoantibody is to Dsg1. The mechanism that initiates the formation of anti-Dsg antibodies is unknown, but is presumed to involve loss of B-cell tolerance to these self-antigens.

PV constitutes approximately 80% of pemphigus cases (Tóth and Jonkman 2001). The incidence of PV in the United States is 0.1 to 0.4 in 100,000, with a prevalence of 1 to 5 in 100,000 (Tóth and Jonkman 2001). Onset of disease typically occurs after the age of 50 years, with the incidence in men and women being equal. PV occurs in all races. There may be a genetic predisposition and link to human leukocyte antigen class II alleles, and the disease is more common in people of Eastern European Jewish and Mediterranean descent (Hertl et al. 2006; Feldman and Ahmed 2011).

PV is characterized by fragile and flaccid blisters caused by loss of cohesion between the cells in the lower epidermis. Both skin and mucosal lesions are seen in PV. In approximately 50%–70% of cases, the disease begins with oral lesions (Chryssomallies et al. 1994), which may become painful, rendering patients unable to eat or drink, and leading to malnutrition and debilitation. Left untreated, bullae and erosions spread. As with burns, when these lesions are widespread they can be complicated by severe infection and/or metabolic disturbance, leading to death. Before systemic corticosteroids became available, approximately 75% of patients who developed PV died within a year (Lever 1953). Following the widespread use of systemic corticosteroids to treat pemphigus starting in the 1950s, mortality declined drastically to an average of 29% (Bystryn 1984).

The aim of pharmacologic therapy for PV is to reduce inflammation and enable wound healing. Assessment of disease severity is typically based on clinical presentation (i.e., percentage of body surface area involved, duration of lesions [sustained for more than a week], and location of lesions [mucosal, skin, scalp]). Mild disease typically refers to patients with few lesions, which are progressing slowly and can be treated topically with high-potency corticosteroid ointments or with intralesional injections of corticosteroids. Moderate-to-severely active disease has been characterized in the literature by numbers of cutaneous and/or mucosal lesions, percentage of body surface involvement, or Pemphigus Disease Area Index (PDAI) severity score and the use of oral (PO) or intravenous (IV) corticosteroids, such as prednisone or equivalent

(1.0–1.5 mg/kg per day) to prevent new blister activity (Mimouni et al. 2003; Bystryn and Rudolph 2005; Martin and Murrell 2006; Shimizu et al. 2014).

High doses and prolonged administration of corticosteroids are required, with potentially serious side effects, such as an increased susceptibility to infection, accelerated osteoporosis, diabetes, capillary fragility, cataracts, Cushingoid habitus, glaucoma, gastrointestinal ulceration, hypertension, weight gain, and/or psychiatric symptoms. These side effects have led to an alternative approach to treatment that involves a combination of corticosteroids with a second immunosuppressive agent, such as azathioprine, mycophenolate mofetil (MMF), or cyclophosphamide (Martin et al. 2009; Beissert et al. 2010). The goal of combination therapy is to increase efficacy and provide a steroid-sparing action to reduce corticosteroid side effects. In clinical practice, once new blisters have stopped forming, the dose of the immunosuppressive drug is typically maintained while the dose of corticosteroid is reduced. The aim is to find the lowest dose of corticosteroids needed to control symptoms, and there is significant inter-patient variability in response to therapy. Importantly, care also needs to be taken to monitor for systemic toxicity of the steroid-sparing agents themselves, including the increased risks of bone marrow suppression or hepatotoxicity.

The use of high-dose, long-term systemic corticosteroids, with or without other immunosuppressive agents, has improved outcomes and reduced 1-year mortality to approximately 5%–15% (Baibergenova et al. 2012). However, patients with PV often have a poor quality of life, and many experience severe side effects from immunosuppression and long-term use of corticosteroids, including death (Lester et al. 1998; Tóth and Jonkman 2001; Feldman and Ahmed 2011). Currently, a significant cause of death in treated PV patients is opportunistic infections secondary to prolonged immunosuppression. In addition, many PV patients become refractory to standard therapies and require more aggressive treatments, such as plasmapheresis or intravenous immunoglobulin (IV Ig). Clearly, a major unmet need exists for new treatment options for patients with PV (Feldman and Ahmed 2011).

In the past 17 years, monoclonal antibodies designed to selectively deplete B cells have been developed and used in the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and autoimmune diseases, such as rheumatoid arthritis (RA), granulomatosis polyangiitis (GPA; Wegener's), and microscopic polyangiitis (MPA). Owing to its ability to deplete pathogenic B cells, rituximab has been used off-label for multiple autoimmune conditions, including PV. As described in the literature, therapy with rituximab has additionally aimed to reduce anti-Dsg1 and anti-Dsg3 autoantibody production.

Both rituximab (Rituxan®/MabThera®) and MMF (CellCept®) have been available worldwide for over 15 years to treat other diseases; however, neither of them has been approved for the treatment of PV.

1.2 BACKGROUND ON RITUXIMAB

1.2.1 Rituximab Mechanism of Action

Rituximab is a glycosylated immunoglobulin G1 (IgG1) κ chimeric murine/human monoclonal antibody that binds specifically to the transmembrane antigen CD20, which is located on pre-B and mature B lymphocytes, but not on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissue. Following antibody binding, CD20 is not internalized or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and thus does not compete for antibody binding. Rituximab is believed to exert its therapeutic effect by promoting B-cell lysis, inducing a rapid and sustained depletion of peripheral CD20+ B cells. Possible mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis. Following cessation of treatment, a normal B-cell pool can be reconstituted from hematopoietic stem cells and CD20− precursor B cells, which are not affected by treatment with rituximab.

1.2.2 Rituximab Experience

Rituximab is currently approved for the treatment of relapsed or refractory NHL, CLL, and, in combination with methotrexate, for the treatment of RA patients with an inadequate response to one or more anti-tumor necrosis factor therapies. Rituximab is also approved for the treatment of two forms of anti-neutrophil cytoplasmic autoantibody-associated vasculitis, GPA, and MPA. Rituximab is under investigation in this study as an experimental drug in PV and is currently not approved for the treatment of patients with PV.

Clinical studies have investigated the use of rituximab in other populations of patients with RA and several other autoimmune disorders, including multiple sclerosis and systemic lupus erythematosus.

See the Rituximab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.2.3 Rituximab Drug-Drug Interaction Potential

The elimination of rituximab is mediated by both the specific CD20 receptor-mediated pathway and the nonspecific IgG clearance pathways. Data suggest that rituximab would not be expected to have many of the common mechanisms of drug-drug interactions with small molecules, including changes in protein binding, P450 activity, and transporters. Although no specific drug interaction studies have been performed, based on pharmacokinetic (PK) data from Phase II/III RA clinical studies, cyclophosphamide, methotrexate, and corticosteroids seemed to have little or no effect on the pharmacokinetics of rituximab.

1.2.4 Rituximab Population Pharmacokinetics

A population PK analysis, based on RA clinical trial data from two Phase II and four Phase III studies, demonstrated that weight, sex, and C-reactive protein (CRP) were the most influential covariates on clearance (CL), central compartment volume of distribution (V_c), and peripheral compartment volume of distribution (V_p). However, the covariates explained only a small portion of the variability in PK parameters. Of note, development of human anti–chimeric antibody (HACA) response was not a significant covariate for PK parameters. The typical population estimates of rituximab CL and V_c from 2005 patients with RA who received two rituximab IV doses (of either 2 × 1 g or 2 × 0.5 g) on Days 1 and 15 were 0.335 L/day and 3.10 L/day, respectively, and the mean terminal half-life of rituximab was calculated as 18.0 days (range, 5.17–77.5 days). Co-administration of cyclophosphamide, methotrexate, and corticosteroids seemed to have little or no effect on the pharmacokinetics of rituximab.

Rituximab V_c and the V_p proportionally increased with body weight. However, body weight, sex, and CRP explained a small magnitude of the overall inter-individual variability of the respective physiologically relevant parameters. Therefore, results from the RA analysis suggested that dosing of rituximab should not be adjusted according to demographic or physiologic variables.

1.2.5 Rituximab Clinical Pharmacodynamics

RA patients showed near-complete depletion of peripheral CD19+ B cells by 2 weeks after the first dose, with no differences observed between the 2×1.0 g and 2×0.5 g doses of rituximab. In the majority of patients, peripheral B-cell depletion was maintained over the 24 weeks, with only a small proportion of patients showing signs of peripheral B-cell recovery by Week 24, when serum rituximab concentrations fell below 1–10 μg/mL. The extent and duration of B-cell depletion were similar for each treatment course. Repeat treatments were given on the basis of clinical symptoms and not on patients' CD19+ cell counts, which may or may not have returned to the lower limit of normal or baseline value.

Levels of total Ig, IgA, IgG, and IgM decreased in patients who received rituximab compared with those who received placebo. Mean immunoglobulin levels generally remained within the normal range.

T-cell counts remained stable after a transient decrease, likely because of concomitant RA treatment with corticosteroids. Treatment with rituximab did not appear to have an effect on serum complement, antinuclear antibody titer, or protective immunity to common infectious agents in patients with RA.

1.3 BACKGROUND ON MYCOPHENOLATE MOFETIL

1.3.1 Mycophenolate Mofetil Mechanism of Action

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, noncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and therefore inhibits the de novo pathway of guanosine nucleotide synthesis. The mechanism by which MPA inhibits the enzymatic activity of IMPDH appears to be related to the ability of MPA to structurally mimic both nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthose-5'-monophosphate, which is the committed step in de novo guanosine nucleotide biosynthesis. MPA has more potent cytostatic effects on lymphocytes than on other cells because T and B lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways.

1.3.2 Mycophenolate Mofetil Experience

MMF is approved worldwide to prevent organ rejection in patients who receive kidney, heart, or liver transplants. MMF has been studied in lung transplant and in autoimmune diseases; however, it is not approved for these diseases. MMF is an experimental drug, which has not been approved by health authorities for the treatment of patients with PV.

Several small clinical studies have shown that treatment with MMF may benefit patients with PV by stopping antibody production by B cells.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.4.1 Role of B Cells in Pemphigus Vulgaris

PV is characterized by the deposition of autoantibodies on the keratinocyte cell surface, resulting in suprabasal acantholysis. These autoantibodies are produced by circulating B cells and target Dsg1 and Dsg3. They bind to keratinocytes, inhibit cell-cell adhesion, and cause blister formation and inflammation in the skin and mucous membrane (Feldman and Ahmed 2011). In addition to the role of autoantibodies in PV, dysregulated B cells may further worsen disease by secreting cytokines, co-stimulating T cells, and differentiating into memory B cells and plasma cells, which contribute to persistent autoantibody production and relapsing disease.

1.4.2 Efficacy and Safety of Rituximab in Pemphigus Vulgaris

Owing to its ability to deplete pathogenic B cells, rituximab has been used off-label for multiple autoimmune conditions, and there is increasing evidence for the successful use of rituximab in severe and refractory PV. A review of the literature shows that over 400 PV patients have been treated with rituximab; 44% of them have received the rituximab 2 × 1000 mg IV (Days 1 and 15) dose, with repeat administration in some cases. Several small, investigator-initiated, uncontrolled clinical studies investigating the use of rituximab in PV with variable definitions of response have demonstrated overall complete remission rates of approximately 30%–90%, as determined by the

investigators (Feldman and Ahmed 2011). The high variability in complete remission rates may be due to differences in concomitant therapy, duration of disease, number of cycles of rituximab administered, follow-up periods, and the definition of complete remission (e.g., complete remission on or off corticosteroid treatment by Months 3–6 following rituximab treatment). All patients had active disease, despite immunosuppressant therapy, and had variable durations of disease onset. The results of several uncontrolled studies and selected case reports of rituximab in PV (see Appendix 10) provide supportive data that rituximab has provided significant benefit to PV patients when standard therapies have inadequately controlled their disease.

A summary of the key publications reporting the efficacy of the rituximab 2 × 1000 mg IV (Days 1 and 15) dose in PV patients is provided below:

- Heelan et al. (2014) concluded that rituximab 2×1000 mg IV (Days 1 and 15) appeared to be an effective therapeutic option, with minimal serious adverse events, for patients with severe or refractory pemphigus (N = 92; PV = 84). After a single cycle of rituximab, 74 patients (80%) achieved complete remission while off systemic therapy. The study reported that patients who did not achieve remission after one cycle and those who experienced relapse benefited from further rituximab cycles, which were typically 2 × 1000 mg IV doses repeated at 6 months ([redacted], personal communication).
- Leshem et al. (2014) reported that treatment with rituximab 2×1000 mg IV (Days 1 and 15) resulted in a 90% remission rate 6 months after treatment. Patients enrolled (N=10) were previously part of a larger study (Leshem et al. 2013) evaluating the clinical efficacy of rituximab 2×1000 mg IV (Days 1 and 15). The limitations of this study included the small number of patients and the lack of a control group. Nevertheless, it was a prospective study using rituximab 2 × 1000 mg IV (Days 1 and 15) in patients with severe PV with favorable efficacy and safety results.
- Leshem et al. (2013) also reported, in a study of 47 patients, that rituximab 2 × 1000 mg IV (Days 1 and 15), used typically with concurrent immunosuppressive medications, demonstrated a 76% remission rate in severe PV patients at a median of 4 months after the first treatment cycle. Repeating treatment with rituximab 2 × 1000 mg IV at 6 months increased the remission rate to 91%. The limitations of this study included its retrospective nature and lack of immunologic evaluation of response to therapy. Nevertheless, this was one of the largest published series on rituximab in pemphigus and provides data on the efficacy and safety of both a single cycle and repeated cycles of rituximab 2×1000 mg IV.
- Kanwar et al. (2013) concluded that rituximab may be an important treatment modality for PV patients because of the efficacy observed in patients with resistant and extensive disease. Thirty percent of patients in the study (N = 9) achieved a complete remission and were off all treatment, 40% achieved complete remission and were on low-dose oral prednisolone, and 20% had partial remission and were on low-dose prednisolone. Mean time to disease control was 8 weeks (range, 5–12 weeks).

- Cianchini et al. (2012) (N=37) demonstrated the efficacy of rituximab 2× 1000 mg IV (Days 1 and 15) in combination with prednisone, with 86% of patients with severe PV in complete remission and off corticosteroids within 6 months of induction therapy. Six patients with a partial remission experienced a complete remission after an additional single 500-mg infusion of rituximab.
- An ongoing investigator-sponsored study in France has completed enrollment (N=90), and final results are anticipated in 2015 (ClinicalTrials.gov, Joly P). This randomized, open-label, multicenter trial is comparing rituximab plus low-dose prednisone with standard-dose prednisone in patients with moderate-to-severe PV.

Administration of rituximab in PV patients was associated most commonly with infusion-related events, which occurred primarily with the first infusion and included fever, chills, nausea, and headache (Feldman and Ahmed 2011). Serious adverse events were consistent with the known safety profile of rituximab (Kasperkiewicz et al. 2012a, 2012b; Lunardon et al. 2012; Balighi et al. 2013; Colliou et al. 2013; Leshem et al. 2013). Overall, the adverse events reported in the literature for rituximab use in PV were consistent with those reported in patients with severe PV treated with other immunosuppressants and with the known adverse event profile of rituximab in autoimmune and other indications.

Given the significant data generated to date from multiple case reports and small uncontrolled clinical studies (as outlined above), the Sponsor believes that treatment with rituximab offers a potential benefit for PV patients and that it is becoming an unapproved standard of care, especially in PV patients for whom conventional therapy has failed. In addition to the extensive safety database available from the use of rituximab across multiple indications, demonstration of efficacy and safety in this single pivotal Phase III trial, to be conducted in patients with moderate-to-severely active PV, would enable a benefit-risk assessment in this rare disease.

1.4.3 Efficacy and Safety of Mycophenolate Mofetil in Pemphigus Vulgaris

There have been multiple publications describing the efficacy and safety of MMF in the treatment of PV. Most of these were uncontrolled studies and involved small numbers of patients. Doses ranged from 1–3.5 g/day, and duration of treatment from 1 month to 4 years. These studies showed that MMF was well tolerated in most patients and had a favorable safety profile when prescribed at 2–3 g/day given in divided doses. MMF is associated with dose-limiting toxicity, particularly gastrointestinal and hematologic toxicities, and doses above 3 g/day are not typically used in PV (Beissert et al. 2010). Published studies have also demonstrated that, when combined with prednisone, MMF is very effective in achieving remission (Marzano et al. 2006; Sarma and Ghosh 2007; Zwerner and Fiorentino 2007; Doukaki et al. 2011; Strowd et al. 2011; Eskin-Schwartz et al. 2011, 2012; Ioannides et al. 2012; Almugairen et al. 2013; Vyas et al. 2013).

