Official Title: **A Phase IIA, International, Multicenter, Open-Label, Uncontrolled Study to Evaluate the Safety and Pharmacokinetics of 4 × 375 mg/m2 Intravenous Rituximab in Pediatric Patients With Severe Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis**

NCT Number: **NCT01750697**

Document Date: Protocol, Version 5, dated 26-Apr-2016

PROTOCOL

TITLE:	**A PHASE IIA, INTERNATIONAL, MULTICENTER, OPEN-LABEL, UNCONTROLLED STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF 4 × 375 MG/M2 INTRAVENOUS RITUXIMAB IN PEDIATRIC PATIENTS WITH SEVERE GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S) OR MICROSCOPIC POLYANGIITIS**
PROTOCOL NUMBER:	WA25615
VERSION NUMBER:	5
EUDRACT NUMBER:	2012-002062-13
IND NUMBER:	112501
TEST PRODUCT:	Rituximab (RO0452294)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche, Ltd
DATE FINAL:	Version 1: 02 July 2012
DATE AMENDED:	Version 2: 13 October 2012 Version 3: 31 May 2013 Version 4: 27 March 2015 Version 5: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	26-Apr-2016 22:00:33

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol WA25615 has been amended primarily to modify the exclusion criteria related to general health, prior medications and laboratory findings. These changes have been made in order to extend the possibility of entry into this clinical study to a wider range of suitable GPA and MPA patients, who would otherwise have limited treatment options in this potentially life threatening and organ threatening disease.

The changes to exclusion criteria (Section 4.1.2, see below) require that the treating physician assess benefit/risk, prior to participant study entry. The changes do not have an impact on the scientific value of the trial and will allow a small proportion of patients who were not previously eligible the opportunity to participate in this study.

Since changes have been made to the exclusion criteria, this is considered to be a substantial amendment to the protocol.

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol. The rationale for each of the amendment changes is provided below:

SECTION 4.1.2: Exclusion Criteria

Exclusions Related to General Health

Current active infection is an exclusion criterion, however, a statement has been added to clarify that entry into this study may be reconsidered once any known active infection has fully resolved.

Exclusions Related to Medications

The criteria have been amended to permit prior treatment with rituximab and/or other B cell depleting therapies, provided last dose was more than 6 months before the baseline visit.

Pediatric patients with active GPA or MPA disease require therapy which would likely be either cyclophosphamide or rituximab. Physicians would like to avoid the adverse effects of cyclophosphamide in this age group and the safety of six-monthly dosing of rituximab has been evaluated in MAINRITSAN (ClinicalTrials.gov number, NCT00748644; EudraCT number, 2008-002846-51) showing comparable safety and tolerability to the control (azathioprine). The Sponsor is aware of at least 10 pediatric patients who were previously screened for this study but were excluded because they had previously received off-label rituximab as treatment for their disease. The proposed change has been made in order to extend the possibility of entry into this clinical study to a wider range of suitable GPA and MPA patients, who would otherwise have limited treatment options in this potentially life threatening and organ threatening disease.

Additional courses of rituximab can be administered after Month 6 in this trial. Retreatment with rituximab and entry into this study is at the discretion of the investigator and may be considered based on disease activity, previous tolerability and response to treatment, and the investigator's assessment of any potential risks of repeat rituximab treatment.

Exclusions Related to Laboratory Findings

The laboratory exclusion level of serum IgG has been amended from the central laboratory LLN, which varies according to age, to an absolute exclusionary value of below 5.65 mg/mL. This proposed IgG threshold was used as exclusion criteria in rheumatoid arthritis (RA) global clinical trials for rituximab, where adult patients were observed up to 11 years.

Low IgG has also been observed in patients with GPA and MPA. Severity of the underlying disease and prior immunosuppressive treatment may affect IgG levels at study entry. The labelling documents for rituximab describe how changes in IgG, following rituximab or cyclophosphamide treatment, have been observed and were similar for both treatments in the RAVE randomised controlled study in GPA/MPA. Importantly decreases in immunoglobulins in RAVE were not reported to have been associated with serious infections and there was no increased rate in overall infections or serious infections in patients with low IgG (see rituximab Investigator Brochure *section 5.3.3.2*). Low IgG level is a laboratory abnormality that may have no clinical consequence and often does not require specific medical management. It is of note that there was no protocol-defined low IgG laboratory exclusion level in RAVE.

In this study, the current IgG exclusion criterion is based on the laboratory LLN and is variable depending on age. Pediatric patients with active disease require therapy and there are limited treatment options available. Physicians would like to avoid cyclophosphamide use in this pediatric patient population due to the well-described adverse effects.

If a potential subject for this study, has levels just below LLN (consistent with their disease status and or use of prior therapies) at screening, but within the new data-driven inclusion threshold, a benefit/risk assessment can be made by the treating physician as to whether entry into this study and treatment with rituximab is an option.

SECTIONS 3.1.4 and 4.5.6.4: Extended Follow-Up Visits:

As low IgG laboratory levels can be the result of many factors, including underlying disease and/or treatment with rituximab or other immunosuppressive agents (e.g., cyclophosphamide) typically used in GPA/MPA, the language has been clarified to include extended follow-up of peripherally depleted B cell patients and not to include separate extended safety follow-up of patients with a low IgG level only (without peripheral B cell depletion).

Safety (adverse events), central laboratory and other immunological parameters, including immunoglobulins, will continue to be assessed in extended safety follow-up for peripherally B cell depleted patients. Completion of extended safety follow-up will occur when peripheral B cell levels return to pre-rituximab baseline levels or to within the normal range for the population, whichever is lower.

Text on B cell-depleting therapies (commercial or investigational) has been clarified.

SECTION 3.2 and Synopsis: END OF STUDY

The study will end after all patients in extended safety follow-up have completed B cell follow-up as described above (this is in addition to the protocol-defined 18 months of follow-up that they will have already completed, up to the common close out date).

SECTION 4.5.6.1.2: Rescreening

A statement has been added to clarify that in the case of a protocol amendment, potential patients may be reassessed for eligibility according to any updated inclusion and exclusion criteria.

SECTION 5.2.3.7: Hypogammaglobulinemia

Edits have been made to improve clarity and consistency. Language has been added to indicate that repeat dosing can be considered based on the assessed benefit/risk.

OTHER ADMINISTRATIVE CHANGES:

Remission Induction Phase (Synopsis)

Text updated for consistency with protocol body Sections 4.3.2.2.1 and 4.5.6.2

SECTION 1.2: BACKGROUND ON RITUXIMAB

Updates have been made to disease areas under clinical study and the global markets that the GPA/MPA indication has currently been approved in:

- A clinical study in pemphigus vulgaris has commenced
- Rituximab has been approved in the European Union for the induction of remission in adult patients with GPA and MPA.

SECTION 3.1.1: Overview and Synopsis

Number of sites and countries has been updated to reflect current recruitment strategy: two new countries (Canada and Serbia) have been added.

FIGURE 1: Study Design

Language was clarified for extended safety-follow-up

SECTION 3.1.8 Early Study Drug Withdrawal and SECTION 4.5.7 Early Withdrawal Visit

A sentence has been added to clarify that from the point of early study or treatment withdrawal, a patient may no longer receive rituximab as part of this protocol.

SECTION 3.4.2, SECTION 6.8 and SYNOPSIS: Exploratory Efficacy Outcome Measures

Two duplicate outcome measures have been deleted as they were inadvertently repeated in the previous protocol version.

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2: BACKGROUND ON RITUXIMAB

Clinical studies have been completed or are being undertaken by Roche in various disease areas, including rheumatoid arthritis (RA) and several other autoimmune disorders, including multiple sclerosis, *pemphigus vulgaris,* systemic lupus erythematosus (SLE), and AAV. Rituximab is currently approved in more than 100 countries for the treatment of relapsed or refractory non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and in combination with MTX for the treatment of RA patients who inadequately responded to one or more anti-tumor necrosis factor (anti-TNF) therapies.

Preliminary open-label, single-institution experience suggested that rituximab helped control AAV and could potentially help re-establish tolerance to ANCA-target antigens (Specks et al. 2001; Keogh et al. 2005). This preliminary information generated interest in performing a multicenter trial to assess the ability of rituximab to induce remission in patients with severe AAV. The pivotal double-blind, double-dummy, placebo-controlled randomized trial called RAVE (Stone et al. 2010) provided evidence of a positive benefit–risk for rituximab in GPA (WG) and MPA that resulted in the FDA's approval of rituximab for the treatment of these conditions in 2011. This indication has since been approved in a number of other markets worldwide, including *the European Union,* Canada, Switzerland, South Korea, and Israel~~. Review is underway in the European Union.~~

SECTION 3.1.1: <u>Overview</u>

This is a Phase IIa, international, multicenter, open-label, single-arm study. The primary objectives are to evaluate the safety and tolerability and the PK parameters of rituximab in pediatric patients with severe GPA or MPA. At least 25 patients between 2 and 18 years of age will be enrolled across approximately ~~20~~ *23* sites in France, Germany, Italy, Turkey, *Canada, Serbia,* the United Kingdom (UK), and the United States (US).

SECTION 3.1.4: <u>Extended Follow-Up</u>

At the common closeout date, patients whose *peripheral* B cells remain depleted ~~and/or have immunoglobulin levels below the LLN for the population,~~ will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower. ~~and until their immunoglobulin levels have returned to within normal limits for the population~~ *Safety (adverse events),~~ central laboratory and ~~other~~ immunological parameters, including immunoglobulin, will continue to be assessed in extended safety follow-up* (see Appendix 1).

If a patient receives any B cell-depleting therapy *(commercial or investigational)* or any other agent that affects the return of B cells ~~or decreases immunoglobulin levels,~~ including, but not limited to, rituximab, CYC, and AZA, on or after the common closeout date, he or she will not be followed any further (although routine clinical follow up after the end of the study will continue, according to local practice).

Section 3.1.8: Early Study Drug Withdrawal

The investigator may also withdraw a participant from study treatment if he or she judges that continuing on rituximab is no longer in the participant's best interest. These participants will remain in the study *for follow-up*, but will be asked to complete a withdrawal visit (see Appendix 1). *From the point of withdrawal, a patient may no longer receive rituximab as part of this protocol.* They will continue to be followed until the common closeout date. At the common closeout date, patients whose *peripheral* B cells remain depleted ~~and/or who have immunoglobulin levels below the LLN for the population~~, will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline level or to within the normal range for the population, whichever is lower~~, and until their immunoglobulin levels have returned to within normal limits for the population~~ (see Section 3.1.4).

SECTION 3.2: END OF STUDY

At the time of the common closeout date for each patient, the scheduled study visit occurring before or at the common closeout date will represent the end of main study visit. However, all participants with *peripheral* B-cell counts below the LLN or *pre-rituximab* baseline value ~~or with low immunoglobulin levels following rituximab exposure~~ will enter extended follow up, as described in Section 3.1.4. If the trial is stopped early, all participants will be withdrawn from the study at the time of the termination of the study.

SECTION 3.4.2: Exploratory Efficacy Outcome Measures

- [redacted]
- [redacted]

SECTION 4.1.2: Exclusion Criteria

- 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-infective agents within 4 weeks of baseline or completion of oral anti-infective agents within 2 weeks prior to baseline

  Entry into this study may be reconsidered once the infection has fully resolved

- ~~Previous~~ *T*~~t~~reatment with rituximab *or other biologic B cell–targeted therapy (e.g., anti-CD19, anti-CD20, anti-CD22, or anti-B-lymphocyte stimulator [BLys]/BAFF) within 6 months prior to baseline visit*

- Previous treatment with ~~any~~ *other* cell-depleting therapies, including, but not limited to, investigational agents (e.g., alemtuzumab [CAMPATH®], anti-CD4, anti-CD5, anti-CD3, ~~anti-CD19~~ *and*~~,~~ anti-CD11a~~,~~ ~~anti-CD22~~,~~ anti-B-lymphocyte stimulator [BLys]/BAFF, and anti-CD20~~)
- Level of ~~IgG and/or~~ IgM below LLN of age-specific reference range
- *Level of IgG below 5.65mg/ml*

SECTION 4.5.6.1.2: Rescreening

It will not be considered rescreening if blood samples have to be redrawn because of sample handling problems, breakage, or sample integrity. *In the case of a protocol amendment, potential patients may be reassessed for eligibility according to any updated inclusion and exclusion criteria.*

SECTION 4.5.6.4: Extended Follow-Up Visits

At the common closeout date, patients whose *peripheral* B cells remain depleted~~ and/or who have immunoglobulin levels below the LLN for the population~~, will continue to attend study visits every 3 months~~ until their~~ *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower. ~~and until their immunoglobulin levels have returned to within normal limits for the population~~ *Safety (adverse events), central laboratory and immunologic parameters, including immunoglobulins, will continue to be assessed in extended safety follow-up* (see Appendix 1). If a patient receives any B cell–depleting therapy *(commercial or investigational)* or any other agent that affects the return of B cells~~ or decreases immunoglobulin levels~~, including, but not limited to, rituximab, CYC and AZA, on or after the common closeout date, he or she will not be followed any further (although routine clinical follow-up after the end of the study will continue, according to local practice).

SECTION 4.5.7: Early Withdrawal Visit

If the investigator judges that continuing rituximab is no longer in the participant's best interest, the participant will be asked to complete a withdrawal visit and will remain in the study *for follow-up* (see Section 3.1.8). *From the point of withdrawal, a patient may no longer receive rituximab as part of this protocol.* A schedule of assessments for the withdrawal visit is provided in Appendix 1.

SECTION 5.2.3.7: Hypogammaglobulinemia

Patients with IgG and IgM levels below the ~~LLN of the age specific reference range~~*exclusionary levels per Section 4.1.2*, at screening will not be enrolled in the study. The investigator should closely monitor the patient's immunoglobulin levels during the study. If immunoglobulin levels decrease ~~below the normal range~~*following rituximab treatment, and require specific medical care or management, repeat dosing can be considered at the discretion of the investigator, based on the assessed benefit/risk* ~~dosing should be interrupted or discontinued, as clinically appropriate and at the discretion of the investigator~~. IVIg (restricted to replacement dosing for hypogammaglobulinemia) may be given at the discretion of the investigator.

SECTION 6.8: EXPLORATORY EFFICACY ENDPOINTS

[redacted]

FIGURE 1: Study Design

Language was clarified for extended safety-follow-up

APPENDIX 1: Schedule of Assessments

Footnotes were revised in-line with changes made to the text.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIA, INTERNATIONAL, MULTICENTER, OPEN-LABEL, UNCONTROLLED STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF 4×375 MG/M2 INTRAVENOUS RITUXIMAB IN PEDIATRIC PATIENTS WITH SEVERE GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S) OR MICROSCOPIC POLYANGIITIS**
PROTOCOL NUMBER:	WA25615
VERSION NUMBER:	5
EUDRACT NUMBER:	2012-002062-13
IND NUMBER:	112501
TEST PRODUCT:	Rituximab (RO0452294)
MEDICAL MONITOR:	[redacted], MD
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 retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIA, INTERNATIONAL, MULTICENTER, OPEN-LABEL, UNCONTROLLED STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF 4×375 MG/M2 INTRAVENOUS RITUXIMAB IN PEDIATRIC PATIENTS WITH SEVERE GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S) OR MICROSCOPIC POLYANGIITIS**
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EUDRACT NUMBER:	2012-002062-13
IND NUMBER:	112501
TEST PRODUCT:	Rituximab (RO0452294)
PHASE:	IIa
INDICATION:	Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis
SPONSOR:	F. Hoffmann-La Roche, Ltd

Objectives

Safety Objectives

The primary safety objective for this study is to evaluate the safety and tolerability of rituximab in pediatric patients with severe granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Pharmacokinetic Objectives

The primary pharmacokinetic (PK) objective for this study is to evaluate the PK parameters of rituximab in pediatric patients with severe GPA or MPA.

Exploratory Efficacy Objectives

The efficacy objective for this study is exploratory and is to assess the efficacy of rituximab for the induction of remission in pediatric patients with severe GPA or MPA.

Other Exploratory Objectives

Other exploratory objectives for this study are as follows:

- [redacted]
- [redacted]

Study Design

Description of Study

This is a Phase IIa, international, multicenter, open-label, single-arm study. The primary objectives are to evaluate the safety and tolerability and the PK parameters of rituximab in pediatric patients with severe GPA or MPA. At least 25 patients between 2 and 18 years of age will be enrolled across approximately *23* sites in France, Germany, Italy, Turkey, *Canada, Serbia,* the United Kingdom, and the United States.

The study comprises an initial 6-month remission induction phase, followed by a minimum 12-month follow-up phase. The common closeout date will occur 18 months after the enrollment of the last patient.

At screening, all patients will be assessed for eligibility according to the inclusion and exclusion criteria. Screening assessments will be performed in accordance with the schedule of assessments. The screening visit may occur up to 28 days prior to the baseline visit. Following screening, eligible patients will enter the remission induction phase of the study.

Remission Induction Phase

Prior to the first rituximab infusion, patients must receive three doses of methylprednisolone at 30 mg/kg/day (up to 1 g/day) by intravenous (IV) infusion that can occur any time*,* up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional daily doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day) can be given by IV infusion. No more than six doses of methylprednisolone in total can be given. All methylprednisolone doses must be completed prior to the first rituximab infusion. The first rituximab infusion must occur no later than 14 days after the last dose of methylprednisolone infusion. Subject to the investigator's discretion, corticosteroid premedication with an IV infusion of 100 mg of methylprednisolone may be administered at least 30 minutes prior to the infusion of rituximab (but not prior to clinical assessments) if the patient has experienced an IRR with a previous rituximab infusion.

Rituximab will be administered to patients as four weekly IV infusions of 375 mg/m^2 on Days 1, 8, 15, and 22. The dose will be calculated using a patient's body surface area (BSA) at screening. Infusions can be given in a day care or inpatient setting. It is acceptable to hospitalize a patient as per local clinical practice. All patients will receive concomitant oral prednisolone or prednisone (maximum, 1 mg/kg/day or up to 60 mg/day, whichever is less), which will be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever is lowest) no later than by Month 6. Following completion of rituximab infusions on Day 22, patients will complete study visits at Months 1, 2, 4, and 6 and will undergo assessments in accordance with the schedule of assessments.

