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: Data Analysis Plan, Module 2, Version 1.0, dated 10-Sep-2018

DATA ANALYSIS PLAN – MODULE 2

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

STUDY DRUG: Rituximab (RO0452294)

SPONSOR: F. Hoffmann-La Roche Ltd for 1.0

VERSION NUMBER:

Author:

[redacted] Sep 10, 2018
Date

Approver:

[redacted] 10Sept2018
Date

*** The approver has ensured that key team members have been involved, contributed and reviewed the content of the List of Planned Outputs as described in the DAP Module 2 guideline.**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

1. BACKGROUND

This document provides specifications for the primary analysis including, remission induction phase, follow-up phase and extended follow-up phase, of the study WA25615.

- **Remission Induction Phase:** Day 1 until end of month 6.
- **Follow-Up Phase:** Post month 6 until common closeout date, where common closeout date is 18 months after the enrolment of the last patient.
- **Extended Follow-Up Phase:** Post common closeout date until CD19 B-cell counts have returned to baseline level or within normal range, whichever is lower.

2. STUDY DESIGN

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.

The study comprises an initial 6-month remission induction phase; rituximab is administered on Days 1, 8, 15 and 22 during this phase. The remission induction phase is followed by a minimum 12-month follow-up phase, after which patients are followed up 3-monthly until the common closeout date, which occurs when the final participant enrolled has completed his or her Month 18 study visit (see Appendix 2).

Following the remission induction phase (month 6), if required for the maintenance of remission, further courses of rituximab may be given, with the dose and the frequency of retreatment at the discretion of the investigator.

At the common closeout date, patients whose B cells remain depleted and/or have immunoglobulin levels below the LLN for the population, continue to attend study visits every 3 months until their B-cell counts have returned to 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. Patients that receive any B-cell therapy or other agent that affects the return of B-cells including but not limited to rituximab, CYC, AZA, on or after the common closeout date, he or she will not be followed any further.

The Study Schema is given in Appendix 1 and the Schedule of Assessments is given in Appendix 2.

2.1 Outcome Measures

This section lists all of the study outcome measures that will be included in this analysis.

2.1.1 Primary Safety Outcome Measures

The primary safety outcome measures are:

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

2.1.2 Primary Pharmacokinetic Outcome Measures

The primary PK parameters are:

- Clearance (CL) and volume of distribution

2.1.3 Secondary Pharmacokinetic Outcome Measures

The secondary PK parameters of interest are:

- $AUC_{0\text{-}inf}$ and C_{max}, derived from the primary PK parameters

2.1.4 Primary and Secondary Efficacy Outcome Measures

None

2.1.5 Secondary Safety Outcome Measures

The secondary safety outcome measures are:

- Vital signs

- Electrocardiograms – new or worsened abnormalities are reported as adverse events
- Chest x-ray and computed tomography (CT) scan – to be completed at month 1 if abnormal at baseline and as indicated otherwise at the discretion of the investigator. New or worsened abnormalities are reported as adverse events
- Physical examinations – post-baseline examinations are to be symptom directed only, with new or worsened abnormalities reported as adverse events
- Laboratory parameters (clinically relevant new or worsened abnormalities are reported as adverse events):
    - Hematology: 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 if total bilirubin is greater than the ULN), urea, uric acid, creatinine, potassium, sodium, chloride, calcium, phosphate, and glycosylated hemoglobin (HbA1c)
    - Acute-phase reactants: erythrocyte sedimentation rate and C-reactive protein
    - Urinalysis: dipstick for blood, protein, and glucose, and albumin to creatinine ratio
        - microscopic examination if abnormal and applicable
- Immunologic Assessments
    - B- and T-cell populations - 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
    - Quantitative immunoglobulin levels (including total immunoglobulin, immunoglobulin A [IgA], IgG, and IgM isotype levels)

2.1.6 Exploratory Outcome Measures

2.1.6.1 Exploratory Efficacy Outcome Measures

[redacted]

2.1.6.2 Exploratory Pharmacodynamic Outcome Measures

[redacted]

2.2 Determination of Sample Size

The planned sample size of 25 patients was determined on the basis of the epidemiology of pediatric GPA and MPA plus 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 (a rituximab in ANCA-associated vasculitis trial), protocol number ITN021AI. It would also ensure 95% probability of observing at least one AE when the underlying incidence of that event is ≥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.