The International Pemphigus and Pemphigoid Society endorses published treatment guidelines (Harman et al. 2003), and the European Dermatology Forum, in cooperation with the European Academy of Dermatology and Venereology, developed treatment guidelines generated by expert consensus, which support the use of either MMF or azathioprine as immunosuppressive adjuvants (European Dermatology Forum 2013). A comparison of these two therapies concluded that MMF was slightly better at inducing remission and was associated with fewer adverse events (Beissert et al. 2006).

A pivotal, prospective trial sponsored by Vifor Pharma, Ltd. (Beissert et al. 2010) examined the use of MMF versus placebo in PV patients with mild-to-moderate disease receiving prednisone. While this study did not meet its primary endpoint of complete remission (i.e., absence of new, persistent oral or cutaneous lesions, and prednisone dose $\leq$10 mg/day from Weeks 48–52), it identified that a dose of 2 g/day is considered to be equally effective to 3 g/day when evaluating secondary endpoints, including time to response and duration of response. In addition, MMF was well tolerated in this study over a treatment period of up to 52 weeks, with the majority of adverse events being mild or moderate and most frequently involving infections and infestations, which appeared to be treatment and dose dependent. In the MMF 3 g/day treatment group, frequently reported adverse events included oral candidiasis, headache, and upper respiratory tract infection, which occurred with a higher frequency than in the placebo or MMF 2 g/day groups. The MMF 2 g/day group had the highest incidence of nasopharyngitis, pyrexia, cough, hypertension, and arthralgia. While laboratory values generally remained normal over the course of the study, one subject in the MMF 3 g/day group experienced severe lymphopenia and severe neutropenia and was subsequently withdrawn from the study.

Based on this information, MMF has been selected to be the active comparator in this study at a proposed dose of 2 g/day orally.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of rituximab compared with MMF in achieving sustained complete remission, evaluated by the PDAI (see Section 3.4.1.1), and assessed at Week 52 in patients with moderate-to-severely active PV

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of rituximab compared with MMF, as measured by the time to disease flare, the duration of sustained complete remission, the total number of disease flares during the treatment period, and the time to initial sustained complete remission

- To assess corticosteroid exposure over 52 weeks
- To assess the effect of rituximab compared with MMF on health-related quality of life (HRQoL), as measured by the Dermatology Life Quality Index (DLQI)
- To assess the effect of rituximab compared with MMF on patients' impression of PV symptoms, as measured by the Patient Global Impression of Change (PGIC) questionnaire
- To assess the effect of rituximab compared with MMF on clinician impression of patients' PV symptoms, as measured by the Clinician Global Impression of Change (CGIC) questionnaire

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety of rituximab compared with MMF, with a focus on adverse events and safety laboratory values
- To evaluate corticosteroid-related adverse events in relation to corticosteroid exposure

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study will include, but are not limited to, the following:

- To evaluate the efficacy of rituximab compared with MMF, as measured by the proportion of patients achieving complete or partial remission by 24 weeks and 52 weeks
- To explore the pharmacokinetics and pharmacodynamics of rituximab, and the pharmacodynamics of MMF, in patients with PV
- To evaluate the effect of rituximab as compared with MMF on the change in PDAI activity score
- To evaluate the effect of rituximab as compared with MMF on anti-Dsg autoantibody titers (anti-Dsg1 and anti-Dsg3) and other mechanistic studies of interest in patients with PV
- To assess the effect of rituximab compared with MMF on health utilities as measured by the European Quality of Life (EuroQol) 5-Dimension Questionnaire, 3-level version (EQ-5D-3L)
- To assess the effect of rituximab compared with MMF on HRQoL, as measured by the Skindex-29
- *To evaluate the efficacy of rituximab compared with MMF, as measured by the proportion of patients experiencing treatment failure from Week 12 to Week 52*

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a Phase III, randomized, double-blind, double-dummy, active-comparator, parallel-arm, multicenter study to evaluate the efficacy and safety of rituximab compared with MMF in patients with moderate-to-severely active PV requiring 60–120 mg/day PO prednisone or equivalent (1.0–1.5 mg/kg/day). Patients must have a confirmed diagnosis of PV within the previous 24 months (by skin or mucosal biopsy and immunohistochemistry) and evidence of moderate-to-severely active disease at screening (defined as a total PDAI activity score of ≥15).

This international study will be conducted at investigational sites throughout North America, Europe, the Middle East, and Latin America. It is expected that approximately 60 centers will participate. Approximately *132* patients will be randomized in a 1:1 ratio to receive either rituximab plus MMF placebo or rituximab placebo plus MMF. Randomization will be stratified by duration of illness (newly diagnosed [i.e., diagnosed within the 1 year prior to screening] vs. diagnosed greater than 1 year) and geographical region (North America [U.S./Canada] vs. rest of world).

The study will consist of three periods: a screening period of up to 28 days, a 52-week double-blind treatment period, and a 48-week safety follow-up (SFU) period that begins at the time of study treatment completion or discontinuation.

Rituximab (1000 mg or matching placebo) will be administered by IV infusion on Day 1 and Day 15, with repeat rituximab (or matching placebo) administration on Day 168 and Day 182 provided specific safety criteria have been met (see Section 4.6.4). MMF (500 mg or matching placebo) will be administered PO twice daily (every 12 hours [Q12H]), starting with a total dose of 1 g/day on Day 1. The MMF dose will be titrated to achieve a goal of 2 g/day in divided doses (1 g Q12H) by Week 2. Treatment with MMF (or matching placebo) will continue through Week 52.

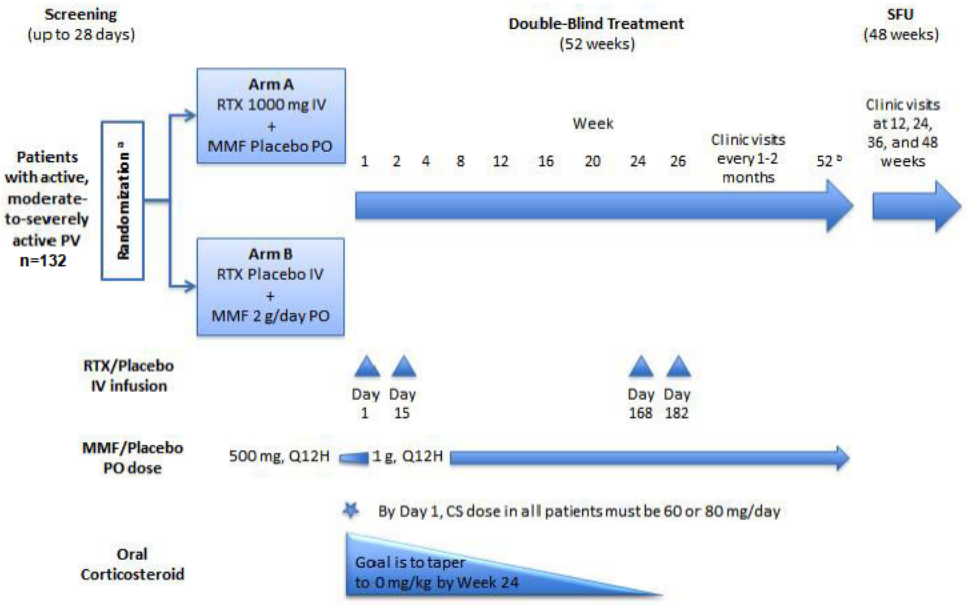
In order to reduce the frequency and severity of infusion-related reactions, all patients will receive methylprednisolone 100 mg or saline solution prior to infusion of rituximab or rituximab placebo, respectively. This premedication will be administered by slow IV infusion, and administration should be completed at least 30 minutes prior to infusion of rituximab or rituximab placebo.

All patients should be premedicated with paracetamol/acetaminophen (1 g PO) and an antihistamine (diphenhydramine HCl 50 mg PO, or IV equivalent, or equivalent dose of a similar agent or in accordance with local approved labeling) 30–60 minutes prior to the start of the infusion of rituximab or rituximab placebo.

Eligible patients will be receiving 60–120 mg/day PO prednisone or equivalent (1.0–1.5 mg/kg/day), with the goal of tapering to 0 mg/day during the course of the study, as described in Section 3.1.2.

An overview of the study design is provided in Figure 1. The schedule of assessments for the screening and treatment periods is provided in Appendix 1.

Figure 1 Overview of Study Design



CS = corticosteroid (prednisone or equivalent); IV = intravenous; MMF = mycophenolate mofetil; PO = by mouth; PV = pemphigus vulgaris; Q12H = every 12 hours; RTX = rituximab; SFU = safety follow-up.

[a] Administrations of the first dose of study treatment (Day 1) should occur within 24 hours following the baseline assessments. However, administration up to 72 hours will be allowed when necessary. The second infusion should occur on Day 15±1 day.

[b] Primary efficacy endpoint evaluated by PDAI is to be measured at Week 52.

The double-blind treatment period will be completed at Week 52. After Week 52, patients will no longer be able to receive further courses of study treatment, but may receive care according to best medical judgment and local standards and practices.

Patients can be discontinued from study treatment at any time during the study. Patients who withdraw from the treatment period will return to the clinic for an early withdrawal visit, per the schedule of assessments (see Appendix 1). If a patient withdraws at or

during a scheduled or unscheduled visit, the visit should proceed as the withdrawal visit, that is, only the withdrawal visit assessments should be conducted. After the withdrawal visit, the patient will be asked to enter the SFU period of the study.

All patients who withdraw from the treatment period or who complete the total 52-week treatment period must return for post–*Week 52* SFU assessments at 12, 24, 36, and 48 weeks after either the early withdrawal visit or study treatment completion, respectively. Thus, patients will be followed for approximately 1 year in the SFU period. A schedule of assessments during the SFU period is provided in Appendix 2.

Before Week 12, patients who experience treatment failure (as defined in Section 3.1.3) will require an early withdrawal visit and will be followed in the SFU period to receive standard-of-care treatment per the investigator's best medical judgment.

From Week 12 through Week 52, patients who experience treatment failure (as defined in Section 3.1.3) are eligible to receive rescue therapy during the treatment period with another immunosuppressive medication, IV Ig, plasmapheresis, or another treatment or procedure as per the investigator's best medical judgment. An early withdrawal visit is not required for a patient to receive rescue therapy, and patients should continue to be followed in the study per the 52-week treatment period (see Appendix 1).

If a patient receives rescue therapy with rituximab, the number and timing of infusions will be at the discretion of the investigator. Every effort will be made to maintain the study blind, but the patient may be unblinded at the discretion of the Principal Investigator's safety assessment. Patients who receive rescue infusions with rituximab from Week 12 through Week 24 will not receive the scheduled rituximab or matching placebo infusions on Days 168 and 182. Careful consideration should also be given as to whether MMF/matching placebo are continued following rescue therapy with any immunosuppressive medication.

Evaluation of the primary endpoint will occur at Week 52. To prevent potential unblinding due to observed efficacy or laboratory changes, a dual-assessor approach will be used to evaluate efficacy and safety.

3.1.2 Corticosteroid Treatment

Patients eligible for this study will be receiving 60–120 mg/day background oral prednisone or equivalent (1.0–1.5 mg/kg/day) at study entry. During the screening period (up to 28 days), the daily corticosteroid dose may be tapered, as directed by the investigator on the basis of disease activity and tolerability to reach a dosage of 60 or 80 mg/day by Day 1. Thereafter, corticosteroid treatment should then be tapered according to the treatment guideline in Table 1, which provides recommended doses based on the presence of disease activity, defined as the appearance of new lesions or the extension of established lesions. The decision to taper the corticosteroid dose can be affected by physician preferences, patient tolerability, and local practices, among

other considerations. The oral corticosteroid dose may be increased during the study as needed as the primary intervention for control of disease activity. Prednisone (or equivalent) will be sourced locally.

The goal of study treatment is to maintain disease control and ultimately achieve disease remission. Oral corticosteroids will be tapered to the target prednisone (or equivalent) dosage of 0 mg/day by Week 24 (or sooner, if appropriate). From Week 24 to Week 52, the corticosteroid dosage should be maintained at 0 mg/day. However, patients who experience a disease flare (as defined in Section 3.4.1.2) at 0 mg/day should restart at Step 5 of Table 1 (20 mg/day). Patients whose disease is not controlled after increasing the corticosteroid dose up to an allowable maximum dose of 240 mg/day will be considered to have experienced treatment failure and may receive standard-of-care treatment per the investigator's best medical judgment. Use of minimal concomitant topical corticosteroids will be permitted at the investigator's discretion but will be tracked carefully during the course of the study.

Table 1 Corticosteroid Treatment Guideline

Step	No. of Weeks	Daily Dose of Prednisone or Equivalent	Presence of Disease Activity [a]	
			No	Yes
1 (start) [b]	1 week	80 mg	Go to Step 2	Go to Step A
A	1 week	120 mg	Go to Step 2	Go to Step B
B	1 week	240 mg	Go to Step A	Discontinue taper [c]
2 (start) [b]	1 week	60 mg	Go 1 step forward	Go to Step 1
3	1 week	40 mg		Go 1 step back
4	2 weeks	30 mg		
5	2 weeks	20 mg		Go 2 steps back
6	2 weeks	15 mg		
7	2 weeks	12.5 mg		
8	2 weeks	10 mg		
9	2 weeks	7.5 mg		
10	2 weeks	5 mg		
11	2 weeks	2.5 mg	Stop corticosteroid	
12	During complete remission	0 mg		Restart at Step 5

Notes: On Day 1, start the oral corticosteroid regimen with an initial dosage of 60 or 80 mg/day prednisone (or equivalent), as outlined in the schedule. Increase the dose if disease activity is present after 1 week. If necessary, increase the dose again (to 240 mg/day) if disease activity is still present after the second week.

[a] Disease activity is defined as the appearance of new lesions or the extension of established lesions.

[b] Patients on 80 mg/d on Day 1 will start at Step 1. Patients on 60 mg/d on Day 1 will start at Step 2.

[c] Patients whose disease is not controlled after increasing the corticosteroid dose to 240 mg/day will be considered to have experienced treatment failure and may receive standard-of-care treatment per the investigator's best medical judgment.

Source: Modified from Mentink LF, Mackenzie MW, Tóth GG, et al. Randomized controlled trial of adjuvant oral dexamethasone pulse therapy in pemphigus vulgaris (PEMPULS Trial). Arch Dermatol 2006;142:570–6.

3.1.3 Definition of Treatment Failure

Treatment failure is the occurrence of any one of the following events:

- After disease control has been achieved, a two-step increase in prednisone (or equivalent) dose to ≥20 mg/day for more than 2 weeks to treat increased disease activity during the corticosteroid taper
- Failure to achieve disease control after receiving 240 mg/day PO prednisone (or equivalent) for 1 week

  Disease control is defined as the time at which new lesions cease to form and established lesions begin to heal (beginning of the consolidation phase).
- Increase in MMF/matching placebo dosage above 2 g/day
- Initiation of any rescue therapy (addition of another immunosuppressive medication, additional rituximab open-label doses, IV Ig, plasmapheresis, or another treatment or procedure) as determined by the investigator's best medical judgment

Patients experiencing treatment failure prior to achieving sustained complete remission will be categorized as non-responders in the primary analysis, but will continue to be followed in the study per the schedule of assessments. Patients who achieve sustained complete remission without experiencing an event constituting treatment failure beforehand will not be categorized as non-responders, regardless of whether they subsequently meet the criteria during the remaining treatment period.

3.1.4 Independent Data Monitoring Committee

Safety data will be reviewed by an independent Data Monitoring Committee (iDMC) as specified in the iDMC Charter and at the following times, whichever occurs first:

- After the first 10 patients have completed at least 3 months of study treatment or have withdrawn early from the study
- After the first 5 telemedicine (TM) patients have completed at least 3 months of study treatment or have withdrawn early

Thereafter, meetings will be held approximately every 4 to 6 months (frequency may be adjusted during the recruitment period), after 10 TM patients have completed at least 3 months of study treatment or withdrawn early from the study, or as requested by the iDMC.