Patients who receive at least part of one IV infusion of rituximab but do not complete four weekly infusions should continue to receive protocol-defined concomitant oral prednisolone or prednisone and/or should receive treatment at the discretion of the investigator (local standard of care) but will remain in the study. Patients who show some initial improvement but then, prior to Month 6, experience disease flare before remission that cannot be controlled by glucocorticoids should receive treatment at the discretion of the investigator (according to local standard of care) and will remain in the study. Patients who, by Month 6, exhibit progressive disease before remission will receive additional treatment as per local standard of care and will remain in the study.

The schedule of assessments will be the same for all patients in the study.

Follow-Up Phase

Following the remission induction phase, patients will be followed for a minimum of 12 months at visits every 3 months, in accordance with the schedule of assessments. The optimal treatment after rituximab induction for GPA or MPA has not been established in adults or in pediatric patients. After Month 6, patients who are protocol remission failures or experience disease flare that cannot be controlled by glucocorticoids alone should receive treatment in accordance with local standard of care at the discretion of the investigator and will remain in the study.

After Month 6, if patients require retreatment with rituximab, additional courses will be provided by the Sponsor until the common closeout date. Retreatment with rituximab is at the discretion

of the investigator and may be considered based on disease activity, previous response to treatment, and the investigator's assessment of the risks with rituximab.

After Month 18, patients will be followed at study visits every 3 months until the common closeout date. The procedures performed at the follow-up visits will be similar to those performed at the Month 18 visit. After the common closeout date, patients whose B cells remain depleted for the population will enter extended follow up.

Extended Follow Up

At the common closeout date, patients whose *peripheral* B cells remain depleted, will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower. *Safety (adverse events), central laboratory and immunological parameters, including immunoglobulins, will continue to be assessed in extended safety follow-up.*

If a patient receives any B cell–depleting therapy *(commercial or investigational)* or any other agent that affects the return of B cells including, but not limited to, rituximab, cyclophosphamide (CYC), and azathioprine, on or after the common closeout date, he or she will not be followed any further (although routine clinical follow up after the end of the study will continue, according to local practice).

Number of Patients

The planned enrollment is at least 25 patients.

Target Population

Patients must meet the following criteria for study entry:

- Written informed consent for study participation obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding
- Age at screening between ≥ 2 and < 18 years
- Diagnosis of GPA (EULAR/PRINTO/PRES 2008, Ankara criteria for childhood Wegner's granulomatosis [WG]) or diagnosis of MPA (according to the Chapel Hill Consensus Conference)
- Newly diagnosed patients or patients with relapsing disease according to the following definition:

  The recurrence or new onset of potentially organ- or life-threatening disease (i.e., one or more major Birmingham Vasculitis Activity Score/WG (BVAS/WG) items listed in the following table or disease severe enough to require treatment with CYC).
- For patients of reproductive potential (males and females), use of a reliable means of contraception (e.g., abstinence, hormonal contraceptive patch, intrauterine device, physical barrier) throughout their study participation
- For all eligible patients, mandatory prophylactic treatment for *Pneumocystis jiroveci* infection

BVAS/WG Features of Limited and Severe AAV

Severe (Major) BVAS/WG Items [a]	Limited (Minor) BVAS/WG Items [b]
Cutaneous gangrene	Arthralgias/arthritis
Scleritis	Fever (> 38°C)
Retinal exudates/hemorrhage	Purpura
Sensorineural hearing loss	Skin ulcer
Mesenteric ischemia	Mouth ulcers
Alveolar haemorrhage	Conjunctivitis/episcleritis
Red blood cell urinary casts	Orbital mass/proptosis
Rise in serum creatinine 30% over baseline value	Uveitis
Aseptic meningitis	Bloody nasal discharge/nasal crusting
Spinal cord lesions	Sinus involvement
Cerebrovascular accident caused by vasculitis	Swollen salivary gland
Cranial nerve palsy	Subglottic inflammation
Sensory peripheral neuropathy	Conductive deafness [c]
Motor mononeuritis multiplex	Pericarditis
	Pleurisy
	Pulmonary nodules or cavities
	Other pulmonary infiltrates secondary to vasculitis, endobronchial lesions, and hematuria

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody
BVAS = Birmingham Vasculitis Activity Score; WG = Wegner's granulomatosis.

[a] Any of these items must be attributable to the active underlying disease.

[b] Minor items with a significant risk of morbidity may be classified as severe (i.e., BVAS/WG 3).

[c] Additional testing may be required to make the diagnosis.

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

Exclusions Related to GPA or MPA

- Diagnosis of Churg–Strauss syndrome, as defined by the Chapel Hill Consensus Conference
- Limited disease that would not normally be treated with CYC
- Severe disease requiring mechanical ventilation due to alveolar hemorrhage
- Requirement for plasmapheresis or dialysis at screening

Exclusions Related to General Health

- Incomplete recovery from recent surgery or < 12 weeks since surgery prior to baseline or planned within 24 weeks of baseline
- Lack of peripheral venous access
- Pregnancy or breastfeeding

- Evidence of 1) other significant uncontrolled concomitant disease, including, but not limited to, cardiovascular disease, nervous system, pulmonary, renal disease (including anti-glomerular basement membrane disease); or 2) hepatic, endocrine, or gastrointestinal disorders that, in the investigator's opinion, would preclude or interfere with patient participation
- Primary or secondary immunodeficiency (history of or currently active), including known history of human immunodeficiency virus infection
- Evidence of active tuberculosis (patients receiving chemoprophylaxis for latent tuberculosis infection are eligible for the study)
- 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-infective agents within 4 weeks of baseline or completion of oral anti-infective agents within 2 weeks prior to baseline.

  Entry into this study may be reconsidered once the infection has fully resolved
- History of deep space/tissue infection (e.g., fasciitis, abscess, osteomyelitis) within 24 weeks prior to baseline
- History of serious recurrent or chronic infection
- History of cancer, including solid tumors, hematologic malignancies, and carcinoma in situ (except basal cell 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

Exclusions Related to Medications

- History of a severe allergic or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of rituximab or to murine proteins
- *Treatment* with rituximab *or a biologic B cell–targeted therapy (e.g., anti-CD19, anti-CD20, anti-CD22, or anti-B-lymphocyte stimulator [BLys]/BAFF) within 6 months prior to baseline visit*
- Previous treatment with an anti-alpha 4 integrin antibody or co-stimulation modulator
- Previous treatment with *other* cell-depleting therapies, including, but not limited to, investigational agents (e.g., alemtuzumab [CAMPATH®], anti-CD4, anti-CD5, anti-CD3, *and* anti-CD11a)
- Receipt of oral or IV CYC within the previous 4 months prior to the baseline visit
- Receipt of infliximab within the previous 3 months prior to the baseline visit
- Receipt of adalimumab within the previous 2 months prior to the baseline visit
- Receipt of etanercept within the previous 1 month prior to the baseline visit
- Treatment with any investigational agent within 28 days of baseline or 5 half-lives of the investigational drug (whichever is longer)
- Receipt of any live or attenuated vaccine within 28 days prior to baseline

  It is recommended that a patient's vaccination record and the need for immunization should be carefully reviewed and updated prior to receiving rituximab.
- Intolerance or contraindications to IV glucocorticoids

In case of receipt of any other immunosuppressant therapy (apart from corticosteroids), contact the Sponsor.

Exclusions Related to Laboratory Findings

- Positive serum human chorionic gonadotropin measured at screening or a positive pregnancy test prior to the first rituximab infusion for participants of childbearing potential

- Positive tests for hepatitis B surface antigen, hepatitis B core antibody, hepatitis B virus, or hepatitis C serology
- Level of IgM below LLN of age-specific reference range
- *Level of IgG below 5.65mg/ml*
- Absolute neutrophil count $< 1.5 \times 10^3/\mu L$
- Platelet count $< 130 \times 10^3/\mu L$
- Estimated glomerular filtration rate (GFR) < 15 mL/min/1.73 m^2 (calculated using the Schwartz formula)
- Alanine aminotransferase or aspartate aminotransferase levels $> 2.5 \times$ the upper limit of normal (for age and sex) that cannot be attributed to underlying GPA or MPA

Length of Study

The duration of the study will be 18 months. Beyond 18 months all patients will be followed until the common closeout date. After the common closeout date, patients whose *peripheral* B cells remain depleted will enter extended follow-up.

End of Study

The end of the study will occur when the last participating patient completes the final scheduled visit (inclusive of extended follow up) or when the Sponsor decides to discontinue the study or development program.

Safety (Primary) Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency, nature, and severity of adverse events (AEs)
- Frequency of laboratory abnormalities

Pharmacokinetic Outcome Measures

The primary PK objective for this study is to evaluate the PK parameters of rituximab in pediatric patients with severe GPA or MPA.

Exploratory Efficacy Outcome Measures

The exploratory efficacy outcome measures for this study will include the following:

[redacted]

[redacted]

Other Exploratory Outcome Measures are as follows:

[redacted]

Investigational Medicinal Products

Test Product

For this trial, rituximab will be given as an IV infusion of 375 mg/m^2 once a week for 4 consecutive weeks, starting at the baseline visit. The dose for rituximab will be calculated according to the participant's BSA at the screening visit after the participant's eligibility has been established, and it will remain the same for all four infusions. Each participant's actual body height and weight, measured during the 28-day period before baseline (i.e., during the 28 days before the start of administration of open-label rituximab) will be used to calculate a patient's BSA according to the Dubois formula.

Comparator

Not applicable.

Non-Investigational Medicinal Products

Patients should be medicated pre-infusion with paracetamol/acetaminophen and cetirizine hydrochloride (or similar antihistamine), both according to labeled age-related doses, to be given 1 hour (± 15 minutes) before each infusion of rituximab. Subject to investigator's discretion, corticosteroid premedication with an IV infusion of 100 mg of methylprednisolone may be administered at least 30 minutes prior to infusion of rituximab (but not prior to clinical assessments) if the patient has experienced an IRR with a previous rituximab infusion.

Methylprednisolone

Prior to the first rituximab infusion, patients must receive three doses of methylprednisolone at 30 mg/kg/day (up to 1 g/day) by IV infusion that can occur any time after screening, up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional daily doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day) can be given by IV infusion. No more than six doses of methylprednisolone in total can be given. All methylprednisolone doses must be completed prior to the first rituximab infusion. The first rituximab infusion must occur no later than 14 days after the last dose of methylprednisolone infusion.

Prednisolone or Prednisone

On Day 1 and following completion of IV glucocorticoids, all patients will receive concomitant oral prednisolone or prednisone (1 mg/kg/day or up to 60 mg/day or equivalent, whichever is lower), the dose of which will be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever is the lowest) no later than Month 6.

The general guidance on the suggested oral steroid dose-tapering schedule is to taper from 1 mg/kg/day (60 mg/day, maximum) at the start of treatment, to 0.8 mg/kg/day by Month 1, and then by 0.1–0.2 mg/kg/day each month to 0.2 mg/kg/day (or 10 mg/day, whichever is the lowest), which should be reached no later than Month 6.

Oral prednisone (used in some non-UK sites) may be substituted for prednisolone at the same dose as long as there is no hepatic impairment.

The steroid-tapering practice is specific to a particular patient and as such should be tailored individually for each patient at the time of study entry, at the discretion of the investigator.

Comparator

Not applicable.

Statistical Methods

Primary Analysis

This is an exploratory, open-label, single-arm study, with the primary objective of evaluating safety and pharmacokinetics of rituximab in pediatric patients with GPA or MPA. Therefore, there will be no formal statistical hypothesis testing. An analysis will be conducted when the last patient enrolled reaches 6 months. Full details of all planned tables, listings, graphs, and descriptive analyses will be provided in a Statistical Analysis Plan, which will be finalized prior to this analysis. An outline of the proposed analyses is provided herein.

The safety and tolerability of rituximab will be evaluated from AEs, laboratory tests, vital signs, ECGs, chest X-rays, and as defined by protocol. Safety parameters will be summarized or listed for the safety population.

Non-linear mixed-effects modeling technique (NONMEM®) will be used to analyze the PK data with the population PK model developed from adult patients with GPA and MPA in the RAVE study. The primary PK parameters will be clearance and volume of distribution. The secondary PK parameters (area under the rituximab plasma concentration–time curve from Time 0 to infinity [AUC_{inf}], maximum plasma concentration [C_{max}]) will be calculated for each patient. PK concentrations will be summarized by visit. PK parameters will be tabulated and summarized (i.e., by mean, standard deviation, coefficient of variation, median, and minimum and maximum). PK exposure and response relationships will be explored.

Determination of Sample Size

The planned sample size of 25 patients was determined on the basis of the epidemiology of pediatric anti–neutrophil cytoplasmic antibody-associated vasculitis (AAV) and information from existing patient cohorts. This sample size takes into the account the number of pediatric patients that would be eligible for treatment with rituximab and that could be expected to be enrolled within a reasonable timeframe. The primary objective of this study is to evaluate the safety and pharmacokinetics of rituximab in these patients. The planned sample size would be sufficient to provide a reasonable estimate of variability for the mean PK parameters based on the observed intra-patient variability from the RAVE study. It would also ensure 95% probability of observing at least one AE when the underlying incidence of that event is $\geq 11\%$.

Given the exploratory nature of this study, there will be no formal statistical hypothesis testing. The study will focus on exploratory estimation of the efficacy and PD endpoints. The planned sample size of 25 would allow estimation of the percentage of patients in remission at 6 months to within 20% of the point estimate (the distance from the point estimate to the upper or lower limit of a 95% confidence interval).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAV	ANCA-associated vasculitis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
AUC_{0-inf}	Area under the rituximab plasma concentration–time curve from Time 0 to infinity
AZA	azathioprine
BE	Behavior
BLys	B-lymphocyte stimulator
BP	bodily pain/discomfort
BSA	body surface area
BVAS	Birmingham Vasculitis Activity Score
BW	body weight
CARRA	North American Childhood Arthritis & Rheumatology Research Alliance
CD	cluster of differentiation
CH	change in health
[redacted]	[redacted]
CI	confidence interval
CL	Clearance
C_{max}	maximum plasma concentration
CT	computed tomography
CTC	Common Toxicity Criteria
CYC	cyclophosphamide
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EC	Ethics Committee
EDC	electronic data capture
EU	European Union
EUVAS	European Vasculitis Study Group
FA	family activities
FACS	fluorescence activated cell sorter
FC	family cohesion
FDA	Food and Drug Administration
GBE	general behavior
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GGH	global health
GH	general health perceptions
GPA	granulomatosis with polyangiitis
HACA	Human antichimeric antibody
[redacted]	[redacted]

Abbreviation	Definition
HbA_{1c}	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV Ab	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	infusion-related reaction
ITP	immune thrombocytopenic purpura
IVIg	intravenous immunoglobulin
IV	Intravenous
IxRS	interactive voice/web-based response system
JIA	juvenile idiopathic arthritis
LLN	lower limit of normal
MH	mental health
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	Methotrexate
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
PD	pharmacodynamics
PE	parent impact – emotional
PF	physical functioning
PhS	physical summary score
PK	Pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PReS	Pediatric Rheumatology European Society
PRES	posterior reversible encephalopathy syndrome
PRINTO	Pediatric Rheumatology International Trials Organization
PRO	patient-reported outcome
PR3	proteinase 3
PsS	psychosocial summary score
PT	parent impact – time
PVAS	Pediatric Vasculitis Activity Score
PVDI	Pediatric Vasculitis Damage Index

Abbreviation	Definition
RA	rheumatoid arthritis
REB	role/social limitations – emotional/behavioral
RP	role social limitations – physical
RPLS	reversible posterior leukoencephalopathy syndrome
RTX	Rituximab
SAE	serious adverse event
SD	standard deviation
SE	self-esteem
SLE	systemic lupus erythematosus
TNF	tumor necrosis factor
TTP	thrombotic thrombocytopenic purpura
UK	United Kingdom
ULN	upper limit of normal
US	United States
VDI	Vasculitis Damage Index
WG	Wegener's granulomatosis

1. BACKGROUND

1.1 BACKGROUND ON GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S) AND MICROSCOPIC POLYANGIITIS

Granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis [WG]) and microscopic polyangiitis (MPA) are the two major forms of small-vessel systemic vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) (Hoffman and Specks 1998). Together, these conditions are termed "ANCA-associated vasculitis" (AAV) because of their strong association with highly specific autoantibodies. AAV encompasses autoimmune disorders in which tolerance has been lost to one of two self-antigens, proteinase 3 (PR3) or myeloperoxidase (MPO), leading to the production of PR3- or MPO-ANCAs. Animal models, in vitro experiments, and many clinical observations in humans suggest that endothelial injury and tissue damage depend on the pro-inflammatory effects of ANCAs resulting from the interaction of these specific antibodies with their target antigens on the surface of activated neutrophils and monocytes.

If untreated, GPA and MPA progress from limited disease processes (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase characterized by multiple complications of small-vessel vasculitis (e.g., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) (Walton 1958; Fienberg 1981; Hoffman et al. 1992; Guillevin and Lhote 1998; Reinhold-Keller et al. 2000). The prognosis for untreated GPA is poor, with a low likelihood of survival (Walton 1958).

In addition, patients can suffer neurological complications. Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), has been described in patients with severe hypertension or renal failure, patients with connective tissue diseases (including GPA and MPA) and patients receiving immunosuppressive treatments such as cyclophosphamide, high-dose corticosteroids and rituximab (Primavera et al. 2001, Foocharoen et al. 2006, Ishikura K et al. 2012, Staykov and Schwab, 2012). Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension and should be investigated as soon as possible. For further information, please refer to the paragraph 6.1.8 Nervous system of the Investigator Brochure.

Conventional therapies for GPA and MPA are associated with a high degree of treatment failures and disease relapses. Preventing fatal outcomes in severe disease requires immunosuppressive therapy consisting of glucocorticoids and cytotoxic agents, usually cyclophosphamide (CYC). Although most patients achieve remission (Hoffman et al. 1992; Nachman et al. 1996; Reinhold-Keller et al. 2000; Jayne 2001), a majority of the patients also experience disease flares when therapy is tapered or discontinued. Moreover, the treatment options currently used for adult GPA and MPA

are associated with substantial toxicities that frequently result in severe and permanent patient morbidity and mortality (Jayne et al. 2003). Although mortality due to GPA and MPA has been significantly reduced through the use of CYC and other therapies, there continue to be major unmet needs, such as improved remission rates, prevention of flares, and reduction of toxicities associated with current therapy. Therefore, novel and targeted mechanism-based treatment approaches are needed.