2.3 Analysis Timing

There is an interim analysis for this study where the study data for the remission induction phase (6-month time-point) is analyzed when the last patient has reached the 6 month visit and the data have been cleaned with the relevant parts of the database locked for editing.

Primary analysis will be done once all of the data, up until the follow-up visit subsequent to the common closeout date (the Withdrawal visit), has been entered into the study database, cleaned and the database locked for editing.

A final analysis will be reported once the extended follow-up for all appropriate patients has been completed, with all data entered into the database, cleaned and the database fully locked.

2.3.1 Data Included in the Remission Induction Phase

The following data will be included in the analysis of the 6-month time-point:

- **Patients entering the follow-up phase:**
  - All screening and post-baseline data with a clinical date (i.e., administration/ assessment/onset/start date) on or before the date of entry into the follow-up phase at Month 6 will be included.

  The only exceptions to this is:

  - Concomitant medications that begin on the date of entry to the follow-up phase will not be included.
- **Patients not entering the follow-up phase:**
  All screening and post-baseline data with a clinical date on or before the date of the patient's last study visit within Study Day 210 will be included; (Day 210 equals 180 days plus a 30-day window).

The data cut will include all data regardless of the type of study visit at which it was collected. This may include data collected at unscheduled visits, dosing termination visits, early termination visits, or safety follow-up visits, if the visit date was on or before the data cutoff date.

2.3.2 Data Included in the Follow-up Phase

For patients who enter the Follow-up phase all of their screening data plus post Month-6 data with a clinical date on or before the date of entry into the Extended Follow-up Phase will be included in this analysis of the Follow-up phase.

- **Patients entering the extended follow-up phase:**
  All screening and post-Month-6 data with a clinical date on or before the date of entry into the extended follow-up phase will be included.
- **Patients not entering the extended follow-up phase:**
  All screening and post-Month-6 data with a clinical date on or before the date of the patient's last study visit within common closeout date will be included.

2.3.3 Data Included in the Extended Follow-up Phase

Patients whose peripheral B cells remain depleted at the common closeout date will enter the Extended Follow-up phase. For patients who enter this phase all of their screening data plus post Follow-up phase data will be included in this analysis.

3. STATISTICAL METHODS OVERVIEW

As this is an open-label, single-arm study, with primary objectives regarding safety and PK there will be no formal statistical hypothesis testing.

The day of enrollment (Day 1) will be considered the day the patient receives their first infusion, or part thereof, of rituximab.

For binary endpoints the number and percentage of patients will be presented by visit. At key time points (Month 6, 12 and 18) two-sided 95% Confidence intervals (CIs) for the percentage of patients will be calculated.

For continuous endpoints, the n, mean, median, standard deviation (SD), minimum and maximum values will be presented by visit with two-sided 95% CIs for the mean presented for the data at key time-points (Months 6, 12 and 18), unless stated otherwise.

When we have 0 counts, please don't display 0.0%

3.1 Analysis Populations

3.1.1 Safety Population

All patients who received at least part of one infusion of rituximab will be included in the safety population.

Safety and efficacy analyses will be based on the safety population.

3.2 Baseline Demographics and Baseline Information

Details of the analyses and outputs are given in Section 4.

3.2.1 Definition of Remission Induction Phase Baseline

Baseline will be defined as the last available pre-treatment value taken on or before the initiation of rituximab (RTX) treatment on study treatment Day 1, and will be used for summary of demographic characteristics, as well as for all change-from-baseline analyses of efficacy, safety, and PD endpoints.

Special rules apply for the determination of the PVDI baseline score to account for missing individual scores: see Section 10.

For endpoints that are defined in terms of change from baseline, patients who do not have a pre-treatment value reported for a particular assessment (if any) will be excluded from the change-from-baseline analyses for that assessment.

3.2.2 Follow-up Phase Baseline

The Follow-up phase will use the same baseline values as the Remission Induction phase for all analyses.