The safety evaluations will be detailed in the iDMC Charter and will include review of conventional safety variables, such as serious adverse events, infusion-related reactions, and infections. Any safety event that requires unblinding will be immediately reported to the iDMC and to the U.S. Food and Drug Administration (FDA) in a U.S. Investigational New Drug (IND) safety report. The iDMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of patients. The iDMC will also review the TM data (see Section 7.3). After reviewing safety data, the iDMC will make recommendations regarding continuation, termination,

or modification of the study. The details of the iDMC roles and responsibilities and the logistics of the iDMC activities will be outlined in an iDMC Charter.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 2 years after the last patient is enrolled, assuming a 52-week treatment period and a 48-week SFU period for the last patient.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Rituximab Dose and Schedule

In 2006, rituximab was approved by the FDA for use in RA at a dosing schedule in adults that is irrespective of body weight (i.e., 2×1000 mg IV [Days 1 and 15 with repeated infusions between Months 4 and 6]). Rituximab is under investigation in this study as an experimental drug in PV and is currently not approved for the treatment of patients with PV.

In previous studies of rituximab in PV, investigators have used the proposed 2 × 1000 mg IV dose in the initial cycle (Days 1 and 15) as well as 4×375 mg/m^2 IV dose (Days 1, 8, 15, and 22). If a 70-kg person of average height were to be treated with the 375 mg/m^2 approach, the total dose for their initial cycle would be approximately 2.8 g, versus 2 g if the 2×1000 mg IV approach were used. PV (like RA) is an autoimmune disease, and an effective treatment does not require depletion of malignant B-cell clones, as in lymphoma (Leshem et al. 2013). Given the experience with 2×1000 mg IV dose in autoimmune indications, the literature supporting this dose in PV patients, and the fact that this dose results in a lower total exposure and fewer infusions, the Sponsor has selected this dose and schedule for this trial.

In RA, the rituximab dose 2×1000 mg IV (Days 1 and 15) has been demonstrated to be an effective dose, sufficient to sustain B-cell depletion for 6–9 months. Achieving other therapeutic outcomes in PV, such as complete removal of autoantibodies via sustained B-cell depletion in both the periphery and secondary lymphoid organs, is also a target in the management of PV. Sustained complete remission is the ultimate therapeutic goal. A single cycle of rituximab, although generally effective for at least 6 months (24 weeks), is not considered a cure in this autoimmune-relapsing disease. In RA, it is recommended that, until the desired treatment target is reached, drug therapy should be repeated at least every 6 months (Smolen et al. 2010). Additionally, a recent clinical trial investigating the use of rituximab in patients with severe and/or refractory pemphigus (84 PV patients; 8 pemphigus foliaceus patients) showed that patients who do not achieve remission after 1 cycle and those who experience relapse benefit from further cycles of rituximab. This recent study suggested that the majority of PV patients receiving a single cycle of rituximab will experience a disease flare, further supporting the rationale for an additional treatment cycle at 6 months (Heelan et al. 2014).

3.3.2 Rationale for Active Comparator Arm (MMF)

Corticosteroids are felt to be the mainstay of initial therapy for PV patients, and 64% of patients with mild-to-moderate disease achieved a complete remission with initial corticosteroid infusion and prednisone taper without the use of additional immunosuppressants (Beissert et al. 2010). Patients who have persistent disease that is not fully responsive to corticosteroid treatment and those who have a higher risk of prednisone-related complications require additional immunosuppressive therapy (i.e., typically with azathioprine [2 mg/kg PO] or MMF [2 g/day PO]) (Grundmann-Kollmann et al. 1999; Nousari et al. 1999; Powell et al. 2003; Marzano et al. 2006; Sarma and Ghosh 2007; Zwerner and Fiorentino 2007; Doukaki et al. 2011; Strowd et al. 2011; Eskin-Schwartz et al. 2011, 2012; Ioannides et al. 2012; Almugairen et al. 2013; Vyas et al. 2013). A comparison of these two therapies concluded that MMF was slightly better at inducing remission and was associated with fewer adverse events (Beissert et al. 2006).

MMF (CellCept®) is marketed in oral and intravenous dosage forms and is currently approved for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants. For these approved uses, concomitant treatment with cyclosporine and corticosteroids is recommended.

Clinical studies have investigated the use of MMF in other populations, and MMF is currently used to treat other conditions, including PV; however, it is not approved for indications unrelated to organ transplant. As such, MMF is under investigation in this study as an experimental drug in PV and is currently not approved for the treatment of patients with PV. For additional information on the approved indications and relevant safety information, see the local prescribing information for MMF.

The International Pemphigus and Pemphigoid Society has published treatment recommendations that were generated by consensus, and these support the use of either MMF or azathioprine. Internal marketing data from the Sponsor on U.S. practice has determined that a higher proportion of U.S. dermatologists use MMF versus azathioprine (33% vs. 25%, respectively [internal data]), further confirming that MMF is a significant part of the standard-of-care treatment for PV patients. Multiple publications have assessed the efficacy and safety of MMF in the treatment of PV (Eskin-Schwartz et al. 2011).

MMF has typically been prescribed at 2 to 3 g/day given in divided doses in immunologic (non-transplant) indications. A pivotal, prospective, company-sponsored study was conducted that examined the use of MMF for the treatment of PV patients with mild-to-moderate disease. While this study did not meet its primary endpoint of complete remission (i.e., absence of new, persistent oral or cutaneous lesions, and prednisone dose ≤10 mg/day from Weeks 48–52), it identified that a dose of 2 g/day is considered to be equally effective to 3 g/day when evaluating secondary endpoints, including time to response and duration of response. MMF is associated with

dose-limiting toxicity, particularly gastrointestinal and hematologic toxicities, and doses above 3 g/day are not typically used in PV (Beissert et al. 2010). Dose adjustments above 2 g/day are not recommended.

For these reasons, MMF has been selected to be the active comparator in this study. The proposed MMF dosing of 2 g/day PO is consistent with the CellCept® U.S. Package Insert, publications, and guidelines, and represents a strong clinical comparator in the proposed study.

3.3.3 Rationale for Use of the PDAI as the Key Assessment of Disease Activity

Several different instruments assessing clinical disease activity have been developed to capture distribution, activity, and severity of pemphigus. The most commonly used instrument is the PDAI, developed by the International Pemphigus Committee (Murrell et al. 2008; Rosenbach et al. 2009; Daniel et al. 2012). Rahbar et al. (2014) evaluated the PDAI and a number of other validated instruments in a large number of patients with PV. Inter-rater reliability and convergent validity according to anti-Dsg titers (which correlate with pemphigus disease activity) were evaluated, and the authors concluded that the PDAI had the highest reliability and validity. It is recommended for use in multicenter studies of rare diseases, such as PV. The PDAI can be completed in less than 5 minutes. The PDAI will provide a reliable and validated measurement of disease activity and severity in this study.

3.3.4 Rationale for Corticosteroid Treatment Guidelines

There is no uniformly accepted taper regimen for oral corticosteroids. The initial use of high-dose systemic corticosteroids, typically 60–120 mg/day PO prednisone or equivalent (1.0–1.5 mg/kg/day) is frequently used in the treatment of moderate-to-severely active disease. Recent studies employed a similar regimen and suggest that a dose of 1.0–1.5 mg/kg per day PO prednisone (or equivalent) tapered over 3–6 months is a standard regimen (Beissert et al. 2006, 2010). The decision to taper can be affected by various considerations, including physician preferences, patient tolerability, and local practices.

The rate at which corticosteroids are tapered in this study is based on the clinical manifestations of the disease, and tapering too rapidly increases the chances of a disease flare. The suggested taper and initial dose were discussed with expert advisors in an advisory board and deemed desirable (Advisory Board Meeting 12 February 2014). Patients who experience disease flare will receive an increase in prednisone up to 240 mg/day at the investigator's discretion. Patients who require prednisone 240 mg/day for 1 week and are still not controlled and patients who require a two-step increase in prednisone dose to ≥20 mg/day for more than 2 weeks to treat increased disease activity during the corticosteroid taper will be considered non-responders in the primary efficacy analysis. There are additional treatment failure criteria that lead to protocol-defined non-response, outlined in Section 3.1.3.

3.3.5 Rationale for Biomarker Assessments, including Optional Whole Blood and Serum Samples for Storage and Future Research

PV is a heterogeneous disease, and anti-Dsg1 and anti-Dsg3 autoantibodies expression has been shown to vary among patients (Harman et al. 2001). Autoantibody titers may influence responses to rituximab or MMF. Predictive biomarker samples collected during the study will be assessed in an effort to identify those patients with autoantibody-driven pathogenesis and, potentially, those who are most likely to respond to rituximab.

Identification of proteins targeted by autoantibodies in PV is a subject of intense research. There is evidence that keratinocyte antigens other than Dsg1 and Dsg3 are pathophysiologically relevant (Nguyen et al. 1998). Current understanding, however, does not adequately explain the mechanism of acantholysis in patients lacking anti-Dsg1 and anti-Dsg3 antibodies. Results of a recent study indicate that autoreactivity in PV relies on somatic mutations generated in response to an antigen unrelated to Dsg3 (Di Zenzo et al. 2012). Taken together, these observations justify a search for novel targets of pemphigus autoimmunity via collection of additional optional blood samples for the Roche Clinical Repository (RCR) for storage and future research in PV. These samples include serum for biomarker analysis and whole blood samples for RNA and DNA analysis.

Other pharmacodynamic (PD) biomarkers, including CD19, will be assessed to demonstrate evidence of biologic activity of rituximab in patients and to inform potential revisions to the PK sample collection schedule. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is as follows:

- Proportion of patients *(excluding TM patients)* who achieve a sustained complete remission without experiencing an event that constitutes treatment failure (as defined in Section 3.1.3), as measured at Week 52

  Sustained complete remission is defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for a total of at least 16 consecutive weeks, during the 52-week treatment period.

  Patients with transient new lesions for 1 week or less that heal without additional systemic corticosteroid therapy will not be considered to have experienced treatment failure.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Cumulative oral corticosteroid dose (prednisone or equivalent) over the treatment period
- Total number of disease flares during the treatment period
- Time to sustained complete remission
- Time to disease flare

  Disease flare is defined as appearance of three or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved disease control.
- Change in HRQoL, as measured by the DLQI score from baseline to Week 52
- Duration of sustained complete remission
- Patients' impression of change in PV symptoms, as measured by the PGIC score during the treatment period
- Clinician impression of change in patients' PV symptoms, as measured by the CGIC score during the treatment period

3.4.2 Safety Outcome Measures

The safety outcome measures include, but are not limited to, the following:

- Nature, frequency, and severity of adverse events, including serious adverse events and adverse events leading to discontinuation
- Vital signs and clinical laboratory test results (including complete blood count and blood chemistry)
- Incidence of HACA
- Circulating B cells, T cells, natural killer (NK) cells, plasma cells, and other leukocytes
- Plasma Ig levels (total Ig, IgG, IgM, and IgA)
- Corticosteroid-related adverse events in relation to corticosteroid exposure

3.4.3 Exploratory Outcome Measures

The exploratory outcome measures for this study will include, but are not limited to, the following:

- Proportion of patients achieving a complete remission by Week 24 and by Week 52

  Complete remission is defined as achieving wound healing with no new active lesions (i.e., PDAI activity score of 0) for at least 8 consecutive weeks during the 52-week treatment period.
- Proportion of patients achieving a partial remission by Week 24 and by Week 52

  Partial remission is defined as the presence of transient new lesions that heal within 1 week (while the patient is receiving minimal therapy, including topical

corticosteroids). Minimal therapy is defined as ≤10 mg/day prednisone (or equivalent) for at least 8 consecutive weeks during the 52-week treatment period.

- Pharmacokinetics/pharmacodynamics of rituximab

  PK/PD parameters include, but are not limited to, serum levels of rituximab, peripheral CD19+ B-cell counts, HACA, and autoantibody concentrations.

- To explore the pharmacodynamics of MMF in patients with PV
- Change in total PDAI activity score during the treatment period
- Change from baseline in anti-Dsg1 and anti-Dsg3 autoantibodies
- Change in health utilities as assessed by the EQ-5D-3L score from baseline to Week 52
- Change in HRQoL, as measured by the Skindex-29 from baseline to Week 52
- *Proportion of patients who experience treatment failure from Week 12 to Week 52*

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *132* patients with active moderate-to-severely active PV will be recruited into this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 18–75 years
- Signed Informed Consent Form
- First confirmed diagnosis of PV within the previous 24 months, based on the presence of histological features of acantholysis via skin or mucosal biopsy and one of the following: tissue-bound IgG antibodies by direct immunofluorescence on the surface of affected epithelium or serological detection of serum Dsg3 autoantibodies against epithelial cell surface either by indirect immunofluorescence microscopy or by enzyme-linked immunosorbent assay
- Presence of moderate-to-severely active disease, defined as overall PDAI activity score of ≥15
- Receiving standard-of-care corticosteroids consisting of 60–120 mg/day PO prednisone or equivalent (1.0–1.5 mg/kg/day) and, in the judgment of the investigator, expected to benefit from the addition of immunosuppressive therapy
- For women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two effective methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 12 months after the last dose of study treatment

Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Barrier methods must always be supplemented with the use of a spermicide.

Examples of contraceptive methods with a failure rate of <1% per year (highly effective contraceptive methods) include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

- For men (including those who have undergone a vasectomy): agreement to remain abstinent or use a condom during the treatment period and for at least 12 months after the last dose of study treatment and agreement to refrain from donating sperm during this same period

  Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  In addition to male contraception, agreement to advise female partners of childbearing potential to use highly effective contraception during the study and for at least 12 months after the last dose of study treatment
- Agreement to avoid excessive exposure to sunlight during study participation
- Able to comply with the study protocol, in the investigator's judgment

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Diagnosis of pemphigus foliaceus or evidence of paraneoplastic pemphigus or other non-PV autoimmune blistering disease
- History of a severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies, or known hypersensitivity to any component of rituximab
- Known hypersensitivity or contraindication to MMF, mycophenolic acid, polysorbate, or oral corticosteroids
- Lack of peripheral venous access
- Pregnant or lactating, or intending to become pregnant during the study

  Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have two negative results with a sensitivity of ≥25 mIU/mL: one from a serum pregnancy test at Day −8 to Day −10 of screening and another from a urine pregnancy test at Day 1 prior to randomization.
- Participated in another interventional clinical trial within 28 days prior to randomization

- Use of any investigational agent within 28 days or 5 elimination half-lives prior to randomization (whichever is the longer)
- Significant cardiovascular or pulmonary disease (including obstructive pulmonary disease)
- Evidence of any new or uncontrolled concomitant disease that, in the investigator's judgment, would preclude patient participation, including but not limited to nervous system, renal, hepatic, endocrine, malignant, or gastrointestinal disorders
- Any concomitant condition that required treatment with oral or systemic corticosteroids within 12 weeks prior to randomization
- Treatment with IV Ig, plasmapheresis, or other similar procedure within 8 weeks prior to randomization
- Treatment with immunosuppressive medications (e.g., azathioprine, MMF) within 1 week prior to randomization
- Treatment with cyclophosphamide within 12 weeks prior to randomization
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection and other severe Immunodeficiency blood disorders
- Known active infection of any kind (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to screening, or completion of oral anti-infectives within 2 weeks prior to randomization

  Entry into this study may be reconsidered once the infection has fully resolved.
- History of or current cancer, including solid tumors, hematologic malignancies, and carcinoma in situ (except basal cell carcinoma and squamous cell carcinoma of the skin that have been excised and cured)
- Currently active alcohol or drug abuse, or history of alcohol or drug abuse within 24 weeks prior to screening
- Major surgery within 4 weeks prior to randomization, excluding diagnostic surgery
- Treatment with rituximab or a B cell–targeted therapy (e.g., anti-CD20, anti-CD22, or anti-BLyS) within 12 months prior to randomization
- Treatment with a live or attenuated vaccine within 28 days prior to randomization

  It is recommended that a patient's vaccination record and the need for immunization prior to study entry be carefully investigated.
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase $>2.5\times$ the upper limit of normal (ULN)
- Absolute neutrophil count (ANC) $<1.5\times10^3/\mu L$
- Hemoglobin <8.0 g/dL
- Positive test results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) serology at screening

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

A total of approximately *132* patients will be recruited into this study and will be randomized in a 1:1 ratio to two treatment arms using an interactive/web voice response system (IxRS). Patient randomization numbers will be generated by the IxRS vendor. A unique randomization number will be linked to the patient's identification number (electronic Case Report Form [eCRF] number) via the IxRS. Patients may not be dosed at any visit prior to receiving the IxRS-assigned medication numbers. Patients who enroll in this study and who have completed treatment as specified are not permitted to be re-randomized to this study; however, re-screening is allowed as described in Section 4.5.1.3.