Pediatric patients with GPA and MPA share many signs and symptoms of the disease with adults. Similar to adults, the majority of pediatric patients have respiratory tract symptoms and/or renal involvement. Similar to adult disease, wider organ involvement may occur because of complications of small-vessel vasculitis, but the relative frequencies of certain clinical manifestations may differ. For example, in one study, nasal deformity and fixed subglottic stenosis were 2-fold and 4-fold more common at onset in childhood GPA than in adult-onset GPA (Rottem et al. 1993).

Outcomes in pediatric GPA and MPA are also similar to those associated with adult disease. Childhood disease carries considerable disease-related morbidity and mortality, mainly from progressive renal failure or aggressive respiratory involvement. In a review by Eleftheriou and Brogan (2009), flares of GPA occurred in up to 75% of pediatric patients as treatment was weaned, and significant long-term renal impairment was observed in 17%–40% of patients across studies. However, treatment-related morbidity (e.g., infections) and malignancies are less common compared with those observed in adults (Rottem et al. 1993; Frosch and Foell 2004).

Data on the epidemiology of vasculitides in children are limited and difficult to interpret, owing to the varying nature of data (e.g., prospective vs. retrospective) and changing classifications over the past 20 years. A recent apparent increase in incidence may in part be due to better case recognition after the introduction of ANCA testing. Despite these limitations, the data clearly show that GPA and MPA are very rare conditions in children and adolescents, with estimated annual incidences of <1 to 2.75 cases per million (Gardner-Medwin et al. 2002; Watts et al. 2009; Grisaru et al. 2010).

Treatment recommendations in pediatric GPA and MPA are extrapolated from evidence and expert consensus in adults, and there are no guidelines for the dosage or duration of immunosuppressive therapy in children with these diseases. Standard practice in severe disease is remission induction with CYC (in combination with glucocorticoids), followed by maintenance with azathioprine (AZA) or methotrexate (MTX) (Vanoni et al. 2010). Twilt et al (2012) provide an overview of the current status of the epidemiology, pathogenesis, and treatment of childhood GPA. Reported rates of remission and relapse vary. However, comparisons with adult disease are based on limited data and should be interpreted with caution because of the differing definitions of outcomes (e.g., remission) and length of follow-up in the few pediatric studies reporting outcomes.

The current mainstay of therapy, CYC, targets only proliferating cells (e.g., newly formed immune cells from the bone marrow). Consequently, the expansion of pathogenic clones is blunted by CYC, but memory B and T cells are likely not affected. The indiscriminate anti-proliferative effect of CYC causes dose-limiting adverse effects and might not eliminate pathogenic lymphocyte clones. This failure may explain the chronically relapsing nature of GPA and MPA in patients treated with CYC.

There is strong support for a crucial role for B cells in the pathogenesis of GPA and MPA (Fauci et al. 1971, 1974; Fauci and Wolff 1973; Wolff et al. 1974). The number of activated B cells in the periphery has been shown to correlate with the extent of active disease (Popa et al. 1999). There is also a significant body of evidence indicating that the loss of B-cell tolerance to PR3 and MPO plays a critical role in GPA and MPA.

The rationale that B cells and ANCAs play a role in pathogenesis, together with the subsequent small studies of rituximab in GPA and MPA, generated the groundwork for the National Institutes of Health (NIH)-sponsored study ITN021AI (RAVE) with subsequent partial funding provided by the Immune Tolerance Network. The results of this study provided the basis for submission of the supplemental Biologics License Application to the Food and Drug Administration (FDA) and for regulatory submissions worldwide, and they supported approval of rituximab for the treatment of severe GPA and MPA in adults.

1.2 BACKGROUND ON RITUXIMAB

Rituximab (MabThera®/RITUXAN®) is a chimeric murine/human monoclonal antibody specific for the cluster of differentiation (CD) 20 antigen on the surface of B cells. Potential mechanisms of action for rituximab include complement-mediated toxicity and antibody-dependent cell-mediated cytotoxicity, as well as the inhibition of B-cell proliferation and the induction of apoptosis (Reff et al. 1994). Treatment with rituximab induces a rapid and sustained depletion of CD20-positive B lymphocytes. Short-lived plasma cells are thought to be the primary source of pathogenic autoantibodies such as ANCAs. Because short-lived plasma cells are the terminally differentiated progeny of antigen-specific B-cell precursors, they disappear after approximately 2 weeks when the precursor cells are no longer available (Reff et al. 1994). Thus, rituximab may be used to disrupt B-cell pathogenic mechanisms to disease and suppress autoantibody production.

Clinical studies have been completed or are being undertaken by Roche in various disease areas, including rheumatoid arthritis (RA) and several other autoimmune disorders, including multiple sclerosis, *pemphigus vulgaris,* systemic lupus erythematosus (SLE), and AAV. Rituximab is currently approved in more than 100 countries for the treatment of relapsed or refractory non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and in combination with MTX for the treatment of RA patients who inadequately responded to one or more anti-tumor necrosis factor (anti-TNF) therapies.

Preliminary open-label, single-institution experience suggested that rituximab helped control AAV and could potentially help re-establish tolerance to ANCA-target antigens (Specks et al. 2001; Keogh et al. 2005). This preliminary information generated interest in performing a multicenter trial to assess the ability of rituximab to induce remission in patients with severe AAV. The pivotal double-blind, double-dummy, placebo-controlled randomized trial called RAVE (Stone et al. 2010) provided evidence of a positive benefit–risk for rituximab in GPA (WG) and MPA that resulted in the FDA's approval of rituximab for the treatment of these conditions in 2011. This indication has since been approved in a number of other markets worldwide, including *the European Union,* Canada, Switzerland, South Korea, and Israel.

The safety and effectiveness of rituximab in pediatric patients have not been established. Off-label use of rituximab for a wide range of immune-mediated diseases in pediatric populations has been noted. The most frequent reporting of adverse events (AEs) in autoimmune indications in children has been in SLE and immune thrombocytopenic purpura (ITP). Controlled clinical trials for the pediatric population are difficult to conduct because of the small number of eligible patients. Interpretation of the safety and efficacy of rituximab therapy in pediatric autoimmune diseases relies largely on analysis of retrospective case studies and extrapolation from adult populations.

The data on the use of rituximab in pediatric patients with GPA and MPA are sparse and are based on case reports in off-label use. The published case studies on 7 patients ≤18 years old who were treated with rituximab are presented in Table 1. Of the 7 patients, 4 achieved remission, whereas another patient was reported as being successfully treated. There was one fatal event: pulmonary fibrosis in a 7-year-old male whose history included severe pulmonary fibrosis and an unclassified acute adenovirus, as well as treatment with multiple prior and/or concomitant immunosuppressant therapies. There was no apparent difference in the pattern of AEs compared with the adult patients in the same trials.

Table 1 Pediatric Patients with GPA or MPA Treated with Rituximab (Literature Reports)

Reference	Age (yr)/ Sex	Organ Involvement	Previous Treatment	Rituximab Regimen	Efficacy (BVAS before/after RTX)	Safety
Keogh et al. 2005	17/M	Kidney and skin	CYC and MTX	375 mg/m^2 weekly × 4	BVAS/WG 7/0	None
	14/F	ENT and lung	CYC and MTX	375 mg/m^2 weekly × 4	BVAS/WG 3/0	Mild angioedema (during first infusion); polyarthritis following fourth infusion that responded to short term treatment with GC
Aries et al. 2006	4/M	ENT and eye	CYC, GC, and IFX	RTX 375 mg/m^2 q4w × 4; CYC 100 mg od; PRD 10 mg od	BVAS 10/7; active scleritis persisted	NR
Smith et al. 2006	18/F	Lung, kidney, and eye	Six prior IS agents, including CYC and MMF	375 mg/m^2 weekly × 4	Remission achieved by 5 months	NR (no deaths or serious IRRs in the study)
Di Maria et al. 2008	13/M	Lung, kidney	CYC	700 mg weekly × 4	Successful treatment	NR
Brunner et al. 2009	14/F	Lung, kidney	CYC and MMF	375 mg/m^2 weekly × 2	Remission	NR
Jones et al. 2009	7/M	Lung (NOS)	NR	RTX (regimen not specified)	NR	Death due to vasculitis (pulmonary fibrosis) 8 months after RTX

BVAS = Birmingham Vasculitis Activity Score; CYC = cyclophosphamide; ENT = ear, nose, and throat; F = female; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; IFX = infliximab; IRR = infusion-related reaction; IS = immunosuppressant; M = male; MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; MTX = methotrexate; NOS = not otherwise specified; NR = not reported; od = oral; q4w = every 4 weeks; RTX = rituximab; yr = year; WG = Wegener's granulomatosis.

Additional published data include information on single cases or limited case series in pediatric patients treated with rituximab for a range of malignant and non-malignant hematologic diseases, including, for example, post-transplant lymphoproliferative disorder, graft-versus-host disease, autoimmune hemolytic anemia, chronic ITP, thrombotic thrombocytopenic purpura (TTP), and congenital and acquired hemophilia. Some of the data in pediatric autoimmune cytopenias have been reviewed (Singer and Scalzi 2004).

There are several reports of rituximab treatment in children with a range of other autoimmune conditions, including juvenile idiopathic arthritis (JIA), SLE, Type I diabetes mellitus, juvenile dermatomyositis, opsoclonus–myoclonus syndrome, and childhood pemphigus vulgaris. The following is a brief summary of these publications.

SLE: Recent studies have shown that children with SLE (Marks et al. 2005) and lupus nephritis caused by childhood-onset SLE (Barillas-Arias et al. 2006) respond well to a combination of rituximab and CYC. Therapy was well tolerated, with no reported serious adverse events (SAEs).

JIA: Alexeeva et al. (2011) reported a significant reduction in systemic manifestations in a case series of 55 patients with JIA refractory to infliximab and standard immunosuppressive therapy following treatment with repeat courses of rituximab. Consistent with data from adult populations, the most frequent AE was infusion reactions, which decreased with repeated courses. The incidence of infections and neutropenia increased as serum concentrations of immunoglobulin M (IgM) and immunoglobulin G (IgG) decreased, highlighting the need for careful monitoring of children who are receiving rituximab for treatment of JIA.

Other Autoimmune Diseases: El Hallak (2007) presented findings from a retrospective study in which 10 patients were treated with rituximab for a range of severe, refractory autoimmune diseases, including SLE, Evans syndrome, vasculitis, and insulin-dependent diabetes mellitus. Of the 10 patients, 9 experienced clinical improvements after rituximab therapy and treatment was associated with a decrease in mean corticosteroid dose. Rituximab was well tolerated in this population, and the number and severity of infections did not change significantly after B-cell depletion.

Fuertes et al. (2010) reported long-term clinical remission in 7 children and adolescents treated with rituximab for childhood pemphigus vulgaris, with no clinically relevant side effects.

Pranzatelli et al. (2006) evaluated whether rituximab (plus corticotropin and/or intravenous [IV] immunoglobulins [IVIgs]) reduces cerebrospinal fluid B-cell expansion in opsoclonus–myoclonus syndrome and results in clinical improvement in 16 children. Following rituximab treatment, a significant proportion of patients experienced improved

outcomes, and the authors concluded rituximab is effective and safe as adjunctive therapy for opsoclonus–myoclonus syndrome.

Chiu and Co (2011) reviewed the use of rituximab in juvenile dermatomyositis and reported the use of rituximab in 12 children (8–22 years old). Most patients received 375 mg/m^2 weekly for 4 weeks. Cutaneous or muscle disease was improved in 9 patients (75%) following rituximab treatment, and 5 patients (42%) achieved remission of disease with one course of rituximab. Only minor side effects were reported.

Pescovitz et al. (2009) conducted a randomized, double-blind study in which 87 patients between 8 and 40 years old (median age: 16 years in the rituximab group, 14 years in the placebo group) with newly diagnosed Type 1 diabetes received four infusions of rituximab or placebo. At 1 year, the mean area under the concentration–time curve (AUC) for the level of C peptide was significantly higher in the rituximab group than in the placebo group. More patients in the rituximab group relative to the placebo group had AEs, mostly Grade 1 or 2, after the first infusion. The reactions appeared to be minimal with subsequent infusions. There was no increase in infections or neutropenia with rituximab treatment. The authors concluded that a four-dose course of rituximab partially preserved B-cell function over a period of 1 year in patients with Type 1 diabetes.

In general, the safety of rituximab infusions in children is consistent with the profile observed in adults. However, data are limited, especially for rituximab treatment in children <2 years old.

1.2.1 Efficacy and Safety of Rituximab in Adult Patients with GPA and MPA

RAVE was a multicenter, randomized, double-blind, placebo-controlled trial conducted to assess whether treatment with rituximab (375 mg/m^2 IV weekly $\times 4$) was not inferior to CYC (2 mg/kg/day by mouth [PO]) for inducing remission in severe GPA and MPA (Stone et al. 2010). Once remission was achieved, CYC was replaced by AZA between Months 3 and 6 (AZA placebo for patients in the rituximab group). All patients received the same glucocorticoid treatment according to the protocol: 1–3 g of IV methylprednisolone followed by 1 mg/kg/day PO of prednisone, which was reduced to 40 mg/day by Month 1, then tapered and discontinued completely by Month 6. The 6-month remission induction phase was followed by a 12-month remission maintenance phase (Months 6–18). The primary endpoint was disease remission in the absence of prednisone therapy at 6 months. Remission was defined as a Birmingham Vasculitis Activity Score for WG (BVAS/WG) of 0.

Efficacy in RAVE

Results of the RAVE study support the conclusion that rituximab is non-inferior to oral CYC over 6 months of treatment; a higher percentage of patients in the rituximab group (64%) achieved a complete remission at 6 months compared with patients in the CYC group (55%). The lower limit of the 95.1% confidence interval (CI) for the absolute difference was −4.3% and met the predefined protocol-specified non-inferiority criterion. Similar rates of severe and limited disease flares and similar mean BVAS/WG AUC values were observed over the first 6 months in the two treatment groups, suggesting comparable control of disease activity over the 6-month period. The cumulative prednisone dose from randomization to 6 months was numerically lower in the rituximab group ($p = 0.055$), supporting the conclusion that the efficacy results seen in the rituximab group were not due to increased prednisone exposure compared with the CYC group. Non-inferiority to CYC was observed consistently across subgroups defined by demographic and disease characteristics.

At 18 months, efficacy findings were similar to those observed at 6 months. The proportion of patients who maintained their complete remission at 12 months and 18 months was similar between treatment arms after a single cycle of rituximab. Rates of remission (BVAS/WG of 0) for patients on a prednisone dose of < 10 mg/day, as well as rates of remission irrespective of prednisone dose, were similar across treatment groups. The rates of remission were similar across groups despite a numerically lower cumulative steroid dose and lack of AZA maintenance therapy in the rituximab group. Over 18 months, the overall rates of severe and limited flares were comparable between treatment groups. However, after 6 months, slightly more flares occurred in the rituximab group than the CYC group.

Safety in RAVE

Overall tolerability was similar between the rituximab and CYC groups at 6 months, and the proportion of patients experiencing any AE, any severe (Grade ≥ 3) AE, or any SAE was comparable, as was the rate of AEs and SAEs. The proportion of patients with AEs leading to a permanent discontinuation of study drug was slightly higher in the CYC group (13.3%) than in the rituximab group (8.1%).

The prespecified secondary analysis of safety of rituximab relative to CYC focused on the following selected events, which were considered key safety outcomes associated with underlying disease or treatment:

- Deaths
- Bone marrow suppression
- Infections
- Hemorrhagic cystitis
- Malignancies
- Venous thromboembolic events

- Hospitalizations as the result of disease activity or treatment, according to investigator assessment
- Cerebrovascular accidents
- Infusion-related reactions (IRRs) leading to cessation of further infusions

The proportion of patients who experienced at least one of the above selected AEs was numerically lower in the rituximab group (22.2%) than in the CYC group (34.7%). However, the rates of selected AEs were similar between the two treatment groups (0.78 events/patient-year in the rituximab group vs. 0.96 events/patient-year in the CYC group; $p = 0.250$). The difference in the proportion was due largely to the greater number of CYC-treated patients with National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade ≥ 2 leukopenia, although this did not translate into a higher number of infections during the first 6 months in the CYC group. More patients in the rituximab group (10 patients; 10.1%) than in the CYC group (4 patients; 4.1%) required hospitalization that was considered by the investigator to be related to disease activity or study therapy. The incidence of events of special interest for rituximab, such as serious infections, serious cardiac AEs, and malignancies, was similar across the two treatment groups over the 6-month treatment period. A similar proportion of patients experienced infusion reactions in each group, and no serious reactions were reported.

The long-term safety of rituximab was evaluated on the basis of the 18-month data post-randomization. Overall safety, including the incidence and rate of any AE, selected AEs, Grade ≥ 3 AEs, SAEs, and serious infections, was comparable between the rituximab and CYC groups. The overall profile of AEs reported over 18 months of follow-up in RAVE was similar to that observed over the study's first 6 months.

1.2.2 Overall Safety of Rituximab in Rheumatoid Arthritis

Safety data have been collected in clinical trials in a variety of indications, particularly oncology and RA, following IV administration of rituximab.

Safety data are available from 3194 patients with RA who were exposed to rituximab in clinical trials. The total duration of observation is approximately 12,000 patient-years, with 627 patients followed for > 5 years, as of September 2010. The long-term safety profile of rituximab is similar to that observed in the pooled placebo population (the placebo control groups from the randomized RA studies). The rates of infection, myocardial infarction, stroke, and malignancies were consistent with those observed in other RA cohorts. Key findings were as follows (see the Investigator's Brochure for more details):

- Adverse events: The overall rate of AEs (263.1/100 patient-years; 95% CI: 260.21, 266.02), SAEs (14.4/100 patient-years; 95% CI: 13.73, 15.09), and deaths (0.5/100 patient-years; 95% CI: 0.39, 0.65) has remained stable across multiple courses and over time. The most common SAEs were infections (most frequently pneumonia).