3.2.3 Extended Follow-up Phase Baseline

Baseline will be defined as the last available value taken on or before the start of the Extended Follow-up phase, and will be used for all change-from-baseline analyses of safety and PD

endpoints. For B cell deplection (absolute CD19 count) we should use the baseline value prior to receiving study medication.

For endpoints that are defined in terms of change from baseline, patients who do not have a pre-treatment value reported for a particular assessment (if any) will be excluded from the change-from-baseline analyses for that assessment.

3.3 Visit Windows

For summarization by time-point data will be assigned to an analysis visit based on the date of the assessment relative to the date of study treatment Day 1 (treatment start). The visit assessment windows given in Table 1 will be used to assign data to planned study assessments:

Table 1 Analysis Visit Time-point Windows

Assessment Month	Planned Treatment Day (1)	Day Number (1) Range
Baseline	1	Day 1
Week 1	8	Days 5 – 11
Week 2	15	Days 12 – 18
Week 3	22	Days 19 – 25
Month 1	29	Days 26 – 44
Month 2	60	Days 45 – 75
Month 4	120	Days 105 – 135
Month 6	180	Days 165 – 210
Month 9	270	Days 240 – 300
Month 12	365	Days 335 – 395
Month 15	455	Days 425 – 485
Month 18	545	Days 500 – 590
Month 21 or Follow-up month 3	**	Planned Treatment Day ± 45 days
Month 24 or Follow-up month 6	**	Planned Treatment Day ± 45 days
…	…	…

** Planned Treatment Day = Month 18 Planned Treatment Day + 92 × (number of follow-up month /3)

Assessments made outside of these assessment windows will be listed but not used in *by time-point* summaries.

(1) *For each patient, the day of the baseline visit will be defined as treatment day 1 and subsequent time-points will be assigned a treatment day calculated as:*
(date of assessment − date of baseline) + 1

For a given measurement and analysis visit the following rules will be used to decide which value to use in the analysis:

- Protocol defined visit assessments will take priority over unscheduled visit data; that is, unscheduled visit data will only be used if there is no scheduled visit results within the same time window.
- If more than one assessment falls within the same window, then use the measurement taken nearest to the planned day. In the case of a tie, use the earlier measurement.
- Assessments made outside of these analysis visit windows will be listed but not used in by time-point summaries.

3.4 Analysis Overview

Safety Analyses

All safety analyses will be done on safety population and by study phase.

Abnormal electrocardiogram (ECG), chest X-ray and chest CT scan findings are to be reported.

Details of the analyses and outputs are given in Section 5 to 9.

Efficacy Analysis

[redacted]

[redacted]

Pharmacodynamic Analyses

[redacted]

Subgroup Analyses

The sample size for this study is too small to permit subgroup analyses.

4. BASELINE DEMOGRAPHICS AND BASELINE INFORMATION

Descriptive summaries of the following information will be produced to characterize baseline characteristics for the safety population:

- Demographic characteristics, including:
  - age, both as descriptive summary and as counts and percentages falling into the following categories:
    - 2 – 11 years
    - 12 – 17 years
  - sex
  - race
  - ethnicity
  - height
  - weight
  - body surface area
- Baseline disease characteristics:
  - GPA or MPA disease
    - ANCA result (C-ANCA, P-ANCA, Negative)
  - Duration of disease
  - Pediatric Vasculitis Damage Index (PVDI)
- Previous and current treatment for GPA or MPA
  - A glossary showing the mapping of investigator verbatim terms to coded medications will be produced also
- Immunization history
- Patients' medical history, grouped by preferred term within SOC
  - A glossary showing the mapping of investigator verbatim terms to coded diseases will be produced also
- Alcohol, tobacco and substance use
- Female reproductive status

4.1 Analysis of Study Conduct

The following data will be summarized for the safety population, giving the number and percentage of patients who:

- Had major protocol deviations occurring during the remission induction phase
- Were withdrawn prematurely from the study
- Entered extended follow-up (To be added later as CSR addendum)
- Entered extended follow-up
- Switched to local standard care during the study by study phase

In addition, summaries will be provided of:

- Non-study treatments given for GPA and MPA by study phase
- Concomitant medications received by study phase

4.2 Analysis Populations and Disposition

The following summaries will be produced:

- Analysis populations
- Patient disposition by study phase (remission induction phase, follow-up phase, extended follow-up phase)

4.3 Baseline Output Specifications

ID: DS101SP Analysis Populations	**STREAM Template**: APT01 **Analysis Population:** Treated Patients (Assigned Treatment) **Analysis Variables:** Number of patients for the only analysis population, as shown in the mockup. **Numeric Precision and Formatting of Statistics:** Use mockup.