Randomization will be stratified by duration of illness (newly diagnosed [diagnosed within 1 year prior to screening] vs. diagnosed greater than 1 year from screening) and geographical region (North America [U.S./Canada] vs. rest of world). Patients prematurely discontinued from the study will not be replaced.

The randomization list will not be available at the study center, to the Sponsor monitors, or the Sponsor's project team, including the project statisticians. The medication allocation will only be known to the unblinded drug accountability monitors and an unblinded on-site pharmacist who will prepare locally sourced methylprednisolone for patients receiving rituximab and a saline solution for patients receiving rituximab placebo, to be administered prior to the infusion.

Every effort will be made to maintain the blind; for example, opaque infusion bags and IV lines will be used if local methylprednisolone has noticeable coloring compared with the saline solution. To maintain the blind, investigational sites will not receive data related to CD19+ B-cell counts, PK results, or HACA results. CD19+ B-cell counts will be made available to the investigator at the end of SFU period. In addition, to prevent potential unblinding, there will be an efficacy assessor and a safety assessor for observed efficacy and safety evaluations. Only the safety assessor will have access to adverse event reports and laboratory test results, and will determine dose adjustments and treatment decisions.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blind, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator MMF arm will not be analyzed for rituximab PK except by request (i.e., to evaluate a possible error in dosing).

If the identity of the test medication is necessary for either patient management (in the case of a serious adverse event) or independent pharmacologic analysis of biologic samples, adequate procedures will be in place to maintain the integrity of the data.

Treatment codes should not be broken except in emergency situations, i.e., when knowledge of the treatment is essential for the immediate further management of the patient. For emergency unblinding, the Principal Investigator or designee will contact IxRS prior to unblinding a patient's treatment assignment. IxRS will provide the site with the patient's unblinding treatment code. The Medical Monitor will be notified of this event.

The Principal Investigator should make every attempt to contact the Sponsor before unblinding any patient's treatment assignment, but in any case must do so within 1 working day after the event and, if appropriate, complete an adverse event form. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Unblinding does not in itself necessitate patient withdrawal from study, which would be determined at the discretion of the investigator.

In case of accidental unblinding, all the above procedures should be followed, except an adverse event form should not be completed.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all suspected, unexpected, and serious adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

Patients will be randomized in a 1:1 ratio to receive either rituximab plus MMF placebo or rituximab placebo plus MMF.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Rituximab and Placebo

Rituximab (500-mg vials) and matching placebo will be supplied by the Sponsor. For information on the formulation, packaging, and handling of rituximab, see the pharmacy manual and the Rituximab Investigator's Brochure.

4.3.1.2 MMF and MMF Placebo

MMF (500-mg tablets; 140 tablets per bottle) and matching placebo will be supplied by Sponsor. For information on the formulation, packaging, and handling of MMF, see the local prescribing information for MMF.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Rituximab and Rituximab Placebo

Rituximab at a dose of 1000 mg (or matching placebo) will be administered by IV infusion on Day 1 and Day 15, with repeat rituximab (or matching placebo) administration on Day 168 and Day 182 provided specific safety criteria have been met (see Section 4.6.4). Rituximab (and matching placebo) should be administered in a

hospital, clinic, or healthcare-related environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.

After the end of the infusion, the IV line should remain in place for at least 1 hour to enable administration of drugs intravenously, if necessary. If no adverse events occur during this period of time, the IV line may be removed. Rituximab should not be administered in the setting of an active infection.

All patients will receive 100-mg IV methylprednisolone (patients in the rituximab arm) or a saline solution (patients in the rituximab placebo arm) by slow infusion, to be completed at least 30 minutes prior to each infusion of rituximab or rituximab placebo, respectively. All patients should be premedicated with paracetamol/acetaminophen (1 g PO) and an antihistamine (diphenhydramine HCl 50 mg PO [or IV equivalent] or equivalent dose of a similar agent, or in accordance with local approved labeling) 30 to 60 minutes prior to the start of a rituximab infusion.

Detailed guidance for the administration of rituximab, including the rates of infusions and the actions to be taken in the event of an infusion-related reaction, is provided in Appendix 3.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.6.4, Section 5.1.1.9, and Appendix 3.

Any overdose or incorrect administration of rituximab should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of rituximab should be recorded on the Adverse Event eCRF.

4.3.2.2 MMF and MMF Placebo

MMF (500 mg or matching placebo) will be administered orally twice daily (Q12H) starting on Day 1. Patients will be initiated on 1 g/day MMF or matching placebo given as a divided oral dose. MMF dose will then be titrated to achieve a maximum dose goal of 2 g/day given as a divided oral dose (1 g Q12H) by Week 2. Slower titration will be allowed on the basis of tolerability. Treatment with MMF (or matching placebo) will continue through Week 52.

During the 52-week treatment period, the MMF (or matching placebo) dose should remain as stable as possible. If reductions in dose are necessary because of tolerability, decreases will be allowed in 500-mg decrements and must be recorded on the appropriate eCRF. If neutropenia develops (ANC $<1.3\times10^3/\mu L$), dosing with MMF should be interrupted or the dose should be reduced. Guidelines for dosage modification and treatment interruption or discontinuation of MMF are provided in the MMF prescribing information.

In cases where MMF is introduced as a standard-of-care therapy, it should always be initiated on 1 g/day as a divided oral dose for 2 weeks.

Dose adjustments of MMF/matching placebo above 2 g/day are not recommended in this study.

Any overdose or incorrect administration of MMF should be noted on the appropriate eCRF. Adverse events associated with an overdose or incorrect administration of MMF should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Study Drug

The Sponsor will offer post-trial access to the study drug (rituximab/MMF) free of charge to eligible patients in accordance with the Roche group Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient *may* be eligible, *upon the investigator's request,* to receive *post-trial access to* study drug after the end of the *study (i.e., end of SFU)*, if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any *country-specific* legal or *local* regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)

- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for PV
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for PV
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Internet site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any background drug or substance (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from the time the patient is screened in the study until study completion. This includes any preventative vaccines (e.g., tetanus or flu vaccines) that the patient may receive during the course of this study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. It should be noted that live or attenuated vaccines (e.g., certain formulations of influenza vaccines) are not permitted. Additional use of immunosuppressive medications, cell-depleting agents, or other standard-of-care therapies per best medical judgment must be reported as concomitant medications.

4.4.1 Corticosteroids

Oral prednisone (or equivalent) dose adjustments will be the main approach to treat either new or worsened disease activity. Patients who experience disease flare (defined as appearance of three or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved disease control) or who are unable to adhere to the protocol-defined prednisone tapering regimen (see Table 1) prior to Week 52 because of ongoing disease activity should interrupt the protocol-defined prednisone taper and be given therapy with prednisone (up to 240 mg/day) at the discretion of the investigator, according to the guideline in Table 1. The patient should continue to receive blinded study treatment (rituximab, MMF, or matching placebo) and should continue with all study assessments as per Appendix 1 for the duration of the 52-week, double-blind treatment period. Ongoing prednisone use will be at the discretion of the investigator during the treatment period.

Patients who require a two-step increase in corticosteroid dose to $\geq$20 mg/day for more than 2 weeks to treat increased disease activity will be deemed non-responders in the primary analysis.

All prednisone (or equivalent) doses and adjustments should be recorded on the appropriate eCRF.

4.4.2 Additional Permitted Therapy and Procedures

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Patients not already taking vitamin D (400 IU/day) and calcium supplements (1200 mg/day calcium citrate or 1500 mg/day calcium carbonate) may start these supplements at study initiation. *Pneumocystis jirovecii* pneumonia prophylaxis may be performed according to local clinical practice guidelines and investigator judgment.

From Week 12 through Week 52, an additional provision is made for patients who would otherwise be withdrawn from the study because of lack of efficacy. Specifically, patients who experience treatment failure between Week 12 through Week 52 are eligible to receive rescue therapy with another immunosuppressive medication, IV Ig, plasmapheresis, rituximab, or another treatment or procedure as per the investigator's best medical judgment and continue to be followed in the 52-week treatment period per the treatment period schedule of assessments (see Appendix 1). Details of additional therapies for PV should be reported as concomitant medications.

If a patient receives rescue therapy with any medication, dose and dosing schedule will be at the discretion of the investigator. Every effort will be made to maintain the study blind, but the patient may be unblinded at the discretion of the Principal Investigator's safety assessment. Patients who receive rescue infusions with rituximab from Week 12 through Week 24 will not receive the scheduled rituximab or matching placebo infusions on Days 168 and 182. Careful consideration should also be given as to whether MMF/matching placebo are continued following rescue therapy with any immunosuppressive medication.

4.4.3 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 28 days or 5 elimination half-lives prior to initiation of study treatment, unless otherwise specified below, with prior approval of the Sponsor, or required for a medical emergency:

- Investigational therapy
- Live or attenuated vaccines (i.e., measles, mumps, rubella, oral polio, bacillus Calmette-Guérin, typhoid, yellow fever, vaccinia, some forms of influenza [e.g., FluMist®], or any other live vaccines not yet licensed but belonging to this category) are prohibited during the study and while the patient's peripheral CD19+ B cells are depleted below the central laboratory lower limit of normal.
  - Non-live or inactivated vaccine (e.g., some forms of influenza) is not prohibited during the study; however, the efficacy of certain vaccines during or following periods of B-cell depletion has not been studied.
  - Patients who are eligible for yearly influenza vaccine or who require other non-live booster vaccinations can receive vaccination with killed/toxoid vaccines consistent with normal clinical practice.

Although not prohibited, caution should be especially used with the following:

- Immunosuppressants/immunomodulators, antacids containing aluminum and/or magnesium, antivirals (e.g., acyclovir, ganciclovir, valganciclovir), calcium-free phosphate binders (e.g., aluminum products, lanthanum, sevelamer), rifampin, H_2 blockers, and proton-pump inhibitors

If concomitant medications (including prescription and over-the-counter medications, dietary and herbal supplements, vitamins, and nutritional supplements) are required, the investigator should use caution and monitoring when considering concomitant use with rituximab or MMF.

4.5 STUDY ASSESSMENTS

To prevent potential unblinding due to observed efficacy or changes in laboratory test results, a dual-assessor approach will be used to evaluate efficacy and safety. The efficacy assessor should be a dermatologist or skilled physician PV assessor. To ensure consistency, wherever possible it is required that the same efficacy assessor continues to assess all efficacy parameters throughout the study for any particular patient. The efficacy assessor will have access only to the efficacy data. The safety assessor should be a dermatologist. The safety assessor will have access to both safety and efficacy data and will make all treatment decisions based on the patient's clinical response and laboratory test results.

It is essential that assessments by the patient (e.g., patient-reported outcomes [PROs]) and efficacy assessor are made before those of the safety assessor. Consequently, assessments should be made in the following order:

1. Patient-reported outcomes: DLQI, PGIC, EQ-5D-3L, and Skindex-29
2. Clinician-reported outcome (efficacy assessor): CGIC
3. Efficacy assessor: PDAI (activity scale), lesion count, flare assessment
4. Safety assessor: adverse event and laboratory assessments, corticosteroid dose assessment, and all treatment decisions

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

4.5.1.1 Screening Examination

The screening visit can occur up to 28 days prior to the first dose of study treatment. The timing of the pregnancy test during the screening period (8 to 10 days prior to the planned pregnancy test on Day 1) may require the patient to return to the clinic for an

additional visit. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization on Day 1 (see Section 4.1.1 and Section 4.1.2). Screening assessments will be performed in accordance with the schedule of assessments (see Appendix 1). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.1.2 Re-Testing: Laboratory Inclusion/Exclusion Criteria

If a patient does not meet the laboratory eligibility criteria at screening (see Section 4.1.1 and Section 4.1.2), the investigator may repeat the test twice within the screening period. If the patient does not meet the laboratory criteria for a third time, the patient will be considered a screen failure. It is possible to re-screen a patient (see Section 4.5.1.3).

It will not be considered re-testing if blood samples have to be redrawn owing to sample handling problems, breakage, or sample integrity.

4.5.1.3 Re-Screening

Re-screening refers to repeating the entire screening process if a patient has not met all the eligibility criteria within 28 days of the original screening visit.

Patients are allowed to be re-screened only once. Each patient must be re-consented before re-screening occurs.

It will not be considered re-screening if blood samples have to be redrawn owing to sample handling problems, breakage, or sample integrity.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all previous medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 6 months prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position.

4.5.5 Assessments of Disease Activity

Disease status and activity will be evaluated using the PDAI and the CGIC at the timepoints specified in Appendix 1.

The PDAI integrates cutaneous with mucosal disease in well-defined anatomical locations, assesses number and sizes of lesions, and scores post-inflammatory hyperpigmentation of resolving lesions (Murrell et al. 2008). It is a validated instrument with a high inter-rater reliability.

The CGIC is a measure of perceived change in PV symptoms as assessed by the clinician using a 7-item categorical scale ranging from “very much improved” to “very much worse.”

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Pregnancy test

  All women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits.
  If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Prior to starting study drug, female patients of childbearing potential must have two negative pregnancy tests. The second test on Day 1 prior to randomization should be performed 8 to 10 days after the first test during the screening period.

- Safety laboratory assessments

  Hematology (white blood cell [WBC] count, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count, differential [neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells])

  Serum chemistry (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen [BUN] or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and lactate dehydrogenase [LDH])

  Viral serology

  – HBsAg
  – HBcAb
  – HCV antibody

  Urinalysis dipstick (glucose, protein, blood); if abnormal findings are present, a microscopic examination should be performed (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria)

- Immunology and other laboratory assessments

  Lymphocyte subtypes and FACS analysis

  – Determination of NK-, T-, and B-cell populations will be performed via FACS analysis; lymphocyte subtypes of interest may include but are not limited to CD56+ NK cells; CD3+, CD4+, CD8+, and NK T cells; CD19+ and CD27+ B cells; CD19+ CD27-naive B cells; CD19+CD27+ memory B cells; and $CD24^{high}CD38^{high}$ transitional B cells.

  Quantitative Ig levels: total Ig, IgA, IgG, and IgM

  Autoantibodies: anti-Dsg1 and anti-Dsg3 antibodies

  HACA

  Rituximab PK analysis (see Appendix 1 and Appendix 2 for timepoints)

  Optional whole blood sample for DNA, whole blood sample for RNA, and serum biomarker sample (for patients who sign the Optional Research Informed Consent Form [see Section 4.5.10])

Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.7 Electrocardiogram

An electrocardiogram (ECG) should be taken at the time indicated in Appendix 1 and reviewed by the investigator or designee.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Any abnormality identified at baseline should be recorded on the eCRF. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.8 Chest Radiograph

Posterior-anterior (P/A) and lateral chest radiographs (or chest radiographs in accordance with local requirements) should be obtained at screening and reviewed by the investigator or designee. Any abnormality identified at baseline should be recorded on the eCRF. At screening, if chest radiographs have been taken within the past 3 months that show no clinically significant abnormality, and there are no signs or

symptoms suggestive of pulmonary disease that would exclude the patient, then chest radiograph does not need to be repeated.

4.5.9 Patient-Reported and Clinician-Reported Outcomes

PRO and clinician-reported outcomes (ClinRO) data will be collected via questionnaires to more fully characterize the clinical profile of rituximab. The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO and ClinRO assessments and the administration of study treatment.

The DLQI is a 10-item, validated questionnaire used routinely in clinical practice to evaluate the impact of dermatologic diseases on patients' lives. The DLQI questionnaire refers to the previous 7 days and questions are categorized into 6 domains: symptoms and feelings (2 items), daily activities (2 items), leisure (2 items), work and school (1 item), personal relationships (2 items), and treatment (1 item). A total DLQI score is calculated on a scale of 0 to 30, where higher scores mean greater impairment of the patient's HRQoL. A copy of the DLQI is provided in Appendix 6.

The PGIC is a measure of perceived change in PV symptoms as assessed by the patient using a 7-item categorical scale ranging from "very much improved" to "very much worse." The PGIC asks patients to rate the change of their PV symptoms. The recall period of the PGIC is from the start of treatment. A copy of the PGIC is provided in Appendix 8.