- IRRs: In total, 23% of all rituximab-treated patients with RA experienced an IRR following the first infusion. Subsequent infusions were better tolerated. Premedication with an IV corticosteroid reduced the proportion of affected patients and severity of events. Most events were mild or moderate and resolved without complication. Less than 1% of patients (16 of the 3194 patients) experienced a total of 18 serious IRRs, none of which was fatal. Of the 18 events, 10 occurred with Course 1 (8 with the first infusion), 5 with Course 2, and 1 each with the first infusions with Courses 4, 5, and 6. The events were variable in nature and included rash, headache, blood pressure changes, anaphylactic or anaphylactoid reactions, and edema. Severe IRRs with fatal outcome have been reported in patients with RA treated with rituximab in the postmarketing setting.
- Infections: The overall rates of infections (81.64/100 patient-years; 95% CI: 80.04, 83.27) and serious infections (3.94/100 patient-years; 95% CI: 3.60, 4.31) have remained stable across multiple treatment courses. There was no evidence of increased rates of serious infection following the use of other biologic agents, including TNF inhibitors, subsequent to rituximab treatment. No cases of hepatitis B reactivation or atypical mycobacterium infections were reported in clinical trials. Opportunistic infections were rare. One case of progressive multifocal leukoencephalopathy (PML) was observed in RA clinical trials. Other cases of PML and hepatitis B reactivation have been reported in the postmarketing setting, outside of clinical trials.
- Malignancy: The incidence of malignancy did not increase with multiple courses of rituximab. No difference was observed in the overall rate or pattern of malignancy in patients treated with rituximab compared with other patients with RA described in epidemiologic studies.

Data received since 2010 are consistent with this profile. See the Investigator's Brochure for details about the nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The data from the RAVE trial in adults with GPA and MPA have demonstrated that patients with severely active GPA and MPA can achieve complete remission with an acceptable safety profile in the absence of conventional CYC and maintenance AZA treatment. Given the adult data, the expectation is that rituximab treatment would be associated with a positive benefit–risk, providing at least equivalent efficacy to current treatments employed in children with severely active GPA or MPA.

The overall safety profile of rituximab in adult GPA and MPA was consistent with the known safety profile of rituximab and the underlying disease, with no new safety signals identified during a mean follow-up period of 3 years in the RAVE study. Longer-term safety data on rituximab in other indications do not suggest an association with the known long-term toxicities associated with conventional CYC treatment such as infertility or malignancies.

Rituximab treatment offers a therapy with a novel mode of action that may be associated with significant efficacy and safety benefits for children with severe GPA or MPA. The safety and effectiveness of rituximab in pediatric patients with GPA and MPA have not been studied, with only limited data for 7 patients available in the published literature (see Section 1.2 and Table 1). There are also no available pharmacokinetic (PK) and/or pharmacodynamic (PD) data on rituximab in pediatric patients with GPA and/or MPA. Therefore, the primary objectives of the present study are to evaluate the safety and pharmacokinetics of rituximab in pediatric patients with GPA or MPA. Moreover, given that outcomes with current treatments such as CYC are unsatisfactory and are associated with high relapse rates and significant morbidity and toxicity, the present study will also include exploratory efficacy objectives. Because this study represents the first global clinical trial investigating the use of rituximab in pediatric patients with GPA and MPA, a relatively small number of patients will be enrolled, and an open-label, single-arm design has been adopted.

2. OBJECTIVES

2.1 SAFETY OBJECTIVES

The primary safety objective for this study is to evaluate the safety and tolerability of rituximab in pediatric patients with severe GPA or MPA.

2.2 PHARMACOKINETIC OBJECTIVES

The primary PK objective for this study is to evaluate the PK parameters of rituximab in pediatric patients with severe GPA or MPA.

2.3 EXPLORATORY EFFICACY OBJECTIVES

[redacted]

2.4 OTHER EXPLORATORY OBJECTIVES

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

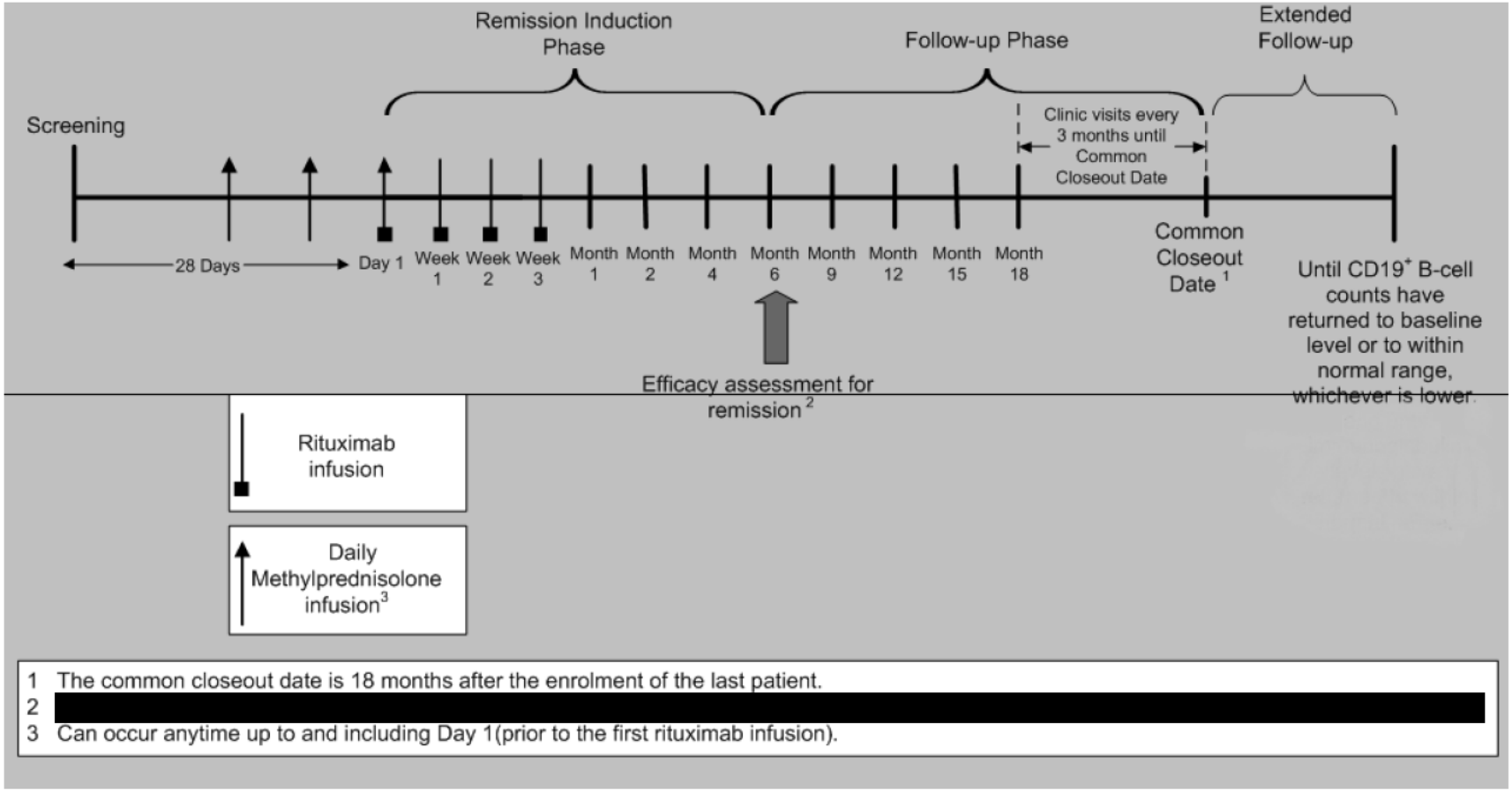
This is a Phase IIa, international, multicenter, open-label, single-arm study. The primary objectives are to evaluate the safety and tolerability and the PK parameters of rituximab in pediatric patients with severe GPA or MPA. At least 25 patients between 2 and

18 years of age will be enrolled across approximately *23* sites in France, Germany, Italy, Turkey, *Canada, Serbia,* the United Kingdom (UK), and the United States (US).

The study comprises an initial 6-month remission induction phase, followed by a minimum 12-month follow-up phase. The common closeout date will occur 18 months after the enrollment of the last patient (see Figure 1).

At screening, all patients will be assessed for eligibility according to the inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2, respectively). Screening assessments will be performed in accordance with the schedule of assessments (see Appendix 1). The screening visit may occur up to 28 days prior to the baseline visit. If the patient is receiving treatment with an agent such as mycophenolate mofetil (MMF), the agent should be washed out prior to baseline according to local practice. The recommended washout period for MMF is at least 48 hours. Following screening, eligible patients will enter the remission induction phase of the study.

Figure 1 Study Design



[redacted]

3.1.2 Remission Induction Phase

Prior to the first rituximab infusion, patients must receive three doses of methylprednisolone at 30 mg/kg/day (up to 1 g/day) by IV infusion that can occur any time after screening, up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional daily doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day) can be given by IV infusion. No more than six doses of methylprednisolone in total can be given. All methylprednisolone doses must be completed prior to the first rituximab infusion. The first rituximab infusion must occur no later than 14 days after the last dose of methylprednisolone infusion. Subject to the investigator's discretion, corticosteroid premedication with an IV infusion of 100 mg of methylprednisolone may be administered at least 30 minutes prior to the infusion of rituximab (but not prior to clinical assessments) if the patient has experienced an IRR with a previous rituximab infusion.

Rituximab will be administered to patients as four weekly IV infusions of 375 mg/m^2 on Days 1, 8, 15, and 22. The dose will be calculated using a patient's body surface area (BSA) at screening. Infusions can be given in a day care or inpatient setting. It is acceptable to hospitalize a patient as per local clinical practice. All patients will receive concomitant oral prednisolone or prednisone (maximum, 1 mg/kg/day or up to 60 mg/day, whichever is less), which will be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever is lowest) no later than by Month 6. Following completion of rituximab infusions on Day 22, patients will complete study visits at Months 1, 2, 4, and 6 and will undergo assessments in accordance with the schedule of assessments (see Appendix 1). For more details about rituximab administration, pre-infusion medications, and monitoring of patients during infusion, see Section 4.3.2.

Patients who receive at least part of one IV infusion of rituximab but do not complete four weekly infusions should continue to receive protocol-defined concomitant oral prednisolone or prednisone and/or should receive treatment at the discretion of the investigator (local standard of care) but will remain in the study. Patients who show some initial improvement but then, prior to Month 6, experience disease flare (Section 3.1.6) before remission that cannot be controlled by glucocorticoids should receive treatment at the discretion of the investigator (according to local standard of care) and will remain in the study. Patients who, by Month 6, exhibit progressive disease before remission (see Section 4.5.9) will receive additional treatment as per local standard of care and will remain in the study.

The schedule of assessments (Appendix 1) will be the same for all patients in the study.

3.1.3 Follow-Up Phase

Following the remission induction phase, patients will be followed for a minimum of 12 months with visits every 3 months, in accordance with the schedule of assessments (see Appendix 1). The optimal treatment after rituximab induction for GPA or MPA has

not been established in adults or in pediatric patients. After Month 6, patients who are protocol remission failures or experience disease flare that cannot be controlled by glucocorticoids alone should receive treatment in accordance with local standard of care at the discretion of the investigator and will remain in the study (see Section 4.4.2.1).

After Month 6, if patients require retreatment with rituximab, additional courses will be provided by the Sponsor until the common closeout date. Retreatment with rituximab is at the discretion of the investigator and may be considered based on disease activity, previous response to treatment, and the investigator's assessment of the risks with rituximab.

After Month 18, patients will be followed at study visits every 3 months until the common closeout date. The procedures performed at the follow-up visits will be similar to those performed at the Month 18 visit. After the common closeout date, patients whose B cells remain depleted and/or who have immunoglobulin levels below the lower limit of normal (LLN) for the population will enter extended follow up.

The schedule of assessments is provided in Appendix 1.

3.1.4 Extended Follow-Up

At the common closeout date, patients whose *peripheral* B cells remain depleted will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower. *Safety (adverse events), central laboratory and immunological parameters, including immunoglobulin, will continue to be assessed in extended safety follow-up* (see Appendix 1).

If a patient receives any B cell-depleting therapy *(commercial or investigational)* or any other agent that affects the return of B cells including, but not limited to, rituximab, CYC, and AZA, on or after the common closeout date, he or she will not be followed any further (although routine clinical follow up after the end of the study will continue, according to local practice).

3.1.5 Unscheduled Visits

Patients may attend the clinic for unscheduled visits at any time for additional safety monitoring or disease surveillance at the discretion of the investigator.

3.1.6 Disease Relapse/Flare

Relapse is defined as the recurrence or new onset of disease attributable to active GPA/MPA.

By Pediatric Vasculitis Activity Score (PVAS), major relapse/flare is defined as the recurrence or new onset of potentially organ- or life-threatening disease (i.e., the

recurrence or new appearance of one or more major PVAS items listed in Table 2 or disease that is severe enough to require treatment with CYC).

By PVAS, minor relapse/flare is defined as the recurrence or new onset of disease that is neither potentially organ- or life-threatening (i.e., the recurrence or new appearance of at least three minor PVAS items listed in Table 2).

By BVAS/WG, major relapse/flare is defined as the recurrence or new onset of potentially organ- or life-threatening disease (i.e., the recurrence or new appearance of one or more major BVAS/WG items listed in Table 3 or disease that is severe enough to require treatment with CYC).

By BVAS/WG, minor relapse/flare is defined as the recurrence or new onset of disease that is neither potentially organ- or life-threatening (i.e., the recurrence or new appearance of at least three minor BVAS/WG items listed in Table 3).

Table 2 PVAS Features of Limited and Severe AAV

Severe (Major) PVAS Items[a]	Limited (Minor) PVAS Items[b]
	Myalgia
Gangrene (extensive necrosis)	
Significant proptosis	Arthralgia or arthritis
Red eye scleritis [c]	Fever ≥38°C
Sudden visual loss	Weight loss of ≥5% body weight
Retinal vasculitis/retinal vessel thrombosis/retinal exudates/hemorrhages	Polymorphous exanthema
Subglottic stenosis/hoarseness /stridor	Livedo
Sensorineural hearing loss	Panniculitis
Massive hemoptysis/alveolar hemorrhage	Purpura
Respiratory failure	Skin nodules
Loss of pulses	Infarct (nail edge lesion, splinter hemorrhage)
Ischemic cardiac pain	Ulcer (full-thickness necrosis)
Cardiomyopathy	Other skin vasculitis
Congestive cardiac failure	Mouth ulcers/granulomata
Peritonitis	Genital ulcers
Bowel ischemia	Adnexal inflammation
Hematuria with red cell casts [d]	Red eye episcleritis [c]
Rise in creatinine >10% or creatinine clearance or GFR fall >25%	Red eye conjunctivitis/blepharitis/keratitis
Meningitis/encephalitis	Uveitis
Organic confusion/cognitive dysfunction	Blurred vision
Seizures (not hypertensive)	Nasal discharge/crusts/ulcers/granuloma

Severe (Major) PVAS Items[a]	Limited (Minor) PVAS Items[b]
Stroke	Paranasal sinus involvement
Cord lesion	Conductive hearing loss
Cranial nerve palsy	Wheeze or expiratory dyspnea
Motor mononeuritis multiplex	Endobronchial/endotracheal involvement
	Nodules or cavities
	Pleural effusion/pleurisy
	Infiltrate
	Bruits over accessible arteries
	Blood pressure discrepancy
	Caudication of extremities
	Valvular heart disease
	Pericarditis
	Abdominal pain
	Blood in stools or bloody diarrhea
	Hypertension >95th centile (for height)
	Proteinuria >0.3 g/24h, creatinine >20 mg/mmol
	Hematuria ≥2+ or 5 rbc/hpf
	Headache
	Sensory peripheral neuropathy

AAV = ANCA-associated vasculitis; ANCA = anti–neutrophil cytoplasmic antibody; PVAS = Pediatric Vasculitis Activity Score; GFR = glomerular filtration rate.

[a] Any of these items must be attributable to the active underlying disease.

[b] Minor items with a significant risk of morbidity may be classified as severe.

[c] Ophthalmologist should be consulted to distinguish scleritis and episcleritis.

[d] Presence of casts should be carefully examined.

3.1.7 Early Study Termination

The investigator or the Sponsor may withdraw a participant from the study if the participant does not comply with study procedures or withdraws consent. The participant will be asked to complete a withdrawal visit (see Appendix 1).

3.1.8 Early Study Drug Withdrawal

The investigator may also withdraw a participant from study treatment if he or she judges that continuing on rituximab is no longer in the participant's best interest. These participants will remain in the study *for follow-up*, but will be asked to complete a withdrawal visit (see Appendix 1). *From the point of withdrawal, a patient may no longer receive rituximab as part of this protocol.* They will continue to be followed until the common closeout date. At the common closeout date, patients whose *peripheral* B cells remain depleted, will continue to attend study visits every 3 months until their

peripheral B-cell counts have returned to *pre-rituximab* baseline level or to within the normal range for the population, whichever is lower (see Section 3.1.4).

3.2 END OF STUDY

Follow up of all participants will continue until the common closeout date, when the final participant enrolled has completed his or her Month 18 study visit.

At the time of the common closeout date for each patient, the scheduled study visit occurring before or at the common closeout date will represent the end of main study visit. However, all participants with *peripheral* B-cell counts below the LLN or *pre-rituximab* baseline value will enter extended follow up, as described in Section 3.1.4. If the trial is stopped early, all participants will be withdrawn from the study at the time of the termination of the study.

The end of the study will occur when the last participating patient completes the final scheduled visit (inclusive of extended follow up) or when the Sponsor decides to discontinue the study or development program.

3.3 RATIONALE FOR STUDY DESIGN

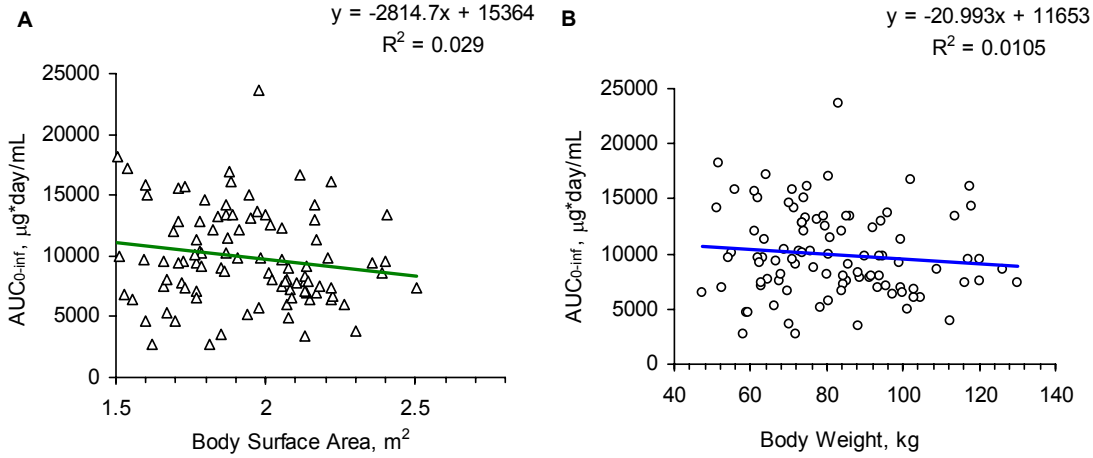
3.3.1 Rationale for Test Product Dosage

Rituximab will be administered to patients as 4 weekly IV infusions (375 mg/m^2).