Analysis Population	Rituximab
Treated Patients **AASL.RP** (Assigned Treatment **AASL.ARM**)	nn
Safety Evaluable Population **ASL.SE** (Treatment Received **AASL.ACTARM**)	nn (xx.x%)
Population (Safety population with at least one evaluable PK sample)	nn (xx.x%)

ID: DS001SP Enrolment by Region, Country, and Investigator Number and Name	**STREAM Template**: ENT02 **Analysis Population:** Samedical history fety Evaluable Population **Analysis Variables:** Group centers by region and country. **Sort order:** Alphabetical by region, and then by decreasing total number of patients treated. Percentages are based on N. **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup.

Region **ASL.GEOREGC1** Country **ASL.COUNTRY**, Investigator Number **ASL.INVID** / Name **ASL.INVNAM**	Rituximab (N=nnn)
Region 1	nn (xx.x%)
Country 1	nn (xx.x%)
9318 / Name 1	nn (xx.x%)
11518 / Name 2	nn (xx.x%)
…	nn (xx.x%)
Country 2	nn (xx.x%)
88431 / Name 1	nn (xx.x%)
8876 / Name 2	nn (xx.x%)
…	nn (xx.x%)
Region 2	nn (xx.x%)
Country 1	nn (xx.x%)
77649 / Name 1	nn (xx.x%)
…	nn (xx.x%)

ID: DM001SP Demographic and Baseline Characteristics	**STREAM Template**: DMT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup. **Statistics and Calculation Methods:** For each variable, summary statistics are based on the number of patients in the corresponding "n" row. Number of concomitant diseases started before or at baseline and continued after. **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup.

	Rituximab (N=nnn)
Age (yr) **ASL.AGE**	
n	nnn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx–xx
Age group (yr) **ASL.AGEG**	
n	nnn
2 to 11	nn (xx.x%)
12 to 17	nn (xx.x%)
Sex **ASL.SEX**	
n	nnn
Male	nn (xx.x%)
Female	nn (xx.x%)
Ethnicity **ASL.ETHNIC**	
n	nnn
Hispanic or Latino	nn (xx.x%)
Not Hispanic or Latino	nn (xx.x%)
Not Reported	nn (xx.x%)
Unknown	nn (xx.x%)
Race **ASL.RACE**	
n	nnn
American Indian or Alaska Native	nn (xx.x%)
Asian	nn (xx.x%)
Black or African American	nn (xx.x%)
Native Hawaiian or other Pacific Islander	nn (xx.x%)
White	nn (xx.x%)
Multiple	nn (xx.x%)
Other	nn (xx.x%)
Unknown	nn (xx.x%)
Height (cm) **ASL.BWT**	
n	nnn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx–xx