The EQ-5D-3L is a generic, preference-based, health-utility measure including questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. It is accompanied by a visual analog scale (VAS) on which the patient provides a self-assessment of their own health in a range from 0 (worst imaginable health state) to 100 (best imaginable health state) (Gusi et al. 2010). The EQ-5D-3L will be used in this study for economic modeling. A copy of the EQ-5D-3L is provided in Appendix 7.

The Skindex-29 is a 30-item questionnaire used to assess the impact of dermatologic diseases on patients' health-related quality of life (Chren et al. 1996). The Skindex-29 refers to the previous 4 weeks, and questions are categorized into four domains: emotions (10 items), symptoms (7 items), functioning (12 items), and treatment (1 item) and ask patients to think back over the previous 4 weeks. The questions are assessed on a 5-point Likert-like scale. A total Skindex-29 score is calculated on a scale of 0 to 100, where a higher score indicates a higher impact of the patient's skin disease. A copy of the Skindex-29 is provided in Appendix 5.

The CGIC is a measure of perceived change in PV symptoms as assessed by the clinician using a 7-item categorical scale ranging from "very much improved" to "very

much worse." The CGIC asks clinicians to rate the change of patients' PV symptoms. The recall period of the CGIC is start of treatment. A copy of the CGIC is provided in Appendix 9.

4.5.10 Samples for Roche Clinical Repository

4.5.10.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section *4.5.10*) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to rituximab, pemphigus, or autoimmune-related diseases:

- Whole blood for RNA extraction

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to rituximab, pemphigus, or autoimmune-related diseases:

- Whole blood for DNA extraction

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to rituximab, pemphigus, or autoimmune-related diseases:

- Serum for biomarker analysis

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.10.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.10.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WA29330 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WA29330.

4.5.10.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with protocol procedures

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment and not receive repeat treatment if they experience any of the following:

- Pregnancy
- Progressive multifocal leukoencephalopathy (PML)
- Malignant events (except basal cell carcinoma and squamous cell carcinoma of the skin that have been excised and cured)
- Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
- Severe allergic or anaphylactic study drug treatment-related reaction
- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 4 (life-threatening) event during or within 24 hours of an infusion
- Pure red cell aplasia

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

In the event that the patient develops a medically significant NCI CTCAE Grade 3 or 4 infection, see Section 4.6.4.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International *Council for* Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

4.6.4 Dose Modification and Treatment Interruption

In the event that the patient develops a medically significant NCI CTCAE Grade 3 or 4 infection, no further doses of rituximab/placebo or MMF/placebo study drug treatment should be provided until the infection has resolved.

Rituximab and matching placebo: Prolonged B-cell depletion is the expected outcome of rituximab treatment and is not considered a toxicity.

Patients who experience a Grade 4 (life-threatening) event during an infusion of rituximab (or matching placebo) should have their infusion stopped. Additional infusions of rituximab (or matching placebo) should not be given.

MMF and matching placebo: During the 52-week treatment period, the MMF (or matching placebo) dose should remain as stable as possible. If reductions in dose are necessary because of tolerability, decreases will be allowed in 500-mg decrements and must be recorded on the appropriate eCRF. If neutropenia develops (ANC $<1.3\times10^3/\mu L$), dosing with MMF (or matching placebo) should be interrupted or the dose should be reduced.

Guidelines for dosage modification and treatment interruption or discontinuation of MMF are provided in the MMF prescribing information.

In addition to the above, the following safety criteria must be met prior to resuming either rituximab/placebo or MMF/placebo study drug treatment:

- ANC $\geq 1.3 \times 10^3/\mu L$ at the last blood sample analysis
- The patient has not developed any of the following:
  - Primary or secondary immunodeficiency, including HIV infection
  - Known active infection of any kind (excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to infusion or within 2 weeks prior to oral MMF (matching placebo) and completion of oral anti-infectives within 2 weeks prior to infusion or within 1 week prior to oral MMF (matching placebo)
  - The patient has not developed any conditions that, in the investigator's opinion, would preclude the patient from receiving further courses of treatment, such as: any new or uncontrolled disease including, but not limited to, cardiovascular disease; nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders; or malignancies
- Patient is not pregnant or breastfeeding

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Patient safety will be monitored through physical examination, regular assessment of vital signs, hematologic laboratory tests, and incidence and severity of adverse events potentially due to any of the study medications. Infections will be treated according to local standard of care. Corticosteroid-related adverse events will also be assessed. An iDMC will review all safety data during the course of the study (see Section 3.1.4). Given the known side effects of both rituximab and MMF, abnormalities in hematologic tests, specifically leukocyte count, hemoglobin, and platelet count will be monitored closely. If the patient becomes leukopenic or thrombocytopenic, or experiences intolerable gastrointestinal adverse effects, the dose of MMF or dosing schedule of rituximab will be altered at the investigator's discretion.

5.1.1 Side Effects Known to be Associated with Rituximab

5.1.1.1 Infusion-Related Reactions

Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators.

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe infusion-related reactions with fatal outcomes have been rarely reported in the postmarketing setting. Closely monitor patients with preexisting cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion-related reaction was higher following the first infusion of any treatment

course than following the second infusion. Subsequent rituximab infusions were better tolerated by patients than the initial infusion. Fewer than 1% of patients experienced serious infusion-related reactions, with most of these reported during the first infusion of the first course. The reactions reported were usually reversible with a reduction in rate or interruption of rituximab infusion, and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline, bronchodilators, or glucocorticoids, as required.

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of rituximab.

Infusion-related reactions in patients with GPA and MPA were similar to those seen in RA patients in clinical trials. For patients with GPA and MPA, rituximab was given in combination with high doses of glucocorticoids, which may reduce the incidence and severity of these events.

Patients with a history of a severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies, or known hypersensitivity to any component of rituximab, will be excluded from study participation.

On rituximab infusion days, vital signs will be collected immediately prior to infusion and then every 30 minutes until the end of the infusion. To reduce the frequency and severity of infusion-related reactions, patients will receive premedication prior to the start of each infusion of rituximab or rituximab placebo (see Section 4.3.2.1 and Appendix 3).

5.1.1.2 Cardiovascular Events

Since hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab/matching placebo infusion. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure, or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease should be monitored closely, especially during infusions (see Section 5.1.1.1).

5.1.1.3 Infection

Patients may have an increased risk of infection following rituximab therapy. Rituximab should not be administered to patients with an active infection or to patients who are severely immunocompromised (e.g., where levels of CD4+ or CD8+ cell counts are very low).

Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions that may

further predispose patients to serious infection. Patients with a history of or currently active primary or secondary immunodeficiency, including known history of HIV infection, will be excluded from study participation. Patients with a known active infection of any kind (excluding fungal infections of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to screening, or completion of oral anti-infectives within 2 weeks prior to randomization, will also be excluded.

Patients who develop infection following rituximab therapy should be promptly evaluated and treated appropriately. Repeat infusions of rituximab (or matching placebo) should only be considered once any infection has fully resolved (see Section 4.6.4).

5.1.1.4 Hepatitis B Infection

Cases of hepatitis B virus (HBV) reactivation, including those with a fatal outcome, have been reported in RA, GPA, and MPA patients receiving rituximab. HBV screening should always be performed in high-risk patients before initiation of treatment with rituximab. Carriers of hepatitis B and patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during and for several months following rituximab therapy.

Patients will be tested for HBsAg, HBcAb, and HCV serology at screening. Those testing positive will be excluded from study participation.

5.1.1.5 Progressive Multifocal Leukoencephalopathy

Very rare cases of fatal PML have been reported following use of rituximab for the treatment of autoimmune diseases, including RA. Several, but not all, of the reported cases had potential risk factors for PML, including the underlying disease, long-term immunosuppressive therapy, or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with rituximab. Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated, including further evaluation with magnetic resonance imaging (MRI; preferably with contrast), cerebrospinal fluid testing for JC viral DNA, and repeat neurological assessments.

If PML is diagnosed in a patient receiving rituximab, no additional infusions of rituximab should be administered; reductions in concomitant immunosuppressive therapy and appropriate treatment, including antiviral therapy, should be considered. There are no known interventions that can reliably prevent PML or adequately treat PML, should it occur.

At the time of initiation of this protocol, there were no reports in the literature or in the Sponsor's global safety database of PML in PV patients who have received rituximab.

5.1.1.6 Skin Reactions

Severe skin reactions, such as SJS and TEN, some with fatal outcome, have been reported. In case of such an event with a suspected relationship to rituximab, treatment should be permanently discontinued.

Additional information on side effects associated with rituximab is provided in the Investigator's Brochure.

5.1.1.7 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Therefore, vaccination with live viral vaccines is not recommended while on rituximab or while peripheral B cells are depleted. It is recommended that a patient's vaccination status be reviewed and current immunization guidelines followed prior to study entry. Should non-live vaccinations be required, immunization should be completed at least 4 weeks prior to the first administration of study medication.

Patients treated with rituximab may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomized study of immunization responses, patients with RA, treated with rituximab and methotrexate, had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least two pneumococcal antibody serotypes), and keyhole limpet hemocyanin (KLH) neoantigen (47% vs. 93%), when given at least 6 months after rituximab, compared with patients receiving only methotrexate (Bingham et al. 2010).

In the overall experience of rituximab repeat treatment in RA patients over 1 year, the proportions of patients with positive antibody titers against *S. pneumoniae*, influenza, mumps, rubella, varicella, and tetanus toxoid were generally similar to the proportions at baseline.

Patients who have been treated with a live or attenuated vaccine within 28 days prior to randomization will be excluded from study participation.

The use of live or attenuated vaccines (i.e., measles, mumps, rubella, oral polio, BCG, typhoid, yellow fever, vaccinia, some forms of influenza [e.g., FluMist], or any other live vaccines not yet licensed but belonging to this category) are specifically prohibited during the study and while the patient's peripheral B cells are depleted.

The use of killed or inactivated vaccine (e.g., some forms of influenza) is not prohibited during the study; however, the efficacy of certain vaccines during or following periods of B-cell depletion has not been studied.

Patients who are eligible for yearly influenza vaccine or who require other non-live booster vaccinations can receive vaccination with killed/toxoid vaccines consistent with normal clinical practice.

5.1.1.8 Pregnancy

A reproductive toxicology study was conducted in cynomolgus monkeys to investigate the effects of rituximab on embryo-fetal development. Doses up to 100 mg/kg were administered weekly during the period of organogenesis. There were no findings of toxicity to the dams or the developing fetuses, and the only effect noted was the dose-dependent pharmacologic depletion of peripheral CD19+ B cells in the lymphoid organs of the fetuses.

Studies of the human reproduction have not been performed. It is not known whether rituximab can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. However, since IgG molecules such as rituximab are known to cross the placenta, rituximab may cause fetal CD19+ B-cell depletion. Transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. It is not known whether rituximab is excreted in breast milk and what effect this might have on the breast-feeding infant. However, since immunoglobulins are found in breast milk, breast-feeding mothers are excluded from participation in the study.

Well-controlled reproductive studies with glucocorticoids have not been performed in humans, but high doses of glucocorticoids given during pregnancy have caused hypoadrenalism in newborns.

Female patients should avoid becoming pregnant during this study, including the SFU period. As such, women of childbearing potential should use two effective methods of contraception, including at least one method with a failure rate of <1% per year, for the duration of the study and for 1 year after receiving rituximab. Regular pregnancy tests will be performed per the schedule of assessments (Appendix 1).

Patients who become pregnant will not receive additional doses of rituximab or MMF while pregnant or breast-feeding. Pregnancies occurring during the entire study (including the SFU period) must also be reported to the investigator. The investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Effects on pregnancies in partners of male patients whose peripheral CD19+ B cells are depleted have not been studied. Therefore, it is strongly advised that male patients also use reliable contraception while receiving rituximab in this trial and for 1 year after receiving rituximab.

5.1.1.9 Management of Specific Adverse Events

Infusion-Related Reactions

In the event of a mild infusion-related reaction, the infusion rate should be reduced to half the current rate (e.g., from 100 mg/hr to 50 mg/hr). Once the adverse event has

resolved, the infusion must continue at the reduced rate for an additional 30 minutes. If tolerated, the infusion rate may be increased to the next highest rate on the infusion schedule. Patients who experience a moderate to severe infusion-related reaction (e.g., fever $>38.5°C$, chills, mucosal swelling, or systolic blood pressure decrease of >30 mmHg) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. After all symptoms have resolved, the infusion may be restarted at half the previous rate. If the patient tolerates the reduced rate for 30 minutes, the infusion rate may be increased to the next highest rate following the infusion schedule. Patients who experience a Grade 4 (life-threatening) event during an infusion should have their infusion stopped. Additional infusions should not be given.

Additional instructions pertaining to the rituximab infusion are provided in Appendix 3.

Infections

Rituximab (or matching placebo) should not be administered in the setting of an active infection. If a patient experiences a new infection between the Day 1 and Day 15 infusions of any course, the Day 15 infusion should be delayed (up to a maximum of 28 days from the scheduled Day 1 date) until the infection has completely resolved and treatment with any anti-infective medications has been completed. This will not affect the patient's eligibility to receive additional courses of treatment as required. However, repeat infusions of rituximab (or matching placebo) should only be considered once any infection, experienced at any time during the study, has fully resolved.

5.1.2 Side Effects Known to Be Associated with MMF

MMF has been associated with gastrointestinal intolerance (diarrhea, nausea, vomiting); gastrointestinal disorders (colitis, pancreatitis); fetal malformations (facial malformations such as cleft lip, cleft palate, micrognathia, and hypertelorism of the orbits; abnormalities of the ear (e.g., abnormally formed or absent external/middle ear) and eye (e.g., coloboma, microphthalmos); malformations of the fingers (e.g., polydactyly, syndactyly, brachydactyly); cardiac abnormalities such as atrial and ventricular septal defects; esophageal malformations (e.g., esophageal atresia); and nervous system malformations such as spina bifida); spontaneous abortions; leukopenia; anemia (leading to tiredness, lethargy, or lack of energy), which could be severe and necessitate transfusion of blood; and increased risk of certain types of infections, including PML, reactivation of hepatitis B, tuberculosis, and atypical mycobacterial infection. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. Patients receiving MMF should be monitored for neutropenia. If neutropenia develops (ANC $<1.3\times10^3/\mu L$), dosing with MMF should be interrupted or the dose reduced and the patient should be carefully observed (see Section 4.6.4). Immunomodulatory drugs such as MMF have the ability to alter or regulate one or more immune functions and reduce the body's immunity. Possible development of lymphoma and other cancers, particularly of the skin, may result from the reduction of the body's immunity. As with all patients at an increased risk

for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high sun protection factor.

Females of childbearing potential must have two negative pregnancy tests, with the second test on Day 1 performed 8 to 10 days after the first test, before receiving MMF and must use two effective method of contraception, including at least one method with a failure rate of <1% per year, for the time period as stated in Section 4.1.1.

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of MMF.

Drug interactions with other drugs have been reported with MMF (see the MMF Investigator's Brochure for more information).

Side effects reported in more than 1 out of 10 patients treated with MMF after an organ transplant include, but are not limited to, hypertension asthenia constipation, nausea, vomiting, cough, acne, dizziness, insomnia, and tremors.

Oral fungal infection, headache, nasopharyngitis fever, cough, hypertension, and upper respiratory tract infection were reported in more than 1 out of 10 patients treated with MMF for PV in a clinical trial (Beissert et al. 2010).

At the time of this protocol, there were no reports in the literature or in the Sponsor's global MMF safety database of PML in PV patients who received MMF.

Further information on side effects associated with MMF is provided in the Investigator's Brochure.

5.1.3 Side Effects Known to Be Associated with Corticosteroids

Corticosteroids may have many potential side effects, including increased blood pressure, mood changes, and increased risk for infections. Long-term use or high doses of corticosteroids may also have side effects such as diabetes or changes in bones such as osteoporosis.

Further information on side effects associated with corticosteroids is provided in the local package insert.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section, and in Sections 5.4, 5.5, and 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events). In addition, any adverse events occurring during any corticosteroid dose adjustment during the screening period should be reported.