Currently, there are no guidelines for the dosage or duration of immunosuppressant therapy in children with GPA or MPA. The recommended regimens in pediatric patients described in literature (see Section 1.2.2) are similar to those of adults.

In the RAVE study, a rituximab regimen of weekly infusions of 375 mg/m^2 for 4 weeks was given to adult patients with GPA or MPA. The mean area under the rituximab plasma concentration–time curve from Time 0 to infinity (AUC_{0-inf}) ranged from 3.14 mg/mL/day to 24.5 mg/mL/day (mean ± standard deviation [SD], 10.6 ± 3.93 mg/mL/day). Inter-patient PK variability was 38%. AUC_{0-inf} was independent of either BSA (see Figure 2, Panel A) or body weight (Figure 2, Panel B) in adult patients.

Figure 2 Scatter Plots of AUC_{0-inf} versus Body Surface Area (A) and AUC_{0-inf} versus Body Weight (B) in the RAVE Study



AUC_{0-inf} = area under the rituximab plasma concentration–time curve from Time 0 to infinity.
Note: n = 97.

The analysis of the rituximab exposure–response relationship (i.e., remission at 6 months after the last rituximab infusion) indicated that there was no difference between patients with a lower AUC_{0-inf} (less than the median value) and patients with a higher AUC_{0-inf} (greater than or equal to the median value), with no correlation between achievement of complete remission at Month 6 and individual AUC_{0-inf}, as indicated by a Spearman coefficient of correlation of –0.01. Thus, 375 mg/m^2 of rituximab weekly for 4 weeks appeared to reach a plateau in the exposure–response curve. Assuming that the disease process is similar in adults and pediatric AAV patients, the exposure–response relationship between adult and pediatric patients is expected to be similar.

Given the therapeutic class (i.e., an IgG antibody), mechanisms of clearance (CL) and linear PK properties, the pharmacokinetics of rituximab in children are expected to be similar to those in adults. Four weekly infusions of 375 mg/m^2 of rituximab have been used off-label in pediatric patients with refractory autoimmune disease (i.e., SLE, vasculitis, JIA, ITP, idiopathic autoimmune hemolytic anemia), suggesting efficacy and acceptable tolerability (Jansson et al. 2011). It is reasonable to assume that a comparable PK exposure using the same dosing regimen would produce similar effects in children and adults in the same indication.

Because of the linear pharmacokinetics of rituximab, allometric scaling is the most appropriate method to predict human CL. The following allometric scaling equation has been used for the estimation of CL in children:

$$CL_{children} = CL_{adult} (BW_{children}/BW_{adult})^{0.75}$$

in which age, body weight (BW), and BSA data are taken from reference (Eriksson 2005). The AUC_{0-inf} for children is predicted using the following equation, assuming a weekly dose of 375 mg/m^2 for 4 weeks:

$$AUC_{0-inf} = [BSA\ (m^2) \times 375\ (mg/m^2)/CL\_{children}]$$

The AUC_{0-inf} for children is also predicted using the following equation assuming a 9-mg/kg dose weekly for 4 weeks:

$$AUC_{0-inf} = [BW\ (kg) \times 9\ (mg/kg)/CL\_{children}]$$

The predicted mean $\pm$ SD AUC_{0-inf} of this dosing regimen in children across an age range of 2–18 years is 9592 $\pm$ 272 μg • day/mL for boys and 9538 $\pm$ 279 μg • day/mL for girls, which is comparable to the adult exposure. Importantly, based on allometric scaling, uniform exposure across ages 2–18 years is predicted in both boys (range: 9081–9972 μg • day/mL) and girls (range: 9102–9915 μg • day/mL).

Conversely, if a weight-based regimen of 9 mg/kg weekly for 4 weeks is given to children, the mean $\pm$ SD AUC_{0-inf} is predicted to be 6550 $\pm$ 972 μg • day/mL for boys and 6552 $\pm$ 965 μg • day/mL for girls, which is lower than the adult exposure.

Therefore, 4 weekly infusions of 375 mg/m^2 is the most appropriate dose for all children in the study, on the basis of the following:

- Use of lower doses would be unproven in a condition that requires aggressive treatment with immunosuppressive therapies
- In adult patients with GPA and MPA, a 375 mg/m^2 dose regimen achieved uniform PK exposures across a wide range of body weights or BSA
- The allometric scaling method indicated that 375 mg/m^2 is adequate in children
- In adult patients from the RAVE study, similar to RA patients, an exposure–response relationship for clinical efficacy endpoints indicated that the PK exposure reached a plateau for the exposure–response curve
- A regimen of four weekly infusions of 375 mg/m^2 has been shown to be effective in adults with GPA or MPA and has an acceptable benefit–risk profile in children with autoimmune conditions and hematologic disorders (Giulino et al. 2007; Jansson et al. 2011)
- Currently, there are no guidelines for the dosage or duration of immunosuppressant therapies in children with GPA or MPA. The recommended regimens described in the literature are similar to those used in adults

3.3.2 Rationale for Patient Population

Children ages 2 to 11 years and adolescents ages 12 to < 18 years will be included in the trial, since the safety and effectiveness of rituximab in pediatric patients with GPA and MPA have not been studied.

Inclusion of patients < 2 years old is not considered appropriate on the grounds of safety with respect to the immaturity of the immune system of young children and the risks this could present following treatment with rituximab. Although younger children (i.e., ages 2–6 years) may not have completed their childhood vaccination program, given the severity of GPA and MPA, the potential risk–benefit is considered appropriate so as to include this subset in the clinical trial. Moreover, standard treatment of pediatric GPA and MPA is broadly similar to that in adults (immunosuppression with CYC followed by maintenance of remission with AZA or MTX), which in some cases could be in the context of non-completion of childhood vaccination programs.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measures

3.4.1.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency, nature, and severity of AEs
- Frequency of laboratory abnormalities

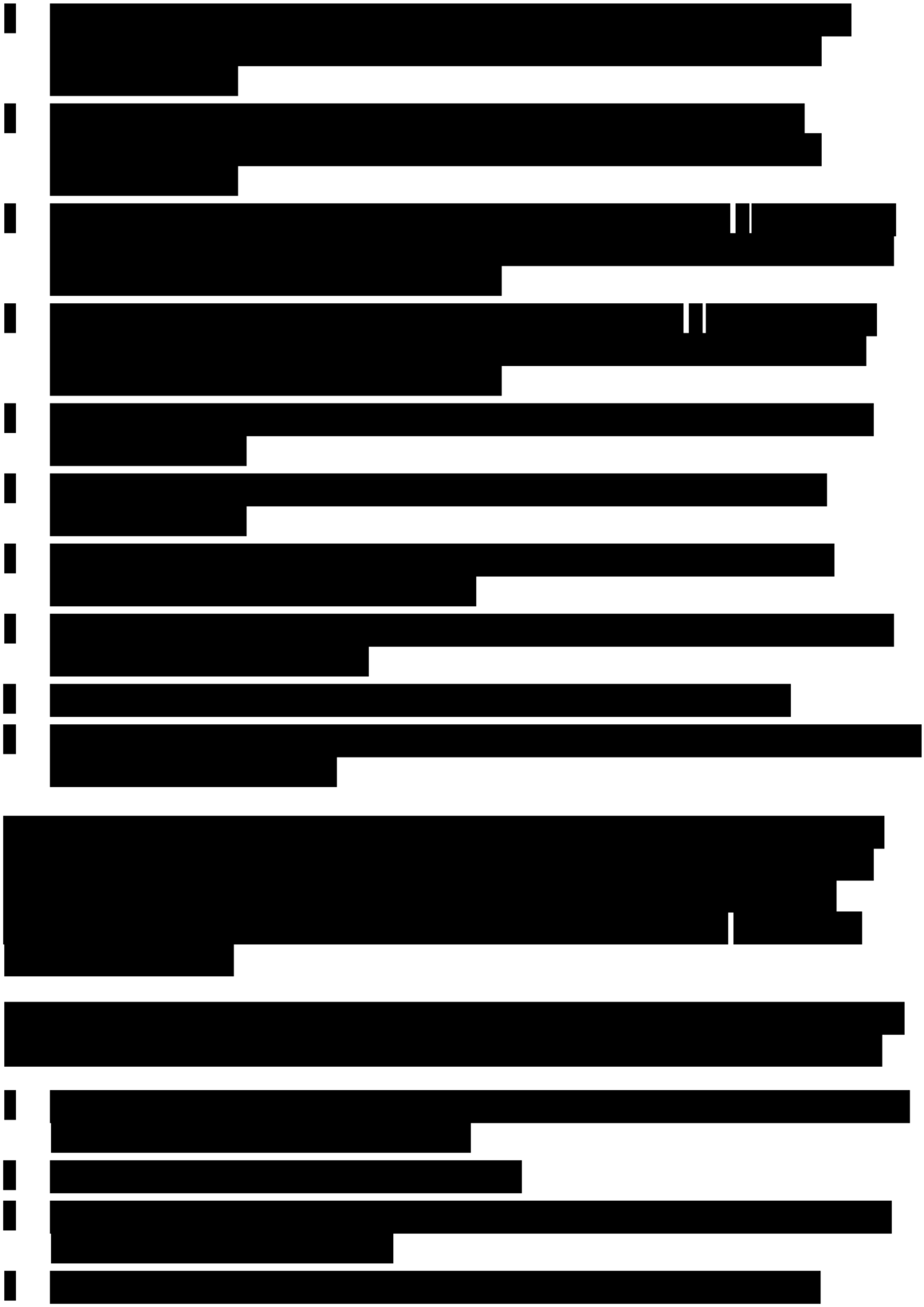
3.4.1.2 Pharmacokinetic Outcome Measures

The primary PK parameters will be CL and volume of distribution estimated from population PK model. The secondary PK exposure parameters ($AUC_{0\text{-}inf}$, maximum plasma concentration [C_{max}]) derived from the primary PK parameters will be computed. The rituximab exposure–response relationship will be explored.

3.4.2 Exploratory Efficacy Outcome Measures

The exploratory efficacy outcome measures for this study will include the following:

[redacted]



3.4.3 Other Exploratory Outcome Measures

3.4.4 Pharmacodynamic Outcome Measures

The exploratory PD outcome measures for this study will include the following:

- [redacted]
- [redacted]
- [redacted]

3.4.5 Patient-Reported Outcome Measures

[redacted]

- [redacted]
- [redacted]

3.4.6 [redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study is pediatric patients ages ≥2 to <18 years with severe GPA or MPA. Newly diagnosed patients and patients with relapsed or refractory GPA or MPA will be eligible.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent for study participation obtained from patient's parents or legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding
- Age at screening between ≥2 and <18 years
- Diagnosis of GPA (EULAR/PRINTO/PRES 2008, Ankara criteria for childhood WG [Özen et al. 2010]; see Appendix 5) or diagnosis of MPA (according to the Chapel Hill Consensus Conference [Jennette 1994]; see Appendix 6)
- Newly diagnosed patients or patients with relapsing disease according to the following definition:

  The recurrence or new onset of potentially organ- or life-threatening disease (i.e., one or more major BVAS/WG items listed in Table 3 or disease severe enough to require treatment with CYC).
- For patients of reproductive potential (males and females), use of a reliable means of contraception (e.g., abstinence, hormonal contraceptive patch, intrauterine device, physical barrier) throughout their study participation

- For all eligible patients, mandatory prophylactic treatment for *Pneumocystis jiroveci* infection

Table 3 BVAS/WG Features of Limited and Severe AAV

Severe (Major) BVAS/WG Items [a]	Limited (Minor) BVAS/WG Items [b]
Cutaneous gangrene	Arthralgias/arthritis
Scleritis	Fever (>38°C)
Retinal exudates/hemorrhage	Purpura
Sensorineural hearing loss	Skin ulcer
Mesenteric ischemia	Mouth ulcers
Alveolar hemorrhage	Conjunctivitis/episcleritis
Red blood cell urinary casts	Orbital mass/proptosis
Rise in serum creatinine 30% over baseline value	Uveitis
Aseptic meningitis	Bloody nasal discharge/nasal crusting
Spinal cord lesions	Sinus involvement
Cerebrovascular accident caused by vasculitis	Swollen salivary gland
Cranial nerve palsy	Subglottic inflammation
Sensory peripheral neuropathy	Conductive deafness [c]
Motor mononeuritis multiplex	Pericarditis
	Pleurisy
	Pulmonary nodules or cavities
	Other pulmonary infiltrates secondary to vasculitis
	Endobronchial lesions
	Hematuria

AAV=ANCA-associated vasculitis; ANCA=anti-neutrophil cytoplasmic antibody
BVAS=Birmingham Vasculitis Activity Score; WG=Wegner's granulomatosis.

[a] Any of these items must be attributable to the active underlying disease.

[b] Minor items with a significant risk of morbidity may be classified as severe (i.e., BVAS/WG 3).

[c] Additional testing may be required to make the diagnosis.

4.1.2 Exclusion Criteria

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

Exclusions Related to GPA or MPA

- Diagnosis of Churg-Strauss syndrome, as defined by the Chapel Hill Consensus Conference (Jennette 1994; see Appendix 6)
- Limited disease that would not normally be treated with CYC
- Severe disease requiring mechanical ventilation due to alveolar hemorrhage
- Requirement for plasmapheresis or dialysis at screening

Exclusions Related to General Health

- Incomplete recovery from recent surgery or < 12 weeks since surgery prior to baseline or planned within 24 weeks of baseline
- Lack of peripheral venous access
- Pregnancy or breastfeeding
- Evidence of 1) other significant uncontrolled concomitant disease, including, but not limited to, cardiovascular disease, nervous system, pulmonary, renal disease (including anti-glomerular basement membrane [GBM] disease); or 2) hepatic, endocrine, or gastrointestinal disorders that, in the investigator's opinion, would preclude or interfere with patient participation
- Primary or secondary immunodeficiency (history of or currently active), including known history of human immunodeficiency virus (HIV) infection
- Evidence of active tuberculosis (patients receiving chemoprophylaxis for latent tuberculosis infection are eligible for the study) (see Section 4.5.6.1)
- 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-infective agents within 4 weeks of baseline or completion of oral anti-infective agents within 2 weeks prior to baseline

  Entry into this study may be reconsidered once the infection has fully resolved
- History of deep space/tissue infection (e.g., fasciitis, abscess, osteomyelitis) within 24 weeks prior to baseline
- History of serious recurrent or chronic infection
- History of cancer, including solid tumors, hematologic malignancies, and carcinoma in situ (except basal cell 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

Exclusions Related to Medications

- History of a severe allergic or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of rituximab or to murine proteins
- *T*reatment with rituximab *or other biologic B cell–targeted therapy (e.g., anti-CD19, anti-CD20, anti-CD22, or anti-B-lymphocyte stimulator [BLys]/BAFF) within 6 months prior to baseline visit*
- Previous treatment with an anti-alpha 4 integrin antibody or co-stimulation modulator
- Previous treatment with *other* cell-depleting therapies, including, but not limited to, investigational agents (e.g., alemtuzumab [CAMPATH®], anti-CD4, anti-CD5, anti-CD3, *and* anti-CD11a)
- Receipt of oral or IV CYC within the previous 4 months prior to the baseline visit
- Receipt of infliximab within the previous 3 months prior to the baseline visit

- Receipt of adalimumab within the previous 2 months prior to the baseline visit
- Receipt of etanercept within the previous 1 month prior to the baseline visit
- Treatment with any investigational agent within 28 days of baseline or 5 half-lives of the investigational drug (whichever is longer)
- Receipt of any live or attenuated vaccine within 28 days prior to baseline

  It is recommended that a patient's vaccination record and the need for immunization should be carefully reviewed and updated prior to receiving rituximab (see Section 4.4.3).
- Intolerance or contraindications to IV glucocorticoids

In case of receipt of any other immunosuppressant therapy (apart from corticosteroids), contact the Sponsor.

Exclusions Related to Laboratory Findings

- Positive serum human chorionic gonadotropin measured at screening or a positive pregnancy test prior to the first rituximab infusion for participants of childbearing potential
- Positive tests for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B virus (HBV), or hepatitis C serology
- Level of IgM below LLN of age-specific reference range
- *Level of IgG below 5.65mg/ml*
- Absolute neutrophil count (ANC) $< 1.5 \times 10^3/\mu L$
- Platelet count $< 130 \times 10^3/\mu L$
- Estimated GFR < 15 mL/min/1.73 m^2 (calculated using the Schwartz formula; see Appendix 3)
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels $> 2.5 \times$ the upper limit of normal (ULN) (for age and sex) that cannot be attributed to underlying GPA or MPA

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. All eligible patients will be assigned to receive rituximab treatment.

4.3 STUDY TREATMENT

	Treatment
Investigational medicinal products	
Test product	Rituximab
Comparator	Not applicable
Non-investigational medicinal products	
Comparator	Not applicable
Background therapy	Prednisone, prednisolone, and methylprednisolone
Premedication	Paracetamol/acetaminophen and antihistamine cetirizine hydrochloride (or similar)

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Rituximab (Investigational Medicinal Product)

The rituximab drug product is manufactured from bulk drug substance by Genentech (US License No. 1048). Study drug packaging will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study drug will be in accordance with Roche standards and local regulations. Study drug must be stored according to the details on the product label. The drug label indicates the storage temperature. Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. The product is supplied at a concentration of 10 mg/mL in either 100-mg (10-mL) or 500-mg (50-mL) single-use vials. Rituximab is formulated for IV administration in sodium chloride 9 mg/mL, sodium citrate dihydrate 7.35 mg/mL, polysorbate-80 0.7 mg/mL, and sterile water for infusion. The pH is adjusted to 6.5. The vials provided to the pharmacy will have study-specific investigational agent labels. Rituximab vials are stable at 2°C–8°C (36°F–46°F) and have a proposed shelf life of 30 months. Once reconstituted into IV bags, rituximab is chemically stable for up to 24 hours at 2°C–8°C (36°F–46°F). Rituximab vials should be protected from direct sunlight.