After initiation of study drug, all adverse events, regardless of relationship to study drug, including corticosteroid-related adverse events, will be reported during the treatment period. During the SFU period, serious adverse events and all infectious adverse events, irrespective of causality, will be reported. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in the NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the PV disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving other/background therapies (e.g., oral corticosteroids), causality will be assessed individually for each protocol-mandated therapy. All adverse events attributed to corticosteroids should also be reported in the Adverse Event eCRF.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" [or] "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome

at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3× ULN) in combination with either an elevated total bilirubin (>2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST (>3× ULN) in combination with total bilirubin >2× ULN
- Treatment-emergent ALT or AST (>3× ULN) in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of PV.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the

cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of PV, "pemphigus vulgaris progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study (i.e., changes from screening). When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Pemphigus Vulgaris

Events that are clearly consistent with the expected pattern of progression of the underlying disease, worsening, disease flare, or treatment failure should not be recorded as an adverse event or serious adverse event. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression, worsening, disease flare, or treatment failure will be based on the criteria described in Sections 3.1.3, 3.4.1.2, and 4.5.5. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression, worsening, disease flare, or treatment failure using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization for elective surgery or procedure

5.3.5.12 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of rituximab are available.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, all adverse events, including serious adverse events and non-serious adverse events, will be reported during the treatment period. During the SFU period, serious adverse events and all infectious adverse events, irrespective of causality, will be reported. Investigators should record all case details that can be

gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-trial adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study (including the 48-week SFU period). A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study (including the 48-week SFU period). A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use

and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail,

and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 12 months [see Section 5.3.1] after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death or other serious adverse event that occurs after the end of the adverse event reporting period, regardless of causality.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Rituximab Investigator's Brochure
- MMF Investigator’s Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical methods and planned statistical analyses will be specified in the Statistical Analysis Plan (SAP), which will be finalized prior to locking and unblinding of the database. All efficacy outcomes will be analyzed according to the *modified* intent-to-treat (*m*ITT) *population* and will include all randomized patients*, with exception of TM patients,* who have received any amount of study drug.

Treatment period data will be locked after all patients have completed the Week 52 visit. The primary efficacy (*excluding TM patients*) and safety analyses will be performed on data for patients through the Week 52 assessments or early discontinuation. A final database lock will occur after all patients have completed the trial, including the SFU period.

Safety assessments will be performed on patients who are evaluable for safety. In all safety analyses, patients will be grouped according to the treatment received rather than the treatment assigned.

Every effort will be made to obtain all scheduled efficacy and safety assessments for each patient. Patients who miss any scheduled doses or assessments will continue participation in the study and will continue to receive study drug.

Primary imputation methods for missing data will be specified in the SAP.

As part of a sensitivity analysis, *the inclusion of TM patients,* missing data patterns and associated missing data mechanisms will be further explored and analyzed as appropriate. The assumptions and methodology will be specified in SAP.

6.1 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of this study is the proportion of patients *(excluding TM patients)* achieving a sustained complete remission, as assessed at Week 52, that has been maintained for ≥16 consecutive weeks during the 52-week treatment period. With use of limited data available in the literature from randomized clinical trials of MMF and investigator-initiated trials of rituximab, it is estimated that approximately 40% of patients with PV receiving MMF will achieve a sustained complete remission. It is estimated that patients receiving rituximab will induce a sustained complete remission rate of 65%. On the basis of these assumptions, a total of *122* patients randomized to the rituximab arm or the MMF arm in a 1:1 ratio (*61* patients in the rituximab arm and *61* patients in the MMF arm) will yield *approximately* 80% power in a two-sided test at the 5% significance level. *To account for the 10 TM patients excluded from the primary efficacy analysis, approximately 132 patients will be randomized in total.*

No adjustment will be made to account for dropouts.

6.2 ANALYSIS POPULATIONS

All patient populations for the analysis of the 52-week, double-blind treatment period will be defined, agreed to, and documented prior to unblinding the data collected up to Week 52.

6.2.1 Safety Population

This population will be used for all summaries of safety data (i.e., adverse events, previous and concomitant medications, previous and concomitant diseases, laboratory data, and compliance with study treatment). The safety population will include all patients who were randomized and received any part of an infusion of study drug. Patients who receive the incorrect therapy from that intended will be summarized according to the therapy actually received. Patients who were not randomized but who receive study drug will be included in the safety population and summarized according to the therapy actually received.

In the unlikely event of a patient commencing one study therapy and crossing over to the other, data for that patient will be included in summaries and analyses for the original treatment arm.

6.2.2 Intent-to-Treat Population

All randomized patients who received any part of an infusion of study drug will be included in the ITT population. *Sensitivity analyses of the efficacy outcomes will be performed using the ITT population.*

Patients who prematurely withdraw from the study for any reason and for whom an assessment is not performed for whatever reason will still be included in the ITT analysis. Patients who received an incorrect therapy (i.e., different from that to which they were randomized) will be summarized in the treatment arm to which they were randomized.

Patients who were not randomized but who received study drug will be excluded from the ITT population and subsequent analyses.

6.2.3 *Modified Intent-to-Treat Population*

The mITT population includes patients in the ITT population, excluding the 10 TM patients. This population will be used in the analyses of efficacy outcomes.

6.3 SUMMARIES OF CONDUCT OF STUDY

Eligibility deviations and major protocol violations will be summarized.

6.4 SUMMARIES OF TREATMENT ARM COMPARABILITY

Patient demographics and baseline characteristics will be listed and summarized for the safety population.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

The proportion of patients (*excluding TM patients*) achieving a sustained complete remission (as defined in Section 3.4.1.1) in the rituximab and MMF arms will be compared using a stratified Cochran-Mantel-Haenszel test, adjusting for randomization stratification variables. Results will be summarized descriptively by treatment arm and expressed as proportions, corresponding adjusted 95% confidence intervals of the difference between response rates, and p-values.

Patients who meet the pre-specified definitions of treatment failure before entering sustained complete remission (as defined in Section 3.1.3) will be deemed non-responders in the primary analysis. Further analysis will be described in full in the SAP.

6.5.2 Secondary Efficacy Endpoints

All secondary efficacy parameters will be listed or summarized and presented in tables or graphs based on the *mITT* population.

The secondary efficacy outcome measures are as follows:

- Cumulative oral corticosteroid dose (prednisone or equivalent) over the treatment period
- Total number of disease flares during the treatment period
- Time to initial sustained complete remission
- Time to disease flare (as defined in Section 3.4.1.2)
- Change in HRQoL, as measured by the DLQI score from baseline to Week 52
- Duration of sustained complete remission
- Patients' impression of change in PV symptoms, as measured by the PGIC score during the treatment period
- Clinician impression of change in patients' PV symptoms, as measured by the CGIC score during the treatment period

Details on the analysis of secondary endpoints will be provided in the SAP.

Given the multiple endpoints, the statistical hypotheses related to the secondary objectives will be tested using a sequential testing procedure to control for the type I error (i.e., probability of a false–positive statistical inference). Full details on methodology to control for the type I error will be provided in the SAP.

6.6 SAFETY ANALYSES

The safety and tolerability of rituximab and MMF will be evaluated from adverse events, clinical laboratory tests, vital signs, and other safety parameters as defined by the protocol. Corticosteroid-related adverse events will also be analysed in relation to

corticosteroid exposure. Safety parameters will be summarized or listed for the safety population.

6.7 PHARMACODYNAMIC ANALYSES

Graphical and statistical techniques, including linear, nonlinear, and logistic regression, may be used to explore potential relationships between treatment regimen, pharmacokinetics, pharmacodynamics, safety, and efficacy.

6.8 PHARMACOKINETIC ANALYSES

Population PK analysis will be performed to describe the time course of serum concentrations of rituximab, if necessary and deemed appropriate. The influence of covariates (e.g., body weight, age, sex, race, and concomitant medications) on PK parameters will be investigated, if necessary and appropriate. If necessary, the data may be pooled with data from previous studies.

Individual and mean serum concentrations at each sampling timepoint for rituximab will be listed, as appropriate.

Summary statistics (e.g., means, standard deviation, coefficient of variation, geometric means, medians, and ranges) for serum concentrations for rituximab will be presented by nominal collection times, as appropriate.

Additional exploratory PK and/or PK/PD modeling may be applied to the data, as appropriate.

Results of PK and/or any population PK or PK/PD analyses may be reported outside the clinical study report.

6.9 EXPLORATORY ANALYSES

All exploratory efficacy parameters will be listed or summarized and presented in tables or graphs.

Descriptive statistics will be provided for the 10 patients recruited via TM.

Further details of the derivation of the endpoints will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 TELEMEDICINE

For a small proportion of patients (approximately 10 patients *at one* investigational site), the Sponsor is proposing the use of TM consultation visits between the patient and the Principal Investigator to make the trial more accessible to this population of patients with a rare disease. The local dermatologist, a research nurse, and other medical personnel in the patient's immediate vicinity will participate throughout the trial as needed. Data collected via TM will be in accordance with the American Telemedicine Association 2012 Guidelines for Teledermatology (ATA 2012). The software platform to be used in the trial will allow efficient, high-quality data collection of all relevant clinical data (including the images of the skin and mucosa, prior medical records, notes, and laboratory tests) for easy and reliable review by the Principal Investigator. This type of assessment has become the standard for TM clinical care for the diagnosis and treatment of both mild and severe types of skin diseases. Images will be time-stamped and stored in a Health Insurance Portability and Accountability Act (HIPAA)-compliant advanced TM platform adapted for this specific trial use. Other safety and efficacy data sets will be transmitted through the TM platform to the Principal Investigator as well. The local dermatologist or other local primary care doctors may still provide standard-of-care services that do not require training on the protocol or investigational drug. All clinical trial-related medical decisions will be made by the Principal Investigator and/or safety assessor.

Appendix 11 provides additional details and procedures related to TM, which will be effective only for TM site(s), as identified by the Sponsor. Based on the iDMC review of the safety data*, health authority interactions,* and the Sponsor's review of the TM data quality, the Sponsor may elect to increase *or limit* the number of patients and/or sites participating in TM.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. IND Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC), as amended.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Informed Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Informed Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Informed Consent Forms for continued participation in the study.

A copy of each signed Informed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Informed Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Informed Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

This multicenter, international study will be sponsored by F. Hoffmann-La Roche Ltd and managed in partnership with a clinical research organization. Approximately 60 sites in North America, Europe, the Middle East, and Latin America are expected to participate in the study and will enroll approximately *132* patients.

Patients will be randomized to one of the two treatment arms through a centralized computerized IxRS (see Section 4.2).

All samples collected per the schedule of assessments (see Appendix 1 and Appendix 2) will be shipped to a central laboratory.

Data for this study will be recorded via an EDC system using eCRFs (see Section 7.2).

The study will be overseen by the Study Management Team (SMT). During the study, the SMT will review study data according to the Data Quality Plan.

Safety data will be reviewed by an iDMC as specified in the iDMC Charter and as outlined in Section 3.1.4. The safety evaluations will be specified in the iDMC Charter and will include review of conventional safety variables, such as serious adverse events, infusion-related reactions, and infections. Any safety event that requires unblinding will be immediately reported to the iDMC. The iDMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of patients. After reviewing the safety data, the iDMC will make recommendations regarding continuation, termination, or modification of the study. The details of the iDMC roles and responsibilities and the logistics of the iDMC activities will be outlined in an iDMC Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Week	Screen	1	2	4	8	12	16	20	24	26	32	40	48	52		
Day	(−28 to −1)	1 (BL and Rz)	15 ±1	28 ±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	182 ±1	224 ±3	280 ±3	336 ±3	364 ±3	WD [a]	SFU [b]
Informed consent	x															
Medical history, [c] previous medications, and baseline conditions	x															
Pregnancy test (serum) [d]	x															
Pregnancy test (urine) [d]		x		x	x	x	x	x	x	x	x	x	x	x		
Complete physical examination [e]	x															
Body weight	x								x					x	x	
Height	x															
Vital signs [f]	x	x [g]	x [g]						x [g]	x [g]				x	x	
ECG	x															
CXR [h]	x															
Efficacy and PRO/ClinRO																
Disease activity (PDAI)	x	x		x	x	x	x	x	x		x	x	x	x	x	x
Flare assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Week	Screen	1	2	4	8	12	16	20	24	26	32	40	48	52		
Day	(−28 to −1)	1 (BL and Rz)	15 ±1	28 ±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	182 ±1	224 ±3	280 ±3	336 ±3	364 ±3	WD [a]	SFU [b]
DLQI [i]		x				x			x			x		x	x	x
PGIC [i]						x			x			x		x	x	x
CGIC [i]						x			x			x		x	x	x
EQ-5D-3L [i]		x				x			x			x		x	x	
Skindex-29 [i]		x				x			x			x		x	x	x
Prednisone (or equivalent) dose assessment/ adjustment [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety and Routine Laboratory Assessments																
Adverse events [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [l]
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [l]
Hematology [m]	x	x [n]	x [n]	x	x		x		x [n]	x [n]	x	x	x	x	x	
Blood chemistry [o]	x	x [n]	x [n]	x	x		x		x [n]	x [n]	x	x	x	x	x	
HBsAg, HBcAb, and HCV antibody	x															
Urinalysis [p]	x	x			x		x		x		x		x		x	

Appendix 1
Schedule of Assessments (cont.)

Week	Screen	1	2	4	8	12	16	20	24	26	32	40	48	52		
Day	(−28 to −1)	1 (BL and Rz)	15 ±1	28 ±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	182 ±1	224 ±3	280 ±3	336 ±3	364 ±3	WD [a]	SFU [b]
Immunology and Other Labs																
Lymphocyte subtypes and FACS panel [q]		x [n]	x [n]	x	x		x		x [n]	x [n]		x		x	x	x
Quantitative Ig [r]		x					x		x			x		x		x
Autoantibodies [s]		x			x				x			x		x	x	x
HACA		x							x					x	x	x
PK samples		x [t]	x [t]	x	x		x		x [t]	x [t]	x	x	x	x	x	
Optional serum biomarker sample for RCR		x [u]		x	x		x		x [u]	x [u]				x	x	
Optional whole blood sample (RNA) for RCR		x [u]		x	x		x		x [u]	x [u]				x	x	
Optional whole blood sample (DNA) for RCR [v]		x														

Appendix 1
Schedule of Assessments (cont.)

Week	Screen	1	2	4	8	12	16	20	24	26	32	40	48	52		
Day	(−28 to −1)	1 (BL and Rz)	15 ±1	28 ±3	56 ±3	84 ±3	112 ±3	140 ±3	168 ±3	182 ±1	224 ±3	280 ±3	336 ±3	364 ±3	WD [a]	SFU [b]
Study Treatment Dispensed																
Methylprednisolone/ saline solution premedication [w]		x	x						x	x						
Rituximab/matching placebo [x]		x [y]	x						x	x						
MMF/matching placebo [z]		x	x	x	x	x	x	x	x		x	x	x			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; BUN = blood urea nitrogen; CGIC = Clinician Global Impression of Change; ClinRO = clinician-reported outcomes; CXR = chest X-ray; DLQI = Dermatology Life Quality Index; Dsg1 = desmoglein 1; Dsg3 = desmoglein 3; ECG = electrocardiogram; eCRF = electronic Case Report Form; EQ-5D-3L = EuroQol 5-Dimension Questionnaire, three-level version; FACS = fluorescence-activated cell sorting; HACA = human anti-chimeric antibodies; HBcAg = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Ig = immunoglobulin; IV = intravenous; LDH = lactate dehydrogenase; MMF = mycophenolate mofetil; PDAI = Pemphigus Disease Area Index; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PRO = patient-reported outcome; Q12H = every 12 hours; RBC = red blood cell; RCR = Roche Clinical Repository; Rz = randomization; SFU = safety follow-up; WBC = white blood cell; WD = withdrawal visit.

Notes: All assessments and laboratory sampling should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who discontinue both study treatments early, and patients who experience treatment failure (as defined in Section 3.1.3) before Week 12, will be asked to return to the clinic for a treatment WD visit. If a patient withdraws at or during a scheduled or unscheduled visit, the visit should proceed as the withdrawal visit, that is, only the withdrawal visit assessments should be conducted. After the withdrawal visit, the patient will be asked to enter the SFU period of the study. An early withdrawal visit is not required for a patient to receive rescue therapy between Week 12 through Week 52, and patients should continue to be followed in the 52-week treatment period.

[b] Safety follow-up required at 12, 24, 36, and 48 weeks (±1 week) after withdrawal from or completion of treatment (see Appendix 2). Required follow-up information will be collected every 3 months or until death, loss to follow-up, or study termination by the Sponsor.

[c] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all previous medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 6 months prior to the screening visit.

Appendix 1
Schedule of Assessments (cont.)

[d] All women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Prior to starting study drug, female patients of childbearing potential must have two negative pregnancy tests. The second test on Day 1 prior to randomization should be performed 8 to 10 days after the first test during the screening period.

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position.