4.3.1.2 Background Therapy (Non-Investigational Medicine Product)

For additional details, see the local prescribing information for IV methylprednisolone and oral prednisolone or prednisone.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Rituximab (Investigational Medicinal Product)

4.3.2.1.1 Dosage and Administration

For this trial, rituximab will be given as an IV infusion of 375 mg/m^2 once a week for 4 consecutive weeks, starting at the baseline visit. The dose for rituximab will be calculated according to the participant's BSA at the screening visit after the participant's eligibility has been established, and it will remain the same for all four infusions. Each participant's actual body height and weight, measured during the 28-day period before baseline (i.e., during the 28 days before the start of administration of open-label rituximab) will be used to calculate a patient's BSA according to the Dubois formula (DuBois and Dubois 1916):

$$\text{BSA } (m^2) = [(\text{Weight in kg})^{0.425} \times (\text{Height in cm})^{0.725}] \times 0.00718$$

Note: Do not round until the end of the calculation.

4.3.2.1.2 Preparation

Use appropriate aseptic technique in preparing rituximab for administration. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1–4 mg/mL into an infusion bag containing 0.9% sodium chloride USP *or* British Pharmacopoeia. The investigator may prescribe a concentration of 4 mg/mL for volume-sensitive participants. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. Reconstituted rituximab is stable at 2°C–8°C (36°F–46°F) for 24 hours. No incompatibilities between polyethylene bags have been observed. However, because rituximab solution does not contain a preservative, diluted solution should be stored refrigerated (2°C–8°C).

4.3.2.1.3 Pre-Infusion Medication

Patients should be medicated pre-infusion with paracetamol/acetaminophen and cetirizine hydrochloride (or similar antihistamine), both according to labeled age-related doses, to be given 1 hour (±15 minutes) before each infusion of rituximab. Subject to investigator's discretion, corticosteroid premedication with an IV infusion of 100 mg of methylprednisolone may be administered at least 30 minutes prior to infusion of rituximab (but not prior to clinical assessments) if the patient has experienced an IRR with a previous rituximab infusion.

4.3.2.1.4 Monitoring

Facilities for immediate emergency intervention, including resuscitation in case of an anaphylactic reaction, must be available. Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, and temperature) will be taken pre-infusion. During the infusions, vital signs will be assessed every 15 minutes for 1 hour, then every 30 minutes, and at least 1 hour after the completion of the infusion. A physician will be available on site. Rituximab must not be administered as an IV push or bolus because

hypersensitivity reactions may occur. After infusion, the IV line should remain in the participant for at least 1 hour to enable the administration of drugs, if necessary. The participant's vital signs must be checked 1 hour after the infusion. For additional information, see Appendix 7.

4.3.2.1.5 Assessment of Compliance

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. A call for drug administration to the interactive voice/web-based response system (IxRS) will also be used to assess compliance.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.2.3.

4.3.2.1.6 Destruction of the Investigational Medicinal Product

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study initiation before destruction.

If there are any issues with the drug, it should be returned to the appropriate Roche Clinical Trial Supplies Department for long-term storage and not be destroyed.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient identification numbers) of destroyed IMP
- Quantity of IMP destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the investigational products

4.3.2.2 Methylprednisolone (Non-Investigational Medicinal Product)

4.3.2.2.1 Dosage, Administration, and Compliance

Patients must receive three daily doses of 30 mg/kg of methylprednisolone (up to 1 g/day) or the equivalent dose of other glucocorticoids by IV infusion, which can occur at any time, up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day, or equivalent) can be given by IV infusion. No more than six doses of methylprednisolone in total may be given. All methylprednisolone doses must be completed prior to the first rituximab infusion.

The first rituximab infusion must occur no longer than 14 days after the final IV glucocorticoid dose; the final IV glucocorticoid dose may be given on Day 1 (prior to the first rituximab infusion).

Compliance will be assessed according to completion of a glucocorticoid log.

4.3.2.3 Prednisolone or Prednisone (Non-Investigational Medicinal Product)

4.3.2.3.1 Dosage, Administration, and Compliance

On Day 1 and following completion of IV glucocorticoids, all patients will receive concomitant oral prednisolone or prednisone (1 mg/kg/day or up to 60 mg/day or equivalent, whichever is lower), the dose of which will be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever is the lowest) no later than Month 6.

The general guidance on the suggested oral steroid dose-tapering schedule is to taper from 1 mg/kg/day (60 mg/day, maximum) at the start of treatment, to 0.8 mg/kg/day by Month 1, and then by 0.1–0.2 mg/kg/day each month to 0.2 mg/kg/day (or 10 mg/day, whichever is the lowest), which should be reached no later than Month 6.

Oral prednisone (used in some non-UK sites) may be substituted for prednisolone at the same dose as long as there is no hepatic impairment.

The steroid-tapering practice is specific to a particular patient and as such should be tailored individually for each patient at the time of study entry, at the discretion of the investigator.

4.3.3 Investigational Medicinal Product Accountability

The IMP required for completion of this study (rituximab) will be provided by Roche. The investigational site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and contents. 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 Roche with the appropriate documentation. The site's method of IMP destruction must be agreed upon by Roche. The site must obtain written authorization from Roche before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Retreatment with Rituximab

After Month 6, if patients require retreatment with rituximab, further courses will be provided by the Sponsor until the common closeout date. The dose of rituximab and the frequency of retreatment for the maintenance of remission will be at the discretion of the investigator.

Following administration of the first infusion the investigator should review the following safety criteria before administering subsequent infusions of rituximab.

The following are absolute contraindications to receipt of further infusions of rituximab in this study:

- An infusion reaction which necessitated complete discontinuation of the study infusions
- Significant deterioration in patient's general health status since inclusion into the study that results in the patient meeting the exclusion criteria related to General Health
- Emergent primary or secondary immunodeficiency recognized during the study period, including new HIV infection, de novo hepatitis B, hepatitis C, or active tuberculosis infection

Patients who have any of the absolute contraindications to receipt of study infusions with rituximab will be withdrawn from the study and should be encouraged to enter Follow Up.

Patients who develop malignancy during the study will not be able to receive further courses of treatment with the study medication. However, patients with basal cell carcinoma, squamous cell carcinoma of the skin or melanoma in situ (Clarke's Level I), or cervical carcinoma in situ with no stromal invasion (stage 0), which have been completely excised and can be considered as cured, may be retreated with study medication at the discretion of the investigator.

4.3.5 Post-Trial Access to Rituximab

Roche does not intend to provide rituximab or other study interventions to patients after conclusion of the study or for any early patient withdrawal.

4.4 CONCOMITANT THERAPY

Prophylactic treatment for *Pneumocystis jiroveci* should be in accordance with local, routine clinical practice. Any concomitant medications (including over-the-counter medications, herbal medications, preventive vaccines, *Pneumocystis jiroveci* prophylactic medications, vitamins, and food supplements) and procedures considered clinically relevant by the investigator must be recorded on the appropriate electronic Case Report Form (eCRF). A description of the type of drug or procedure, the amount, duration, reason for administration of drug, and the outcome of any procedure must be documented. AEs that are judged by the investigator to be related to the administration of a concomitant medication or the performance of a procedure must also be documented on the appropriate Adverse Event eCRF. It is important that dosages of medications received by patients during the remission induction phase (up to Month 6) remain stable. However, changes in treatment will be allowed as clinically required for safety reasons.

4.4.1 Glucocorticoids

Glucocorticoids other than those specified per protocol are permitted. This includes, but is not limited to, the use of inhaled glucocorticoids for participants with documented asthma and for participants with large airway involvement of GPA, as documented on bronchoscopy. Local injections of glucocorticoid into subglottic GPA lesions are also permitted. Doses of glucocorticoids other than those specified in the protocol should, whenever possible, remain stable. All use of additional glucocorticoids for all indications, including GPA and MPA, must be documented accurately on the Glucocorticoid Log.

4.4.2 Plasmapheresis (Plasma Exchange)

Patients requiring plasmapheresis at screening are not eligible to enter the study. Patients requiring plasmapheresis prior to entering the study must have completed the process 28 days prior to screening. During the study, plasmapheresis is permitted if absolutely necessary in the opinion of the investigator, to treat the patient. Plasmapheresis will alter the pharmacokinetics of rituximab, if it occurs during the initial four infusions it may reduce efficacy and should therefore be used with caution.

4.4.2.1 Treatment of GPA and MPA after Month 6

The optimal treatment after rituximab induction for GPA or MPA has not been established in adult or in pediatric patients. After Month 6, treatment for maintenance of remission should be in accordance with clinical judgment of the investigator and can include glucocorticoids, AZA, CYC, MMF, MTX, rituximab, or other therapy.

Recommended non-mandatory treatment for relapse:

Major relapse:

- Treat with CYC, rituximab, or MMF therapy, and with methylprednisolone and/or plasma exchange according to investigator's discretion, or
- Increase prednisolone or prednisone to 1 mg/kg/day; reduce to 20 mg/day by 4 weeks, and return to baseline steroid dose when remission is achieved

Minor relapse:

- Increase prednisolone or prednisone to 0.5 mg/kg/day then reduce to baseline steroid dose over 1 month

Relapsing patients will remain in the study and all changes in drugs and doses are to be recorded in the eCRF.

Patients who are protocol remission failures or experience disease flare that cannot be controlled by glucocorticoids alone should receive treatment in accordance with local standard of care at the discretion of the investigator and will remain in the study, with all changes in drugs and doses to be recorded in the eCRF.

4.4.3 Vaccinations

4.4.3.1 Passive Antibody Titers to Specific Antigens

Review of long-term safety data from patients with RA exposed to rituximab shows that rituximab does not appear to have an effect on specific humoral immunity to several common bacterial and viral antigens over the observation period, including repeat treatment courses. The proportions of patients with positive antibody titers against mumps, rubella, varicella, tetanus toxoid, influenza, and Streptococcus pneumoniae, post-rituximab were similar to the proportions at baseline.

4.4.3.2 Immunization and Humoral Responses to Clinically Relevant Vaccines

In a randomized, controlled study of immunization responses (SIERRA) (Bingham et al 2008), patients with RA who were peripherally depleted of B cells and receiving rituximab + MTX had effective humoral responses to recall antigen (tetanus toxoid) administered 6 months after rituximab, similar to the responses observed in patients receiving MTX alone. Some rituximab-treated patients mounted T-cell–independent responses to the 23-valent pneumococcal polysaccharide vaccine but responses were decreased overall compared with those in patients receiving MTX alone. Because polysaccharide vaccines elicit a T-cell–independent response, and rituximab targets peripheral $CD20^+$ B cells, decreased responses to polysaccharide vaccines are consistent with the mechanism of action of rituximab. Although responses to the 23-valent pneumococcal polysaccharide vaccine were decreased, a significant number of patients were able to mount positive responses. For example, a total of 57% and 43% of patients had at least a 2-fold increase in titers to at least one or two pneumococcal serotypes, respectively.

It is recommended that a patient's vaccination record and the need for immunization be carefully investigated in all patients prior to entering the study or receiving a further course of rituximab. If vaccination is necessary, it is recommended that any required vaccination or booster be given at least 28 days prior to the first infusion of rituximab. The use of live or attenuated vaccines (i.e., measles, mumps, rubella, oral polio, Bacille Calmette Guerin [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 in this patient population.

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

There is no planned analysis of antibody titers to common vaccinations. If clinically indicated, additional analysis of the immune status of patients may be considered using serum samples already collected for other protocol-defined analyses.

4.4.4 Prohibited Therapy

Treatment with any investigational agent, cell-depleting therapy (except for CYC and rituximab), or biologic agents such as TNF antagonists, anti–alpha 4 integrin antibody, or co-stimulation modulator, is prohibited during the main study (until common closeout date). Any patients who do receive a prohibited therapy or any GPA or MPA treatment other than protocol-defined glucocorticoids will remain in the study for follow-up. Thereafter (i.e., at time points after the receipt of prohibited therapy or any GPA or MPA treatment other than protocol-defined glucocorticoids), patients will be considered to have failed to meet the protocol-defined remission endpoints, irrespective of BVAS/WG and PVAS scores.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.2.3.

4.5 STUDY ASSESSMENTS

The sequence of assessments at each visit will be standardized as follows (at visits required by the schedule of assessments) and should be performed prior to infusion, with the exception of the post-dose PK sample.

1. PRO assessments: [redacted]
2. Efficacy assessments: [redacted], and per schedule of assessments (see Appendix 1)
3. Laboratory samples: All samples (including for safety and efficacy) must be obtained prior to study drug treatment, except for some samples for PK analysis, which will be obtained after study drug treatment. The laboratory samples can be drawn either at least 30 minutes before or at any time after the nurse or investigator assessments.
4. Safety assessments: review of AEs, vital signs, concomitant medications, and laboratory data
5. Post-dose PK sample (at scheduled visits, where indicated). The post-infusion PK sample should be taken from the opposite arm to that into which the rituximab infusion was administered.

4.5.1 Medical History and Demographic Data

Medical history includes life-long clinically significant diseases, surgeries, birth and developmental history, cancer history (including cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse, immunization history, and all previous and current clinically relevant concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements)

used by a patient within 365 days prior to the screening visit, except for the history of use of medications for GPA or MPA (e.g., CYC, AZA, MTX, glucocorticoids) when all available data should be recorded.

Demographic data will include age, sex, and patient- or parent/guardian-reported race/ethnicity.

4.5.2 Efficacy Assessments

[redacted]

4.5.2.1 [redacted]

[redacted]

4.5.2.2 [redacted]

[redacted]

[redacted]

4.5.2.3 [redacted]

[redacted]

4.5.2.4 [redacted]

[redacted]

4.5.2.5 Patient-Reported Outcomes

[redacted]

[redacted]

4.5.3 Safety Assessments

4.5.3.1 Vital Signs

Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, and temperature) will be taken at the times indicated in the schedule of assessments (see Appendix 1). Assessments will be taken after the patient has been in a semi-supine position for at least 5 minutes. Blood pressure measurements should be obtained using a child-appropriate cuff size.

4.5.3.2 Electrocardiograms

Twelve-lead electrocardiograms (ECGs) should be performed according to the schedule of assessments (see Appendix 1) and reviewed by the investigator or his or her designee. Whenever possible, the same machine should be used for each patient. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to receipt of study drug, any scheduled vital sign measurements, and blood draws. For safety monitoring purposes, the investigator or his or her designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at study sites. ECG outcomes of “normal” or “abnormal” should be reported on the eCRF. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.3.3 Chest X-Rays and Computed Tomography Scans

Posterior–anterior chest X-rays (or chest X-ray in accordance with local requirements) should be obtained at screening and, if normal, only if indicated thereafter. If chest X-ray is abnormal, it should be repeated at Month 1 and as indicated thereafter.

At screening, if a chest X-ray has been obtained within the past 90 days that shows no clinically significant abnormality and if the patient exhibits no signs or symptoms suggestive of pulmonary disease that would exclude the patient, then an additional chest X-ray is not required.

A chest computed tomography (CT) scan is to be completed only if indicated and at the discretion of the investigator.

4.5.3.4 Physical Examinations

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

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.3.5 Laboratory Assessments

The following laboratory tests will be recorded at the time points indicated in the schedule of assessments (see Appendix 1). Whenever possible, laboratory samples should be drawn in the morning. Unscheduled laboratory assessments for safety issues are permitted at any time.

With the exception of samples for rituximab and HACA levels (for PK/PD assessments) obtained according to the schedule of assessments, all laboratory assessments requiring a blood sample are to be performed as part of routine clinical care.

The total volume of blood loss for laboratory assessments (including all safety, efficacy, PK/PD, and immunologic assessments) does not exceed the per-visit and per-cumulative visit recommendations made by the University of Pittsburgh's Institutional Review Board (IRB) and the NIH for the expected average weights of the patient. However, if the enrolled patient weighs <13 kg, please check with the Roche Medical Monitor for planning the blood draws. This weight is based on acceptable blood draw limits of 2 mL/kg (blood draw in a day) or 4 mL/kg (blood draw in a month) at Children's Hospital Seattle.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Sample Handling and Logistics Manual supplied to sites.

The samples for this study should be classified, packed, and shipped as UN3373 Biological Substance, Category B.

Local Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Serum ANCA sample: ANCA testing performed at the screening visit may be performed locally or centrally. All other ANCA testing should be performed centrally.
- Acute-phase reactants: erythrocyte sedimentation rate and C-reactive protein
- Urinalysis: dipstick for blood, protein, and glucose, and albumin to creatinine ratio
- Pregnancy test: urine dipstick test for all females of childbearing potential

Central Laboratory Assessments

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum ANCA sample: ANCA testing performed at the screening visit may be performed locally or centrally. All other ANCA testing should be performed centrally.
- Hematology or complete blood count: hemoglobin, hematocrit, red blood cells and indices (mean corpuscular volume, mean cell hemoglobin, mean corpuscular hemoglobin concentration), white blood cells, absolute differential, and platelet counts
- Serum chemistry: AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN), urea, uric acid, creatinine, potassium, sodium, chloride, calcium, phosphate, and glycosylated hemoglobin (HbA_{1c}).
- Urinalysis: microscopic examination if abnormal and applicable
- Pregnancy test: A serum pregnancy test will be performed at screening for all females of childbearing potential
- Hepatitis serology: HBcAb, HBsAg, and hepatitis C antibody (HCV Ab) at screening only or if clinically indicated during the trial

4.5.3.6 Immunologic Assessments

Determination of B- and T-cell populations will be performed by fluorescence-activated cell sorter (FACS) analysis, including, but not limited to, CD3, CD4, CD8, CD16/56, CD19, CD27, CD4/45RA/45RO, and CD8/45RA/45RO. In addition, quantitative immunoglobulin levels (including total immunoglobulin, immunoglobulin A [IgA], IgG, and IgM isotype levels).

4.5.4 Pharmacokinetic Assessments

During the remission induction phase of the study, each patient will provide serum samples for PK analysis (rituximab levels) prior to the first, second, third, and fourth doses; after completion of the first and fourth infusions; and subsequently on Days 29 (Month 1), 60 (Month 2), 120 (Month 4), and 180 (Month 6). The post-infusion PK sample should be taken from the opposite arm to that into which the rituximab infusion was administered.

4.5.5 Pharmacodynamic Assessments

[redacted]

4.5.6 Timing of Study Assessments

4.5.6.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. It will be obtained from parents or patient's legal guardian, with assent as appropriate by the patient, depending on the patient's level of understanding. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed at the screening visit and should be completed within 28 days of the baseline visit. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 14 days prior to the screening visit may be used and do not need to be repeated for screening, at the discretion of the investigator. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before study enrollment. Please see Appendix 1 for the schedule of screening assessments.