[g] Vital signs should be taken immediately prior to infusion and then every 30 minutes until completion of the rituximab or rituximab placebo infusion.

[h] If screening chest radiographs taken within the past 3 months show no clinically significant abnormality, further radiographic assessment is not required.

[i] The DLQI, PGIC, EQ-5D-3L, and Skindex-29 will be completed by the patient before any other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit. The CGIC, where possible, will be completed prior to the completion of other non-PRO assessments.

[j] To be captured on the eCRF.

[k] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. In addition, any adverse events occurring during any corticosteroid dose adjustment during the screening period should be reported.

[l] See Appendix 2.

[m] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Samples to be collected prior to administration of IV methylprednisolone or saline solution and 30 minutes following completion of rituximab or rituximab placebo infusion, respectively.

[o] Includes sodium, potassium, chloride, bicarbonate, glucose (except at 30 minutes following completion of study drug infusion at Weeks 1, 2, 24, and 26), BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH.

[p] Dipstick for blood, protein, and glucose (microscopic examination at central laboratory if abnormal and applicable).

[q] See Section 4.5.6 for T- and B-cell assessments.

[r] Total Ig, IgG, IgA, and IgM.

[s] Anti-Dsg1 and anti-Dsg3 antibodies.

[t] On infusion days, PK samples will be collected prior to administration of IV methylprednisolone or saline solution and 30 minutes following

Appendix 1
Schedule of Assessments (cont.)

completion of rituximab or rituximab placebo infusion, respectively.

[u] Samples to be collected prior to administration of IV methylprednisolone or saline solution for patients in the rituximab or rituximab placebo arms, respectively.

[v] The optional DNA sample can be collected prior to or after study drug administration.

[w] Methylprednisolone or saline solution should be administered by slow IV infusion to be completed at least 30 minutes prior to each infusion of rituximab or rituximab placebo, respectively.

[x] Rituximab at a dose of 1000 mg (or matching placebo) will be administered by IV infusion on Day 1 and Day 15, with repeat rituximab (or matching placebo) administration on Day 168 and Day 182 provided specific safety criteria have been met (see Section 4.6.4). See Appendix 3 for administration instructions.

[y] Administration of the first dose of study treatment (Day 1) should occur within 24 hours following the baseline assessments; however, administration up to 72 hours will be allowed when necessary. The second infusion should occur on Day 15 ± 1 day.

[z] MMF (500 mg or matching placebo) will be administered orally twice daily (Q12H) starting on Day 1. Patients will be initiated on MMF at 1 g/day or matching placebo in divided oral doses (Q12H). The MMF dose will be titrated to achieve a goal of 2 g/day in divided oral doses (1 g Q12H) by Week 2.

Appendix 2
Schedule of Assessments for the Safety Follow-Up Period

All patients who withdraw from both study treatments or complete the study will enter the safety follow-up period *to receive standard-of-care treatment per the investigator's best medical judgment*. Please note that for patients whose peripheral CD19+ B cells remain depleted (below the lower limit of normal or pre-rituximab baseline level, whichever is lower), safety follow-up will not be extended beyond the standard protocol-defined 48 weeks after treatment withdrawal or completion. CD19+ B-cell counts and other blinded laboratory values will be provided to the investigator at the end of the safety follow-up period.

Assessment	Week			
	12 (±1 week)	24 (±1 week)	36 (±1 week)	48 (±1 week)
Safety Assessments to Be Performed for All Patients				
Adverse events [a]	x	x	x	x
Concomitant medications [b]	x	x	x	x
HACA				x
Autoantibody testing [c]	x			x
Immunology and Other Labs				
Lymphocyte subtypes and FACS panel [d]	x	x	x	x
Quantitative Ig [e]	x	x	x	x
PK sample [f]	x	x	x	x
Disease Status and Activity Limitation Questions				
Disease activity (PDAI) and flare assessment	x	x	x	x
DLQI [g]	x			x
PGIC [g]	x			x
CGIC [g]	x			x
Skindex-29 [g]	x			x
Prednisone (or equivalent) dose assessment/adjustment [h]	x	x	x	x

Appendix 2
Schedule of Assessments for the Safety Follow-Up Period (cont.)

CGIC = Clinician Global Impression of Change; DLQI = Dermatology Life Quality Index; Dsg1 = desmoglein 1; Dsg3 = desmoglein 3; eCRF = electronic Case Report Form; FACS = fluorescence-activated cell sorting; HACA = human anti–chimeric antibodies; Ig = immunoglobulin; PDAI = Pemphigus Disease Area Index; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PV = pemphigus vulgaris; SFU = safety follow-up.

[a] Only serious adverse events and all infectious adverse events, irrespective of causality, will be reported in the SFU period. For all serious infectious adverse events reported, quantitative Ig, and $CD19^+$ cells counts should be determined within 1 week of the adverse event becoming serious. Pregnancy information will be reported for the duration of the SFU period.

[b] During the SFU period, reporting of concomitant medications should be limited to subsequent PV treatments, use of biologics, immunosuppressive medications, and cell-depleting agents.

[c] Anti-Dsg1 and anti-Dsg3 antibodies.

[d] See Section 4.5.6 for T- and B-cell assessments.

[e] Total Ig, IgG, IgA, and IgM.

[f] PK samples will be collected only in patients who withdraw early from study treatment.

[g] The DLQI, PGIC, and Skindex-29 should be completed before all other assessments during the study visit and prior to providing patient with any disease status information. The CGIC, where possible, should be completed prior to the completion of other non-PRO study assessments.

[h] To be captured on the eCRF.

Appendix 3
Procedures for the Intravenous Administration of Rituximab

PROCEDURES FOR ALL INFUSIONS

Although rituximab and matching placebo (for simplicity, referred to as rituximab in the remainder of the appendix) may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Irrespective, rituximab (and matching placebo) should be administered in a hospital, clinic, or healthcare-related environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.

Rituximab should be given as a slow intravenous (IV) infusion through a dedicated line. It should not be administered as an IV push or bolus.

To reduce the frequency and severity of infusion-related reactions, methylprednisolone (100 mg) or a saline solution will be administered by slow IV infusion 30–60 minutes prior to the start of each infusion of rituximab or rituximab placebo, respectively. Patients should also receive prophylactic treatment with acetaminophen or paracetamol (1 g by mouth) and diphenhydramine HCl (50 mg by mouth or IV equivalent, or equivalent dose of a similar agent) 30–60 minutes prior to the start of each infusion of rituximab.

In the event of a mild infusion-related reaction, the infusion rate should be reduced to half the current rate (e.g., from 100 mg/hr to 50 mg/hr). Once the adverse event has resolved, the infusion must continue at the reduced rate for an additional 30 minutes. If tolerated, the infusion rate may be increased to the next highest rate on the infusion schedule. Patients who experience a moderate to severe infusion-related reaction (e.g., fever $>38.5°C$, chills, mucosal swelling, or systolic blood pressure decrease of >30 mmHg) should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. After all symptoms have resolved, the infusion may be restarted at half the previous rate. If the patient tolerates the reduced rate for 30 minutes, the infusion rate may be increased to the next highest rate following the infusion schedule. Patients who experience a Grade 4 (life-threatening) event during an infusion should have their infusion stopped. Additional infusions should not be given.

After the end of each infusion, the IV line should remain in place for at least 1 hour to allow for administration of IV drugs, if necessary. If no adverse events occur during this time, the IV line may be removed.

Rituximab infusions must be administered according to the infusion schedules provided below.

Appendix 3
Procedures for the Intravenous Administration of Rituximab (cont.)

FIRST INFUSION (DAY 1)

The first rituximab infusion (4 mg/mL concentration) should commence at a rate of 50 mg/hr. This may be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Such an infusion schedule is presented below.

Table 1 Schedule for First Infusion (Day 1)

Time (Minutes)	Infusion Rate (mg/hr)	Infusion Rate (mL/hr)	Dose in 30 Minutes (mg)	Cumulative Dose (mg)
0–30	50	12.5 [a]	25	25
31–60	100	25	50	75
61–90	150	37.5 [a]	75	150
91–120	200	50	100	250
121–150	250	62.5 [a]	125	375
151–180	300	75	150	525
181–210	350	87.5 [a]	175	700
212–240	400	100	200	900
241–255 [b]	400	100	100	1000

[a] For countries not able to set the infusion pump to an accuracy of 0.5 mL/hr, the rate is to be rounded down to the nearest whole number.

[b] Should complete total dose of 1000 mg at 255 minutes (4 hr, 15 min).

SECOND INFUSION (DAY 15)

The second rituximab infusion (4 mg/mL concentration) should commence at a rate of 100 mg/hr. This may be escalated in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Such an infusion schedule is presented below.

Table 2 Schedule for Second Infusion (Day 15)

Time (Minutes)	Infusion Rate (mg/hr)	Infusion Rate (mL/hr)	Dose in 30 Minutes (mg)	Cumulative Dose (mg)
0–30	100	25	50	50
31–60	200	,50	100	150
61–90	300	75	150	300
91–120	400	100	200	500
121–150	400	100	200	700
151–180	400	100	200	900
181–195[a]	400	100	100	1000

[a] Should complete total dose of 1000 mg at 195 minutes (3 hr, 15 min).

THIRD INFUSION (DAY 168) AND FOURTH INFUSION (DAY 182)

The Day 168 and Day 182 infusions should be administered according to the schedules for the Day 1 and Day 15 infusions, respectively.

Appendix 4
Pemphigus Disease Area Index (PDAI)

Appendix 4
Pemphigus Disease Area Index (PDAI) (cont.)

Skin — Activity — Damage

Anatomical Locatio	Erosion/Blisters or new erythema		Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent **1** 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm **2** 2-3 lesions, at least two > 2 cm diameter, none > 6cm **3** >3 lesions, none > 6 cm diameter **5** >3 lesions, and/or at least one >6 cm **10** >3 lesions, and/or at least one lesion >16 cm diameter or entire area	Number lesions if ≤ 3	**0** absent **1** present
Ears			
Nose			
Rest of the face			
Neck			
Chest			
Abdomen			
Back, buttocks			
Arms			
Hands			
Legs			
Feet			
Genitals			
Total skin	**/120**		**/12**

Scalp

Scalp	Erosion/Blisters or new erythema	Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent **1** in one quadrant **2** two quadrants **3** three quadrants **4** affects whole skull **10** at least one lesion > 6 cm	**0** absent **1** present
Total Scalp (0-10)	**/10**	**/1**

Mucous membrane

Anatomical Location	Erosion/Blisters	
	0 absent **1** 1 lesion **2** 2–3 lesions **5** >3 lesions or 2 lesions >2 cm **10** entire area	Number lesions if ≤ 3
Eyes		
Nose		
Buccal mucosa		
Hard palate		
Soft palate		
Upper gingiva		
Lower gingiva		
Tongue		
Floor of mouth		
Labial mucosa		
Posterior pharynx		
Anogenital		
Total Mucosa	**/120**	

Total Activity Score: _____ **Total Damage Score** _____

Appendix 4
Pemphigus Disease Area Index (PDAI) (cont.)

The PDAI lesion counts (number of lesions ≤ 3) for the Skin and Mucous membrane are assigned a score used in calculating the Total Skin and Total Mucosa Activity scores, respectively, when the anatomical location activity score is 1 or 2.

Skin

When an anatomical location is scored a 1 ($1-3$ lesions, up to one >2 cm in any diameter, none >6 cm), record the number of lesions at that site, ranging from $1-3$ lesions. Incorporate the lesion count into the scoring by giving each location a score of 1 if 1 lesion is present, a score of 1.3 if 2 lesions are present, and a score of 1.6 if 3 lesions are present.

When an anatomical location is scored a 2 ($2-3$ lesions, at least two >2 cm diameter, none >6 cm), record the number of lesions at that site, ranging from $2-3$ lesions. Incorporate the lesion count into the scoring by giving each location a score of 2 if 2 lesions are present and a score of 2.3 if 3 lesions are present.

Skin anatomical location activity score	Number of lesions if ≤ 3	Final score
1 ($1-3$ lesions, up to one >2 cm in any diameter, none >6 cm)	1	1
	2	1.3
	3	1.6
2 ($2-3$ lesions, at least two >2 cm diameter, none >6 cm)	2	2
	3	2.3

Mucous Membrane

When an anatomical location is scored a 1 (1 lesion), record the number one for number of lesions at that site. Incorporate the lesion count into the scoring by giving each location a score of 1 when 1 lesion is present.

When an anatomical location is scored a 2 ($2-3$ lesions), record the number of lesions at that site, ranging from $2-3$ lesions. Incorporate the lesion count into the scoring by giving each location a score of 2 if 2 lesions are present and a score of 2.3 if 3 lesions are present.

Appendix 4
Pemphigus Disease Area Index (PDAI) (cont.)

Mucous membrane anatomical location activity score	Number of lesions if ≤3	Final score
1 (1 lesion)	1	1
2 (2 – 3 lesions)	2	2
	3	2.3

Source: Rosenbach M, Murrell DF, Bystryn JC, et al. Reliability and convergent validity of two outcome instruments for pemphigus. J Invest Dermatol 2009;129:2404–10; Victoria Werth, personal communication.

Appendix 5
Skindex-29

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DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

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These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

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These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

Appendix 6
Dermatology Quality of Life Index (DLQI) Questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix 7
EuroQol 5-Dimension Questionnaire, Three-Level Version (EQ-5D-3L)

Health Questionnaire

English version for the US

Rituximab—F. Hoffmann-La Roche Ltd
116/Protocol WA29330, Version 5

Appendix 7
EuroQol 5-Dimension Questionnaire, Three-Level Version (EQ-5D-3L) (cont.)

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

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

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

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 7
EuroQol 5-Dimension Questionnaire, Three-Level Version (EQ-5D-3L) (cont.)

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

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

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

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

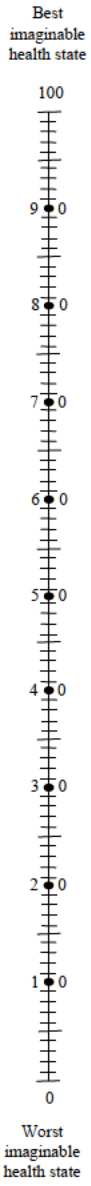
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 7
EuroQol 5-Dimension Questionnaire, Three-Level Version (EQ-5D-3L) (cont.)

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

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

Your own health state today



3

Appendix 8
Patient Global Impression of Change (PGIC)

How would you rate the change of your pemphigus vulgaris symptoms since you started taking the study drug?

☐1 Very much improved
☐2 Much improved
☐3 Minimally improved
☐4 No change
☐5 Minimally worse
☐6 Much worse
☐7 Very much worse

Appendix 9
Clinician Global Impression of Change (CGIC)

How would you rate the change in the patient's pemphigus vulgaris symptoms since the patient started taking the study drug?