For entry into this study, patients will be screened for tuberculosis according to local/national guidelines. Results of screening tests will be reported on the eCRF.

The investigator will maintain a screening log to record details of all patients screened.

Patients who fulfill all the inclusion criteria and meet none of the exclusion criteria will be accepted into the study. The investigator or designated person will inform the IxRS and the patient will be allocated a patient number.

Any new information arising during the study that may affect the willingness of the patient to continue in the trial will be provided to the investigator and the patient as soon

as possible. Any changes to the protocol procedures will be subject to additional explanation and reconfirmation of consent to continue participation in the study.

4.5.6.1.1 Retesting for Laboratory Inclusion and Exclusion Criteria

If a patient does not meet laboratory criteria for a third time, he or she will be considered a screen failure.

It will not be considered retesting if blood samples have to be redrawn because of sample handling problems, breakage, or sample integrity.

4.5.6.1.2 Rescreening

At the discretion of the Sponsor and the investigator, a patient may be rescreened.

Rescreening refers to repeating the whole screening process. Rescreening is required if a patient has not met all the eligibility criteria within 28 days of the original screening visit.

Patients are only permitted to be rescreened once. Each patient must be reconsented before rescreening occurs.

It will not be considered rescreening if blood samples have to be redrawn because of sample handling problems, breakage, or sample integrity. *In the case of a protocol amendment, potential patients may be reassessed for eligibility according to any updated inclusion and exclusion criteria.*

4.5.6.2 Baseline Assessments (Day 1) and Remission Induction Phase

Patients must receive three doses of methylprednisolone at 30 mg/kg/day (up to 1 g/day) or the equivalent dose of other glucocorticoids by IV infusion, which can occur at any time, up to and including Day 1. If clinically indicated, and at the discretion of the investigator, additional daily doses (up to three) of methylprednisolone (30 mg/kg, up to 1 g/day) can be given by IV infusion. No more than six doses in total may be given. All doses of methylprednisolone must be completed prior to the first rituximab infusion.

The first rituximab infusion (baseline visit) must occur no longer than 14 days after the final IV glucocorticoid dose; the final IV glucocorticoid dose may be given on Day 1 (prior to the first rituximab infusion).

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. PRO assessments should be performed prior to the completion of other study assessments.

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

4.5.6.3 Follow-Up Visits

Following the remission induction phase, which ends at Month 6, patients will be followed up for a minimum of 12 months at visits conducted every 3 months. Patients who are protocol remission failures or who experience disease flare that cannot be controlled by glucocorticoids alone should receive treatment according to local standard of care, at the discretion of the investigator and will remain in the study (see Section 4.4.2.1). After Month 18, patients will be followed at study visits every 3 months until the common closeout date. The procedures performed at the follow-up visits will be similar to those performed at the Month 18 visit. The schedule of assessments for the follow-up phase is provided in Appendix 1.

4.5.6.4 Extended Follow-Up Visits

At the common closeout date, patients whose *peripheral* B cells remain depleted, will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower. *Safety, (adverse events), central laboratory and immunologic parameters, including immunoglobulins, will continue to be assessed in extended safety follow-up* (see Appendix 1). If a patient receives any B cell–depleting therapy *(commercial or investigational)* or any other agent that affects the return of B cells, including, but not limited to, rituximab, CYC and AZA, on or after the common closeout date, he or she will not be followed any further (although routine clinical follow-up after the end of the study will continue, according to local practice).

4.5.7 Early Withdrawal Visit

Patients who discontinue from the study early because of non-compliance or withdrawal of consent will be asked to return to the clinic to attend an early withdrawal visit and will be encouraged to enter follow up.

If the investigator judges that continuing rituximab is no longer in the participant's best interest, the participant will be asked to complete a withdrawal visit and will remain in the study *for follow-up* (see Section 3.1.8). *From the point of withdrawal, a patient may no longer receive rituximab as part of this protocol.* A schedule of assessments for the withdrawal visit is provided in Appendix 1.

4.5.8 Unscheduled Visits

Patients may attend the clinic for unscheduled visits at any time for additional safety monitoring or disease surveillance at the discretion of the investigator. If a patient has an unscheduled visit during the study that falls outside of a scheduled visit window, assessments will be performed at the discretion of the investigator. If a patient has an unscheduled visit within a scheduled visit window, it is at the discretion of the investigator to perform the scheduled assessments indicated for the scheduled visit.

4.5.9 Progressive Disease Before Remission

Progressive disease before remission by PVAS is defined as:

1. Persistence or worsening of a major PVAS item present at entry, and/or
2. A new major PVAS item that is not present at entry

Major (and minor) PVAS items are defined in Table 2**.**

Progressive disease before remission by BVAS/WG is defined as:

1. Persistence or worsening of a major BVAS/WG item present at entry, and/or
2. A new major BVAS/WG item that is not present at entry

Major (and minor) BVAS/WG items are defined in Table 3**.**

Patients with progressive disease before remission by Month 6 will receive additional treatment as per local standard of care and will be considered a 'treatment failure' however, data collection should continue within the trial.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients may withdraw early from the study for the following reasons:

- Withdrawal of informed consent
- Loss to follow-up
- Death

Parents or guardians have the right to withdraw their child from the study at any time for any reason. In the case that a patient prematurely discontinues from the study, the parents/guardians should be asked whether they can be contacted for further information. The outcome of that discussion should be documented in both the medical records and on the eCRF. If the patient is lost to follow-up, the investigator should contact the patient's parents/guardian or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation as to why the patient is withdrawing from the study.

4.6.2 Criteria for Premature Study Drug Termination or Study Withdrawal by Investigator or Sponsor

The investigator and Sponsor have the right to discontinue a patient from study drug or withdraw a patient from the study at any time. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following*:*

- Non-compliance with the requirements of the study

- Any AE that in the opinion of the investigator or the Sponsor precludes further study participation
- The best interest of the patient

When applicable, parents/guardians should be informed of circumstances under which their child's participation may be terminated by the investigator without the parent's/guardian's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, AE, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure, or any reason where it is felt by the investigator that it is in the best interest of the patient to be discontinued from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

All patients who permanently discontinue infusions of rituximab but have not terminated study participation (withdrawn consent or have been withdrawn by the investigator or Sponsor according to the above examples) will have safety evaluations, including all withdrawal visits, as shown in the schedule of assessments (see Appendix 1). If the reason for withdrawal of a patient from the study drug is an AE, the principal specific event will be recorded on the eCRF. If possible, the patient should not be withdrawn from the study but only from study drug and, if possible, should be followed until the AE has resolved (see Section 5.5.1). An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.6.3 Documentation at Withdrawal from Study

Every effort should be made to obtain information about patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.4 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 AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program. The Sponsor has the right to replace a site at any time. Reasons for replacing 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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording of AEs, SAEs, and non-serious AEs 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 CLINICAL ADVERSE EVENTS

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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 5.3.6.4
- 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
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive screening procedures such as biopsies)

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4. AEs not listed in the NCI CTCAE will be graded using the following criteria:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local or non-invasive intervention indicated

- Grade 3: severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to an AE

5.2.1 Serious Adverse Events (Immediately Reportable to Roche)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death). (Note: Death is an outcome, not an event. The term "sudden death" should only be used when the cause is of a cardiac origin as per standard definition. The terms "death" and "sudden death" are clearly distinct and must not be used interchangeably.)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization (see Section 5.3.6.5)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a 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 AE (rated as mild, moderate, or severe, or according to 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 AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.2 Relationship to Study Drug

The relationship of the AE or SAE to the rituximab study treatment must be assessed by the investigator or his or her designee.

5.2.3 Management of Specific Adverse Events

Adherence to the planned dosing schedule with rituximab infusions is required unless an adjustment is necessary for safety reasons. The following risk mitigation and dose modification rules apply. Recommendations for vigilance with signs and symptoms of particular safety events of interest are summarized in the following sections. During study visits when the rituximab infusion is interrupted for toxicity, all other study assessments should be performed as per the schedule of assessments (see Appendix 1).

5.2.3.1 Infusion-Related Reactions following Rituximab Administration

Rituximab is associated with IRRs, including, but not limited to, headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, hypotension, and pyrexia, which may be related to release of cytokines and/or other chemical mediators. Participants will receive at least three doses of IV methylprednisolone, followed by oral prednisolone or prednisone (see Section 4.3.2.1.3). IV glucocorticoids may help prevent severe infusion reactions potentially associated with rituximab. Medication, consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered prior to each infusion of rituximab (see Section 4.3.2.1.3). Healthcare professionals administering the rituximab infusions must be trained in the appropriate administrative procedures and be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions.

For patients with RA, GPA, and MPA, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the postmarketing setting in RA patients. Patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions must be closely monitored. In general, the proportion of patients experiencing any infusion 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. Less than 1% of patients experienced serious IRRs, with most of the events reported during the first rituximab infusion. The reactions reported were usually reversible with a reduction in rate or interruption of the infusion and with administration of an anti-pyretic medication, an antihistamine, and occasionally oxygen, IV saline, bronchodilators, or glucocorticoids, as required. Depending on the severity of the IRR and the required interventions, treatment with rituximab should be temporarily or permanently discontinued. In most cases, the infusion can be resumed at a 50% reduction in rate when symptoms have completely resolved.

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) must be available for immediate use in the event of an allergic reaction during administration of rituximab. If a patient has symptoms of anaphylaxis or serious hypersensitivity, or

requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of rituximab must be discontinued permanently. Patients will be asked to complete a withdrawal visit but will remain in the study (see Section 3.1.8). A schedule of assessments for the withdrawal visit is provided in Appendix 1.

5.2.3.2 Cardiovascular Events

Because hypotension may occur during a rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the rituximab infusion.

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure, and myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease should be monitored closely.

5.2.3.3 Infections

Given the mechanism of action of rituximab and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. Rituximab should not be administered to patients with an active infection or to severely immunocompromised patients (e.g., those in whom levels of CD4 or CD8 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 who develop infection following rituximab therapy should be promptly evaluated and treated appropriately. If a patient experiences a new infection during the intervening time between any of the four rituximab infusions, the subsequent infusion should be delayed (up to a maximum of 14 days) until the infection has completely resolved and treatment with any anti-infective medications has been completed. Receipt of further rituximab infusions is at the discretion of the investigator. Remaining infusions should be scheduled so that they are given 1 week apart.

5.2.3.4 Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in patients with RA, GPA, and MPA treated with rituximab.

Screening for HBsAg, HBcAb, hepatitis C serology, and HBV DNA must be performed in all patients before initiation of treatment with rituximab. Patients with positive hepatitis serology will be excluded from the study. Any patient who experiences active hepatitis B disease during the study will be immediately withdrawn from rituximab study therapy and will be followed until the common closeout date or, if required, for longer in extended follow-up (see Section 3.1.4).

5.2.3.5 Progressive Multifocal Leukoencephalopathy

Cases of fatal PML have been reported following use of rituximab for the treatment of autoimmune diseases, including RA and GPA. 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 neurologic symptoms, which may include clumsiness, progressive weakness, visual, speech, and sometimes, personality changes. If PML is considered, then a neurologic consultation should be obtained. 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. Additional information is provided in the Investigator's Brochure.

5.2.3.6 Neutropenia

Decreases in neutrophils have been observed in adult patients with GPA and MPA following treatment with rituximab. Neutropenia was not associated with an observed increase in serious infection in such patients. Patients with an ANC $< 1.5 \times 10^3/\mu L$ at screening will not be enrolled in the study.

5.2.3.7 Hypogammaglobulinemia

Decreases in IgA, IgG, and IgM have been observed in adult patients with GPA and MPA following treatment with rituximab. No increased rate in overall infections or serious infections was observed after the development of low IgA, IgG, or IgM levels. Assessment of the Roche safety database and published literature reveals that development of hypogammaglobulinemia after rituximab treatment in pediatric patients with various underlying disease has been observed, and, in some cases, this has been reported as severe and long term requiring long-term IVIg treatment. However, attribution of these events to rituximab is limited by potential alternate etiologies, such as common variable immunodeficiency disease, severity of underlying diseases, use of rituximab as a last resort after exposure to other immunosuppressive agents, and limited clinical data including lack of randomized clinical trials, retrospective data collection, and lack of detailed safety data reporting. Importantly, the majority of these cases were not reported to have been associated with serious infections.

Patients with IgG and IgM levels below the *exclusionary levels per section 4.1.2*, at screening will not be enrolled in the study. The investigator should closely monitor the patient's immunoglobulin levels during the study. If immunoglobulin levels decrease *following rituximab treatment, and require specific medical care or management, repeat dosing can be considered at the discretion of the investigator, based on the assessed benefit/risk*. IVIg (restricted to replacement dosing for hypogammaglobulinemia) may be given at the discretion of the investigator.

5.2.3.8 Skin Reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens–Johnson syndrome, some with fatal outcome, have been reported. In such cases, treatment should be permanently discontinued.

5.2.3.9 Pregnancy

IgGs are known to cross the placental barrier.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to rituximab were noted to have depleted B-cell populations during the postnatal phase.

B-cell levels in human neonates following maternal exposure to rituximab have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant females; however, transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons, rituximab should not be administered to pregnant females unless the possible benefit outweighs the potential risk.

Female patients in Tanner stages ≥ 2 (see Appendix 4) or post-onset of menarche should employ effective contraceptive methods during and for up to 12 months after treatment with rituximab.

Additional information about rituximab is given in the Investigator's Brochure.

5.2.3.10 Collection of Additional Data for Certain Adverse Events

The Sponsor requires that additional data be collected for certain AEs that are presently closely monitored by the Sponsor. This additional data collection will be performed using dedicated eCRFs. The events are as follows:

- Malignancies
- Hepatitis B
- PML
- Posterior reversible encephalopathy syndrome

5.2.4 Non-Serious Adverse Events of Special Interest (Immediately Reportable to Roche)

Non-serious AEs of special interest are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions). AEs of special interest for general drug development include the following:

- Cases of elevated ALT or AST levels in combination with either an elevated bilirubin level or clinical jaundice, as defined in Section 5.3.6.1
- Suspected transmission of an infectious agent by the study drug

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.1 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 AEs at each patient contact. All AEs, 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 SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures, such as biopsies).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until the common closeout date and during extended follow-up (if applicable). After this time, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points. 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 AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 4 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale

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 NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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 one's self, 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 5.2.1.

[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 5.2.1.

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 AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- 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 (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the 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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

AEs that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For AEs other than IRRs, 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 AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring 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. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment, 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 subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.6 Laboratory Test Abnormalities

Any treatment-emergent abnormal laboratory result (i.e., a result that falls outside the laboratory reference range or is a substantial within-reference range change) that is clinically significant should be recorded as an appropriate clinical diagnosis on the Adverse Event eCRF.

Clinically significant laboratory values are those that:

- Are accompanied by a clinical symptom, in which case the symptom, not the laboratory parameter, is recorded as the adverse event term.
- Lead to a change in study drug (e.g., dose modification, interruption, or permanent discontinuation).
- Require a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication or therapy)

This applies to any protocol-specified and non-protocol-specified safety and efficacy laboratory result from tests performed after the first dose of study drug, which meets the clinical significance criteria above.

This does not apply to any abnormal laboratory result that does not meet the clinical significance criteria or those that are a result of an AE which has already been reported. Any laboratory result abnormality considered to be an SAE should be reported as such.

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 AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 AE. 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.

5.3.6.1 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ the ULN) in combination with either an elevated total bilirubin ($>2\times$ the 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 AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ the ULN in combination with total bilirubin $>2\times$ the ULN
- Treatment-emergent ALT or AST $>3\times$ the 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 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, either as an SAE or a non-serious AE of special interest (see Section 5.4.2).

5.3.6.2 Deaths

All deaths that occur during the protocol-specified AE 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 GPA or MPA.

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 only be used 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 of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and was 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 MPA/GPA, MPA/GPA “progression” should be recorded on the Adverse Event eCRF.

5.3.6.3 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 General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. 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”).

5.3.6.4 Lack of Efficacy or Worsening of Granulomatosis with Polyangiitis (Wegener’s) and Microscopic Polyangiitis

Medical occurrences or symptoms of deterioration that are anticipated as part of MPA and GPA should be recorded as an AE if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of MPA or GPA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated MPA/GPA”).

5.3.6.5 Hospitalization or Prolonged Hospitalization

Any AE that results inpatient hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.1), except as outlined as follows.

The following hospitalization scenarios are not considered to be SAEs:

- 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 suffered an AE.

5.3.6.6 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.3.6.7 Patient-Reported Outcome Data

AE reports will not be derived from PRO data. However, if any patient and/or parent/guardian's responses suggestive of a possible AE are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor within 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 SAEs to the local health authority and IRB/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: [redacted], MD

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternative Medical Monitor Contact Information

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 Special Interest

For reports of SAEs and non-serious AEs of special interest, investigators should record all case details that can be gathered within 24 hours of 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/ Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours day 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.

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 or 90 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 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.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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 or within 90 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 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 spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 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 or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor within 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 AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (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 SAEs, non-serious AEs 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

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management by telephone (see "Protocol Administrative and Contact Information & List of Investigators").

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

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

- Rituximab Investigator's Brochure
- Local prescribing information for rituximab
- Rituximab Core Data Sheet

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is an exploratory, open-label, single-arm study, with the primary objective of evaluating safety and PK of rituximab in pediatric patients with GPA or MPA. Therefore, there will be no formal statistical hypothesis testing. An analysis will be conducted when the last patient enrolled reaches 6 months. Full details of all planned tables, listings, graphs, and descriptive analyses will be provided in a Statistical Analysis Plan, which will be finalized prior to this analysis. An outline of the proposed analyses is provided herein.

6.1 DETERMINATION OF SAMPLE SIZE

The planned sample size of 25 patients was determined on the basis of the epidemiology of pediatric AAV and information from existing patient cohorts. This sample size takes into the account the number of pediatric patients that would be eligible for treatment with rituximab and that could be expected to be enrolled within a reasonable timeframe. The primary objective of this study is to evaluate the safety and pharmacokinetics of rituximab in these patients. The planned sample size would be sufficient to provide a reasonable estimate of variability for the mean PK parameters based on the observed intra-patient variability from the RAVE study. It would also ensure 95% probability of observing at least one AE when the underlying incidence of that event is $\geq 11\%$.