☐1 Very much improved
☐2 Much improved
☐3 Minimally improved
☐4 No change
☐5 Minimally worse
☐6 Much worse
☐7 Very much worse

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Heelan et al. 2014	92 (PV: n=84)	Severe, refractory PV	One cycle 2×1000 mg IV (D1 and D15) followed by 2× or 1000 mg IV or 2×500 mg [b] IV as needed, 6 months or more after first cycle	PRE, IS	80% CR_{off} (Cycle 1), 93% CR_{off} (Cycle 2), 95% CR_{off} (Cycle 3), 100% CR_{off} (Cycle 4)	61% CR_{off} (Cycle 1), 43% CR_{off} (Cycle 2), 27% CR_{off} (Cycle 3), 43% CR_{off} (Cycle 4)	Infusion reactions (16%), bilateral paronychia, and lichen planus. Two unrelated deaths were reported during f/u.
Matsukura et al. 2012	8	Severe (n=6), refractory (n=2) PV	One cycle (repeat cycle for some patients) 2×1000 mg IV (D1 and D15)	PRE, AZA, MMF, MTX, CYC, IV Ig	50% CR (n=4) (6 months) 50% PR (n=4) (6 months)	5 months (n=1) 12 months (n=2) 13 months (n=1)	No SAEs on treatment. One case of pneumonia (Month 7)
Leshem et al. 2014	10 [a]	Severe, refractory PV	One cycle (repeat cycle for some patients) 2×1000 mg IV (D1 and D15)	PRE (n=10), AZA (n=1)	90% CR (6 months post-RTX)	67% (f/u 22 months)	Infusion reaction, thoracic herpes zoster
Leshem et al. 2013	47	Severe PV	One cycle (repeat cycles for some patients) 2×1000 mg IV (D1 and D15)	IS	76% CR (first cycle), 91% CR (repeat treatment cycle)	22% (median: 8 months Cycle 1=15%, Cycle 2=17%, Cycle 3=25%, Cycle 4=0%	Severe infusion reaction (n=2)

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Kanwar et al. 2013	9	Severe (n=7), refractory (n=2) PV	One cycle 2×1000 mg IV (D1 and D15)	PRE, DP, AZA, CYC, DAP	30% CR_{off}, 40% CR_{on}, 20% PR	NA	IRRs (n=3 [fever, chills, angioedema]), 2 cases of sepsis, and 1 death (from sepsis with *S. aureus*)
Cianchini et al. 2012	37	Severe, refractory PV	One cycle 2×1000 mg IV (D1 and D15) Additional 500 mg infusion administered after 6 months if PR or no response	PRE (PO)	86% CR after 6 months	34 relapses (n=20)	No SAEs
Kasperkiewicz et al. 2012b	23	Severe PV	One cycle 2×1000 mg IV (week 1 and 3)	IA IV DP MMF/AZA	83% CR (n=19) 13% PR (n=3)	23% relapse (n=6)	Two patients (9%) with severe AEs

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Kasperkiewicz et al. 2012a	33	Severe PV	One cycle (repeat cycle for some patients) 2 × 1000 mg IV (n = 25) 4 × 375 mg/m^2 (n = 9) 2 cycles of 4 × 375 mg/m^2 (n = 1) 7 × 375 mg/m^2 (n = 1)	PRE, MP, MMF, AZA, MTX, IV Ig, IA, UND IS	58% CR (n = 20) 36% PR 6% NR	NA	SAEs (11%), including severe infusion reaction, bacterial sepsis, DVT, urticaria with dyspnea, and transient granulocyto-penia

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Baum et al. 2013	18	Refractory PV	One cycle 4×375 mg/m^2	AZA, DAP, MMF, MTX, PRE	44% CR (8/18) 44% PR (8/18) 11% NR (2/18)	2/8 with CR relapsed at 9 months	No related SAEs reported
Balighi et al. 2013	40	Unresponsive PV	One cycle 4×375 mg/m^2	PRE (PO)	Sustained remission (n = 19)	52.5% (9 major, 12 minor)	Lung abscess (fatal), sepsis, pneumonia, cavernous sinus thrombosis, skin abscess, DVT, generalized arthralgia, and Stevens-Johnson syndrome

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Colliou et al. 2013	22	Severe PV	One cycle (repeat cycle for some patients) 4×375 mg/m^2	PRE	95% achieved disease control (mean = 3.1 months)	81% relapsed (median time to relapse = 16 months)	One death from septicemia, and another had pyelonephritis. Two patients died of CVD (29 and 51 months after initial RTX infusion).

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Lunardon et al. 2012	24	Severe and/or refractory PV	One cycle (repeat cycles for some patients) 4×375 mg/m^2 vs. 2×1000 mg	PRE, MMF, IV Ig, MTX, CYC, cyclosporine, AZA, DAP	58% response	44% relapse	Six SAEs in 5 patients (osteomyelitis, perirectal phlegmon and intrapelvic abscesses, syncope due to anemia, prostate cancer, and melanoma)
Cho et al. 2013	23	Severe PV (n = 10), mild to moderate PV (n = 13)	Gp 1: 3, 4×375 mg/m^2 Gp 2: 2×375 mg/m^2	PRE, AZA, MP	Gp 1: 60% CR, 40% PR Gp 2: 69% CR, 31% PR	13% relapse (2 pts. flared before Month 12)	No SAEs reported. One patient experienced mild, transient fever and tachycardia during RTX infusion.

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Kim et al. 2011	27	Severe, refractory PV	Gp 1: 2×375 mg/m^2 (n = 12) Gp 2: 3, 4×375 mg/m^2 (n = 15)	NA	59% CR (n = 16) 18% PR (n = 16) No diff. in CR, Gp 2 had fewer flares	Gp 1: 0–67% relapse (to Month 12) Gp 2: no relapses	One death (3 months after RTX therapy) due to gastric perforation (may not have been related to RTX)
Joly et al. 2007	21	Severe PV (CS refractory disease)	One cycle 4×375 mg/m^2	PRE	86% CR at 3 months following RTX cycle	45% relapse after mean of 18.9 ± 7.9 months	Two severe AEs: 1 patient had pyelonephritis 12 months after RTX treatment and 1 patient died from septicemia 18 months after RTX treatment

Appendix 10
Uncontrolled Studies and Selected Case Reports of Rituximab in Pemphigus Vulgaris (cont.)

Study	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies	Remission	Relapse	Adverse Events
Morrison 2004	3	Moderate/ severe PV	One cycle (repeat cycle for 2 cases) 4×375 mg/m^2	CYC, PRE	CR (18 months), CR (4 months), oral lesions healed (9 months)	NA	Fatal PCP, mild leukopenia

AE = adverse event; AZA = azathioprine; CR = complete remission; CR_{off} = complete remission off systemic therapy; CR_{on} = complete remission on systemic therapy; CS = corticosteroid; CVD = cardiovascular disease; CYC = cyclophosphamide; D1 = Day 1; D15 = Day 15; DAP = dapsone; DP = dexamethasone pulse; DVT = deep vein thrombosis; f/u = follow-up; Gp 1 = Group 1; Gp 2 = Group 2; IRR = infusion-related reaction; IV Ig = intravenous immunoglobulin; IA = immunoadsorption; IS = immunosuppressant; MMF = mycophenolate mofetil; MP = methylprednisone; MTX = methotrexate; PCP = *Pneumocystis carinii* pneumonia; NA = not available; NR = no response; PO = oral; PRE = prednisone; PR = partial remission; PV = pemphigus vulgaris; RTX = rituximab; SAE = serious adverse event; UND = undefined.

[a] Patients were previously part of a larger study (Leshem et al. 2013) on the clinical efficacy of rituximab 2×1000 mg IV dose (Day 1 and Day 15).

[b] This dose was used when deemed appropriate by the treating physician or by necessity when the full dose was not affordable for the patient.

Appendix 11
Telemedicine

OVERVIEW

All general study detailsat site(s) using telemedicine (TM) to enroll patients are identical to those sites not participating in TM. The Telemedicine Principal Investigator (TM PI) has the same study-related responsibilities as the Principal Investigators who are not participating in TM. The differences are primarily in the logistics of study assessments, methods of interactions with patients, and data collection through TM. These differences are outlined here.

RECRUITMENT

Patients will be recruited from selected site(s) within the United States where the TM investigators are licensed to practice medicine and provide teledermatology clinical care.

INFORMATIONAL WEBSITES

Patients will be referred to an informational website about the pemphigus vulgaris (PV) study from various recruitment sources. Those who express interest will contact the TM PI or request to be contacted by the TM PI to discuss the details of the PV study and the specifics of the TM.

SCREENING PERIOD PROCEDURES

PRE-SCREENING

The TM research coordinator or TM PI will directly call the patient to confirm the basic eligibility criteria. If the patient meets all pre-screening eligibility criteria and is interested in participating, the following steps will occur:

- The electronic Informed Consent Form (eICF) will be made available for the patient to review, and the TM PI will schedule a follow-up call to review the eICF and any associated questions.
- The patient will be required to complete a medical information release form (compliant with the Health Insurance Portability and Accountability Act [HIPAA]) permitting the TM PI to contact the local dermatologist (LD) to discuss the patient, to obtain relevant medical records, and to verify eligibility criteria.

Informed Consent

- The TM PI will conduct the informed consent process with the patient. The TM PI/TM research coordinator will review the eICF with the patient and answer questions about the study. After the patient has had ample time to review the eICF, the TM PI or TM research coordinator will address any additional questions, the patient will sign the eICF, and the TM PI or TM research coordinator will countersign the eICF. After the informed consent form and eICF have been completed, the

TM PI will continue to verify eligibility and proceed with the standard screening and enrollment procedures, as defined in the protocol.

Verification of Eligibility

- The TM PI will verify with the patient that he or she meets the inclusion and exclusion criteria specified in the protocol.
- The TM PI will contact the LD to obtain pathology reports and any other relevant medical information and supportive records to verify inclusion and exclusion criteria.

Transition of Care Responsibility

- After the eICF is completed, the TM investigators will assume responsibility of care for the patient regarding PV and associated medications (both study-related investigational medications and concomitant therapies for PV) and for all study-related decisions. The TM investigators will interact with the patient via TM, as is typical for this type of care in TM. The TM investigators will coordinate this transition of care with the LD and interact with the LD as needed throughout the study.

SCREENING (DAY −28 TO DAY −1)

Logistics and Planning for Study Visit at the Patient's Home

A mobile research nurse (MRN) will visit patients at their home for the initial (screening) visit if they reside in states that allow the patient-physician relationship to be established through TM.

1. After the eICF is signed and all pre-screening criteria are met, an initial visit from the MRN will be scheduled at the patient's home.
2. An iPhone® will be shipped pre-loaded with the necessary TM applications and software to the MRN.
3. The MRN will be trained on how to use the TM application, how to photograph patients reproducibly, and all relevant details of the study.
4. The MRN will bring the iPhone to the patient's home for the screening visit. The iPhone will remain with the patient for the duration of the study.

Screening Visit in the Patient's Home

1. A secure video conference will take place between the TM investigators, the patient, and the MRN at the patient's home, using the iPhone. During this session, the following will occur:
    - Final details of inclusion and exclusion criteria will be re-confirmed.
    - The patient will be oriented to the functionality and usage of the iPhone and the TM application with assistance of the MRN.

- Study logistics will be discussed, and any additional questions will be answered.

2. The MRN will conduct and record the following assessments:
   - Body weight
   - Height
   - Vital signs
   - Collect all screening laboratory samples
   - Disease activity will be assessed:
     - The MRN will establish the best circumstances and location in the home for medical photography (i.e., lighting, privacy, etc.). The MRN will use the TM application to photograph all areas of the body and mucosa using standardized anatomic positions and transmit the images using a HIPAA-compliant platform in accordance with American Telemedicine Association Teledermatology guidelines. One entire set of images will be transmitted (these will be used to determine the Pemphigus Disease Area Index [PDAI]; see Day 1 assessment of disease activity below). The quality of photographs will be confirmed immediately by the efficacy assessor in the event that additional photographs need to be taken.
     - The efficacy assessor will evaluate the photographs sent by the MRN (see Step 1 above) to determine the screening PDAI.
   - Review all other requirements of the study with the patient using the TM application, including capture of the following information:
     - Any other new medical issues and other relevant medical history
     - Concomitant medications
     - Confirmation of the current prednisone dose and the safety assessor's instructions for the prednisone taper
   - Confirm that the patient is scheduled for a physical examination, electrocardiogram (ECG), and chest X-ray (CXR) with a local healthcare provider and radiology facility, respectively, to occur in a timely fashion. These reports will be reviewed by the safety assessor before any study treatments are initiated and administered.

Assessments

- Complete physical examination:

  A complete physical examination will be conducted by the local healthcare provider. The findings will be reported to the safety assessor, who will review the findings and document appropriately.

- ECGs:

ECGs will be conducted by the local healthcare provider. The findings will be reported to the safety assessor, who will review the findings and document appropriately.

- CXR:

  The patient will go to a local radiology facility for a baseline CXR. The CXR report will be sent to the safety assessor, who will review the report and document appropriately.

Logistics and Planning for Study Visit at TM PI site

In states where the patient-physician relationship must be established in person before TM-based patient care is conducted, the initial (screening) visit will occur at the TM PI site.

After the eICF is signed and all pre-screening criteria are met, the TM research coordinator will schedule a day when the patient will travel to the TM site to complete the screening visit.

1. The screening visit assessments will be completed as outlined in the schedule of assessments (Appendix 1).
2. Study personnel will instruct the patient on the basic functions of the TM technology and iPhone use during the visit.
3. The patient will be sent home with an iPhone pre-loaded with TM technology for study use.

RANDOMIZATION (DAY 1, WEEK 1)

- After all of the screening procedures are confirmed and within 72 hours prior to the Day 1 infusion, the patient will be randomized using an interactive web/voice response system (IxRS), as detailed in Section 4.2.
- Once the patient is randomized, an unblinded TM research pharmacist will prepare study treatments as specified (rituximab, mycophenolate mofetil [MMF], matching placebos, methylprednisolone, and saline solution). Blinded study treatments will be dispensed to the MRN/infusion center staff. The pharmacy will also prepare non-study medications at the discretion of the TM investigator or per local guidelines (e.g., prednisone, gastrointestinal prophylaxis, *Pneumocystis jirovecii* pneumonia prophylaxis, topical agents) to be dispensed to the MRN/infusion center staff. For non-study medications, the patient may use their local pharmacy if desired.

Appendix 11
Telemedicine (cont.)

INFUSION DAYS 1 (WEEK 1), 15 (WEEK 2), 168 (WEEK 24), AND 182 (WEEK 26)

All patients, regardless of state of residence, will receive their infusions and associated study visit assessments at the TM PI site.

- Infusions: Rituximab (and matching placebo) should be administered in a hospital, clinic, or healthcare-related environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.
- All infusion reactions and adverse events will be documented and communicated immediately, as appropriate, to the TM safety assessor and the Sponsor as per the protocol.
- Infusion day laboratory assessments:

  All laboratory assessments scheduled for infusion days should be performed as described in the schedule of assessments (see Appendix 1). Blood draws that are timed to occur before and after the first infusions will be performed at the infusion center.

ALL OTHER STUDY VISITS

Weeks 4–20 and 32–52, Withdrawal, and Safety Follow-Up (Weeks 12, 24, 36, and 48 after Withdrawal or Completion of Treatment)

For all patients, regardless of state of residence, these study visits will be conducted by a MRN at the patient's home.

- TM research coordinator coordinates with MRN to schedule visits to the patient's home

Assessments specified for evaluation days other than infusion days should be performed within 3 days of the scheduled visit.

The MRN will visit the patient's home on each evaluation day noted in the schedule of assessments (see Appendix 1 and Appendix 2). Assessments and procedures, including laboratory assessments and recording of adverse events and concomitant medications will be performed by the MRN. Results will be made available to the safety assessor via the TM application.

For assessments of disease activity:

- Disease activity will be assessed by the patient using the Patient Global Impression of Change (PGIC). The patient will complete the patient-reported outcome (PRO) questionnaires (Dermatology Life Quality Index [DLQI], European Quality of Life

5-Dimension Questionnaire, three-level version [EQ-5D-3L], and Skindex-29), and the MRN will collect and mail the completed forms to the TM site.

- The MRN will use the TM application to photograph all areas of the body and mucosa; these photographs will be transmitted to the efficacy assessor for PDAI scoring and Clinician Global Impression of Change (CGIC) determination. The MRN will use the same location in the home as previously used to limit unnecessary variability.

DATA

All laboratory results will be transmitted securely to the safety assessor. As described in the protocol, the efficacy assessor will review all of the efficacy data and the safety assessor will review the laboratory data and all efficacy and safety data independently.

Within 24 hours, the efficacy assessor will evaluate disease activity, lesion count, flare assessment, calculate the PDAI score, and complete the CGIC. The safety assessor will make all treatment decisions. The safety assessor will call the patient to discuss all study treatment and management decisions. Serious adverse events, non-serious adverse events of special interest, and pregnancies will be reported to the Sponsor within 24 hours.

Safety data from TM will be reviewed by the independent Data Monitoring Committee (see Section 3.1.4).

ANALYSES AND DECISION POINTS TO CONTINUE TM

Initially, approximately 10 patients will be recruited for participation in TM. Adverse events, data quality and completeness, and enrollment statistics will be reviewed monthly by the Sponsor and compared with the general enrollment arms of the study. The TM investigators will ensure that the images and data collected via TM provide adequate information for evaluating the primary efficacy endpoint and for ensuring patient safety.

Appendix 11
Telemedicine (cont.)

The measures of success of TM will include*, but is not limited to,* the screening and enrollment rates at the TM site(s), *iDMC review of the safety data, health authority interactions,* as well as the *Sponsor's review of the* quality and completeness of the data, in determining whether to continue or expand participation in TM. Analyses will be performed comparing the average performance with all other traditional (non-TM) sites, including, but not limited to:

- Total number of missed study days
- Average percentage of missing data per visit
- Screening rate
- Enrollment rate
- Retention rate (or dropout rate)