Given the exploratory nature of this study, there will be no formal statistical hypothesis testing. The study will focus on exploratory estimation of the efficacy and PD endpoints. The planned sample size of 25 would allow estimation of the percentage of patients in remission at 6 months to within 20% of the point estimate (the distance from the point estimate to the upper or lower limit of a 95% CI).

6.2 ANALYSIS POPULATIONS

Safety Analysis Population

All patients who received at least part of one infusion of rituximab will be included in the safety population. Patients will be assigned to a single rituximab treatment group. Safety and efficacy analyses will be based on the safety population.

PK Analysis Population

The PK analysis population will include all patients in the safety population who provide at least one evaluable PK sample.

6.3 SUMMARIES OF CONDUCT OF STUDY

Any eligibility violations or major protocol deviations from the study will be summarized.

6.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

6.5 PATIENT DISPOSITION AND TREATMENTS

The following data will be listed and summarized for the safety population:

- Patients who completed four IV infusions of rituximab study treatment
- Patients withdrawn prematurely from rituximab study treatment
- Cumulative exposure to rituximab study treatment
- Patients who switched to local standard care
- Details about non-study AAV treatments given over time
- Concomitant medications received
- Patients withdrawn prematurely from study follow-up

6.6 SAFETY ANALYSES

The safety and tolerability of rituximab will be evaluated from AEs, laboratory tests, vital signs, ECGs, chest X-rays, and as defined by protocol. Safety parameters will be summarized or listed for the safety population.

6.7 PHARMACOKINETIC ANALYSES

In the PK analysis population, non-linear mixed-effects modeling technique (NONMEM®) will be used to analyze the PK data with the population PK model developed from adult patients with GPA and MPA in the RAVE study (Stone et al. 2010). The primary PK parameters will be CL and volume of distribution. The secondary PK parameters ($AUC_{0\text{-}inf}$, C_{max}) will be calculated for each patient. PK concentrations will be summarized by visit. PK parameters will be tabulated and summarized (i.e., by mean, SD, coefficient of variation, median, and minimum and maximum). PK exposure and response relationships will be explored.

6.8 EXPLORATORY EFFICACY ENDPOINTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.9 EXPLORATORY PHARMACODYNAMIC ANALYSES

[redacted]

6.10 EXPLORATORY PATIENT-REPORTED OUTCOME ANALYSES

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

Roche will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to

Roche, using Roche'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 at Roche and records retention for study data will be consistent with Roche's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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 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, patient-reported outcomes, 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 onto the eCRFs must not be obliterated or destroyed and must be retained according to the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), 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 Roche. Written notification should be provided to Roche 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 US Investigational New Drug (IND) Application will comply with US FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Roche's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Parent or 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. Roche or its designee must review and approve any proposed deviations from Roche'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 Roche 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 Roche for health authority submission purposes.

Patients must be reconsented to the most current version of the 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 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 Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient’s legally authorized representative. All signed and dated 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 Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the US Health Insurance Portability and Accountability Act (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 9.5).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from Roche. 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

Roche 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 Roche location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties 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 US FDA and other national and local health authorities, Roche 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., last patient last visit).

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, which includes an audit trail containing a complete record of all changes to the data.

9.2 SITE INSPECTIONS

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

9.3 ADMINISTRATIVE STRUCTURE

9.3.1 IxRS

An IxRS will be used to manage the dispensing of study drug (rituximab).

9.3.2 Central Laboratory

With the exception of ANCA (at screening only), C-reactive protein, erythrocyte sedimentation rate, urinalysis, and the urine dipstick pregnancy test (see Section 4.5.3.5), all laboratory tests will be analyzed by a central laboratory according to the Laboratory Manual.

9.4 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 Roche 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.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche 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 Roche personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Roche 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 Roche, except where agreed otherwise.

9.5 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).

10. INTERNAL MONITORING COMMITTEE

Because this is an open-label study, an Internal Monitoring Committee (IMC) composed of a Clinical Scientist, a Statistician, a Statistical Programmer Analyst, and a safety representative will review safety data from patients participating in this study. The IMC will be responsible for monitoring the overall safety of the patients in this study and will help to minimize patient exposure to unacceptable risk. From the time of its formation, the IMC will meet to review safety data as described in the IMC Charter.

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Appendix 1
Schedule of Assessments

Visit [a]	Screen [b]	Week				Month								Follow-Up	WD	Extended Follow-Up [e]
		BL [c]	1	2	3	1	2	4	6	9	12	15	18	Every 3 Months after Month 18 [d]		
Day		1	8	15	22	29	60	120	180	270	365	455	545			
Medications																
Glucocorticoids IV [f]		x														
Glucocorticoids PO [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pre-infusion medications [h]		x	x	x	x											
Rituximab IV infusion		x	x	x	x											
General Assessments																
Informed Consent/ Child's Assent	x															
Inclusion/exclusion criteria	x															
[redacted]																
Medical history	x															
Pregnancy test (serum) [i]	x															
Pregnancy test (urine) [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
12-Lead ECG [j]	x															
Height	x	x				x	x	x	x	x	x	x	x	x	x	x
Weight	x	x				x	x	x	x	x	x	x	x	x	x	x
Vital signs (pulse rate, systolic and diastolic blood pressure, and temperature)	x	x [k]	x [k]	x [k]	x [k]	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Visit [a]	Screen [b]	Week				Month								Follow-Up	WD	Extended Follow-Up [e]
		BL [c]	1	2	3	1	2	4	6	9	12	15	18	Every 3 Months after Month 18 [d]		
Day		1	8	15	22	29	60	120	180	270	365	455	545			
General Assessments (cont'd)																
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chest X-ray [l] or CT scan [m]	x														x	
Safety Assessments																
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy Assessments																
[redacted]																
Acute-Phase Reactant Assessments																
C-reactive protein	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Erythrocyte sedimentation rate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Visit [a]	Screen [b]	Week				Month								Follow-Up	WD	Extended Follow-Up [e]
		BL [c]	1	2	3	1	2	4	6	9	12	15	18	Every 3 Months after Month 18 [d]		
Day		1	8	15	22	29	60	120	180	270	365	455	545			
Laboratory Assessments																
Hematology (CBC)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis with microscopy and albumin to creatinine ratio	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HbA_{1c} [s]		x					x	x	x	x	x	x	x	x	x	x
HBsAg, HBcAb, and HCV Ab and HBV DNA [t]	x															
Tuberculosis screening	x															
Immunologic and Antibody Assessments																
Immunoglobulins	x	x				x	x	x	x	x	x	x	x	x	x	x
CD19 B cells		x [q]		x [q]				x	x	x	x	x	x	x	x	x
FACS panel		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum HACA sample		x						x	x	x			x	x [u]	x	x [u]
Serum ANCA sample [v, w]	x					x			x		x		x	x [u]	x	x [u]
Pharmacokinetic Assessments																
Sample for rituximab levels		x [x]	x [y]	x [y]	x [x]	x	x	x	x	x			x	x [u]	x	x [u]

ANCA = anti–neutrophil cytoplasmic antibody; CBC = complete blood count; [redacted]; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic Case Report Form; FACS = fluorescence-activated cell sorter; GFR = glomerular filtration rate; GPA = granulomatosis with polyangiitis; HbA_{1c} = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibodies; IV = intravenous; LLN = lower limit of normal; MPA = microscopic polyangiitis; PK = pharmacokinetic; PO = by mouth; PVDI = Pediatric Vasculitis Damage Index; WD = withdrawal.

Appendix 1
Schedule of Assessments (cont.)

[a] For visit windows, please refer to Appendix 2.
[b] The screening visit must be completed within 28 days of the baseline visit.
[c] Assessments performed within 14 days of the baseline visit do not have to be repeated at the discretion of the investigator and if not clinically indicated.
[d] Until the common closeout date.
[e] At the common closeout date, patients whose *peripheral* B cells remain depleted, will continue to attend study visits every 3 months until their *peripheral* B-cell counts have returned to *pre-rituximab* baseline levels or to within the normal range for the population, whichever is lower.
[f] Three times daily IV infusions of 30 mg/kg of methylprednisolone (up to 1 g/day, or equivalent) may be administered at any time, up to and including Day 1 (prior to the first rituximab infusion). If clinically indicated, and at the discretion of the investigator, an additional three daily doses of methylprednisolone (up to 1 g/day) can be given by IV infusion. No more than six doses in total can be given. All doses must be completed prior to the first rituximab infusion. The first rituximab infusion must occur no later than 14 days after the last dose of methylprednisolone infusion.
[g] All patients will receive concomitant oral prednisolone or prednisone (1 mg/kg/day; up to 60 mg/day, or equivalent), which will be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever is lower) no later than Month 6.
[h] Patients should be premedicated with paracetamol/acetaminophen and cetirizine hydrochloride (or similar antihistamine), both according to labeled age-related doses, to be given 1 hour (±15 minutes) before each infusion of rituximab.
[i] To be completed for female patients of childbearing potential.
[j] After screening, only if clinically indicated.
[k] Vital signs should be taken immediately prior to infusion. During an infusion, record vital signs every 15 minutes for 1 hour; then every 30 minutes; and then at least 1 hour after the completion of the infusion.
[l] To be completed at screening and, if normal, only if indicated thereafter. If the chest X-ray is abnormal, repeat at Month 1 and as indicated thereafter.
[m] CT scan to be completed only if indicated.
[n] Within the last 365 days of the screening visit
[redacted]
[q] CD19 B-cell samples to be obtained prior to infusion of rituximab
[redacted]
[s] Fasting is not required.
[t] After screening, only if clinically indicated.
[u] After the Month 18 visit, samples should be taken every 6 months thereafter.
[v] ANCA testing performed at the screening visit to support a diagnosis of GPA or MPA may be performed locally or centrally. All other ANCA testing to be performed centrally.
[w] Also to be performed at time of flare.
[x] PK samples to be obtained prior to infusion of rituximab and 30 minutes following infusion of rituximab.
[y] PK samples to be obtained prior to infusion of rituximab.

Appendix 2
Study-Specific Visit Windows

Visit	Study Day	Visit Window
Screening	Varies	Before baseline visit (varies)
IV methylprednisolone 1	Varies	Before baseline visit (varies)
IV methylprednisolone 2	At least 1 day after Dose 1	Before baseline visit (varies)
IV methylprednisolone 3 [a]	At least 1 day after Dose 2	Before baseline visit (varies)
Baseline: Rituximab Infusion 1 [a]	1	Within 28 days of screening
Rituximab Infusion 2	8	±3 days of the targeted date
Rituximab Infusion 3	15	±3 days of the targeted date
Rituximab Infusion 4	22	±3 days of the targeted date
Month 1	29	±3 days of the targeted date
Month 2	60	±3 days of the targeted date
Month 4	120	±5 days of the targeted date
Month 6	180	±5 days of the targeted date
Month 9	270	±10 days of the targeted date
Month 12	365	±10 days of the targeted date
Month 15	455	±10 days of the targeted date
Month 18	545	±10 days of the targeted date
Every 3 months until the common closeout date	+3 months after the last visit	±10 days of the targeted date
Extended follow-up	+3 months after the last visit	±10 days of the targeted date

IV = intravenous.

[a] If clinically indicated and at the discretion of the investigator, additional daily doses (up to three) of IV methylprednisolone can be given. No more than six doses of IV methylprednisolone in total can be given. Each of these additional doses must be given at least 1 day after the previous dose. The final IV methylprednisolone dose and rituximab Infusion 1 can be administered on the same day (although IV methylprednisolone must be given before the rituximab infusion). Rituximab Infusion 1 must occur no later than 14 days after the last IV methylprednisolone dose.

Appendix 3

[redacted]

Appendix 4
Tanner Stages

Sexual Maturity Stages in Boys and Girls

Stage	Male Genitalia	Pubic Hair	Female Breasts
1	Preadolescent—testes, scrotum, and penis are childlike in size	None; may be vellus hair, as over abdomen	Preadolescent—elevation of papilla only
2	Slight enlargement of scrotum with reddening of skin; little or no enlargement of penis	Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, primarily at base of penis or along labia	Breast bud stage; breast and papilla form a small mound; areolar diameter enlarge
3	Further enlargement of scrotum; penis enlarges, mainly in length	Hair considerably darker, coarser, and more curled; spreads sparsely over junction of pubes	Further enlargement of breast and areola with no separation of their contours
4	Further enlargement and darkening of scrotum; penis enlarges, especially in breadth; glans develops	Adult-type hair that does not extend onto thighs, covering a smaller area than in adult	Areola and papilla project to form a secondary mound above the contour of the breast; stage 4 development of the areolar mound does not occur in 10% of girls and is slight in 20%; when present, it may persist well into adulthood
5	Adult in size and shape	Adult in quantity and type with extension onto thighs but not up linea alba	Mature female; papilla projects and areola recesses to general contour of breast

Data derived from Tanner JM: Normal growth and techniques of growth assessment. Clin Endocrinol Metab 1986;15:436.

In boys, if different scores are obtained for pubic hair and genitalia, the score for genitalia should be used.

In girls, if different scores are obtained for pubic hair and breast development, the score for breast development should be used.

Appendix 5
EULAR/PRINTO/PRES 2008 Ankara Childhood–Wegener's Granulomatosis Criteria (with Glossary) and Classification Definition

Histopathology	Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area
Upper airway involvement	Chronic purulent or bloody nasal discharge or recurrent epistaxis/crusts/granuloma Nasal septum perforation or saddle nose deformity Chronic or recurrent sinus inflammation
Laryngo-tracheo-bronchial involvement	Subglottic, tracheal or bronchial stenoses
Pulmonary involvement	Chest X-ray or CT scan showing the presence of nodules, cavities, or infiltrates
ANCA	ANCA positivity by immunofluorescence or by ELISA (MPO/p or PR3/c ANCA)
Renal involvement	Proteinuria $>$ 0.3 g/24 hr or $>$ 30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Hematuria or RBC casts: $>$ 5 RBC/high-power field or RBC casts in the urinary sediment or $\geq$ 2+ on dipstick Necrotizing pauci-immune glomerulonephritis
c-WG EULAR/PRINTO/PRES Ankara 2008 classification definition	At least three of the six following criteria: Histopathology Upper airway involvement Laryngo-tracheo-bronchial stenosis Pulmonary involvement ANCA positivity Renal involvement

ANCA = anti–neutrophil cytoplasmic antibody; CT = computed tomography; c-WG = c-Wegener granulomatosis; ELISA = enzyme linked immunosorbent assay; EULAR = European League Against Rheumatism; MPO = myeloperoxidase; PRES = Pediatric Rheumatology European Society; PR3 = proteinase 3; PRINTO = Pediatric Rheumatology International Trials Organisation; RBC = red blood cell.

Adapted from Özen et al. 2010.

Appendix 6
Chapel Hill Consensus Conference

In 1994, the Chapel Hill International Consensus Conference developed definitions for systemic vasculitides. These definitions are useful in formulating the diagnostic criteria that will be applied to determine a participant's eligibility for this clinical trial with respect to MPA or their exclusion with respect to Churg–Strauss syndrome.

Chapel Hill Consensus Conference Definitions for Microscopic Polyangiitis

- Necrotizing vasculitis with few or no immune deposits affects small vessels (i.e., capillaries, venules, or arterioles)
- Necrotizing arteritis involving small and medium-sized arteries may be present.
- Necrotizing glomerulonephritis is very common.
- Pulmonary capillaritis often occurs.

Chapel Hill Consensus Conference Definitions for Churg–Strauss Syndrome

- Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia

Appendix 7
Procedures for the Intravenous Administration of Rituximab

Rituximab should be given as a slow intravenous (IV) infusion (Great Ormond Street Hospital 2012). It should not be administered as an IV push or bolus.

Although rituximab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Irrespective, rituximab should be administered in a hospital or clinic environment where full resuscitation facilities are immediately available, along with qualified resuscitative personnel and under close supervision of the investigator or designee.

Dosage

The dose of rituximab will be calculated by the physician on the basis of 375 mg/m² of body weight (no maximum dose).

Preparation

Use appropriate aseptic technique. Dilute rituximab to a final concentration of 1 mg/mL to 4 mg/mL in 0.9% NaCl, or 5% Dextrose in Water (USP *or* British Pharmacopoeia*)* to a final concentration 1 mg/mL to 4 mg/mL. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

FOR ALL TREATMENT COURSES THE INFUSION RATES FOR THE FIRST AND SUBSEQUENT INFUSION MUST BE ADHERED TO AS FOLLOWS:

Patients should be medicated pre-infusion with paracetamol/acetaminophen and cetirizine hydrochloride (or similar antihistamine), both according to labelled age-related doses, to be given 1 hour (±15 minutes) before each infusion of rituximab.

First Infusion

Rituximab infusions should commence at a rate of 25 mg/h. This may be escalated at a rate of 25 mg/h increments every 30 minutes to a maximum of 200 mg/h. An example of an infusion schedule is presented below.

Appendix 7
Procedures for the Intravenous Administration of Rituximab (cont.)

Final Concentration = 1 – 4 mg/mL		
Infusion Rate		Minutes
mg/h[a]	mL/h[a]	
25	(……)	30
50	(……)	30
75	(……)	30
100	(……)	30
125	(……)	30
150	(……)	30
175	(……)	30
200	(……)	thereafter

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

Subsequent Infusions

Patients who have tolerated the first infusion of rituximab well may receive the second infusion. Infusion schedule described for the first infusion should be used also for all subsequent infusions; the infusion rate can be adjusted if the first infusion was well tolerated. Subject to investigator's discretion, corticosteroid premedication with an IV infusion of 100 mg of methylprednisolone may be administered at least 30 minutes prior to the infusion of rituximab (but not prior to clinical assessments) if the patient has experienced an infusion-related reaction with a previous rituximab infusion.

In the event of the patient experiencing an infusion-related reaction during first or any subsequent infusions, the infusion should be stopped immediately. The patient should be clinically assessed and appropriate treatment should be given as per local policy. The principle investigator or sub-investigator(s) should also be informed as soon as possible and all adverse events should be reported as required in Section 5.2. Once the adverse event has resolved, infusion can be restarted at the previous tolerated rate and should be given at the previous reduced rate for 30 minutes. If tolerated, the rate may be increased to the next closest rate on the patient's infusion schedule. Further information is provided in Section 5.2.3.1.

All rituximab infusions should be made through a dedicated line. After the end of each infusion, the IV line should remain in situ for at least 1 hour in order to be able to administer drugs intravenously if necessary. If there are no adverse events during this period of time, the IV line may be removed.