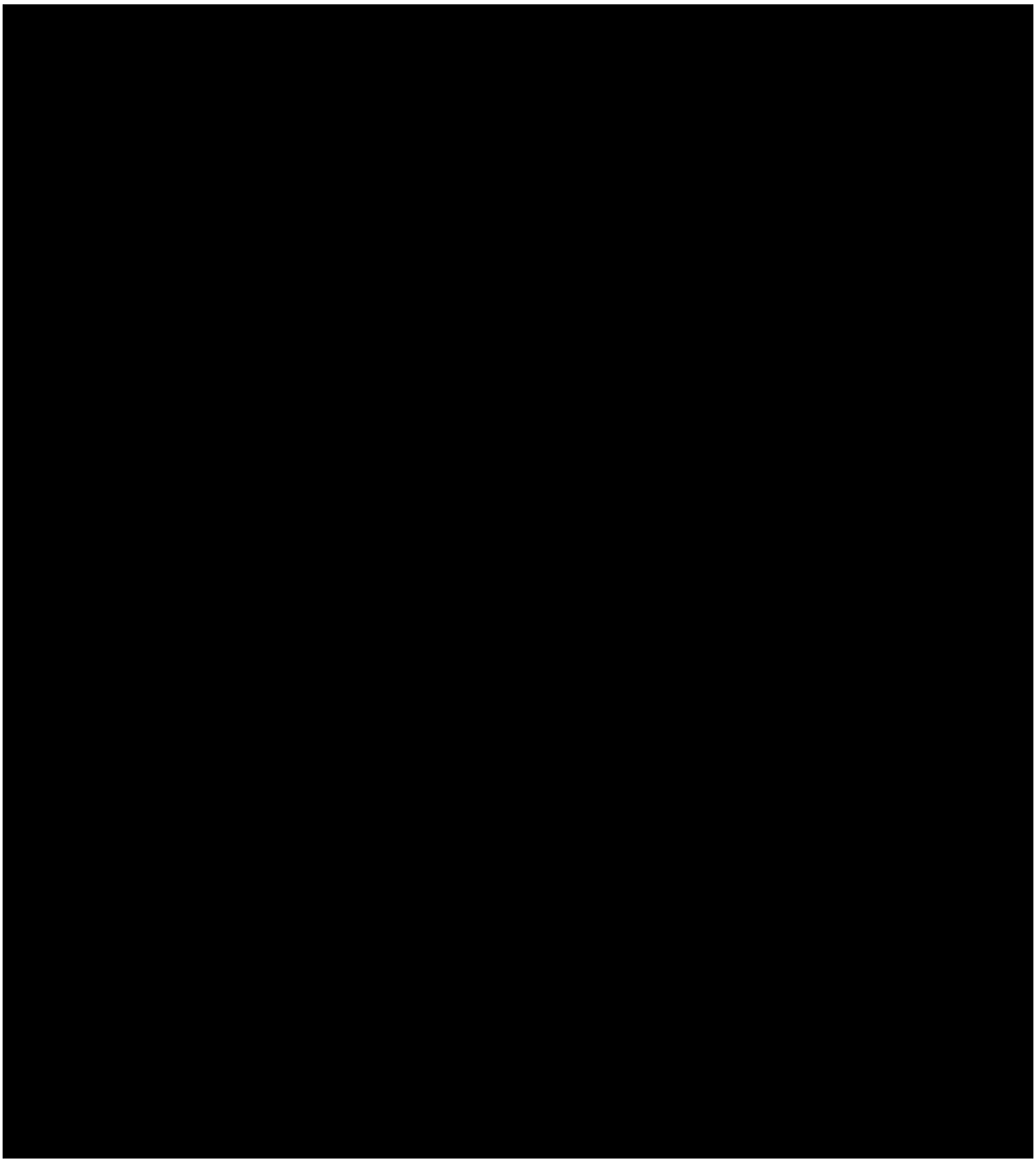
	Rituximab (N=nnn)
Weight (kg) **ASL.BWT**	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx–xx
Body-mass index (kg/m2) **ASL.BBMI**	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx–xx
Concomitant Diseases (continuing at Baseline)	
n	nn
No concomitant diseases	nn (xx.x%)
1 concomitant disease	nn (xx.x%)
2 concomitant diseases	nn (xx.x%)
>=3 concomitant diseases	nn (xx.x%)
Smoking history	
n	nn
Current	nn (xx.x%)
Previous	nn (xx.x%)
Never	nn (xx.x%)
Alcohol history	
n	nn
Current	nn (xx.x%)
Previous	nn (xx.x%)
Never	nn (xx.x%)
Estimated GFR (Schwartz formula) (mL/min/1.73 m2)	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx.x–xx.x
immunofluorescence (IF) ANCA status	
Negative	nn (xx.x%)
cANCA	nn (xx.x%)
pANCA	nn (xx.x%)
MPO	nn (xx.x%)
PR3	nn (xx.x%)
BVAS/WG Score	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx.x–xx.x

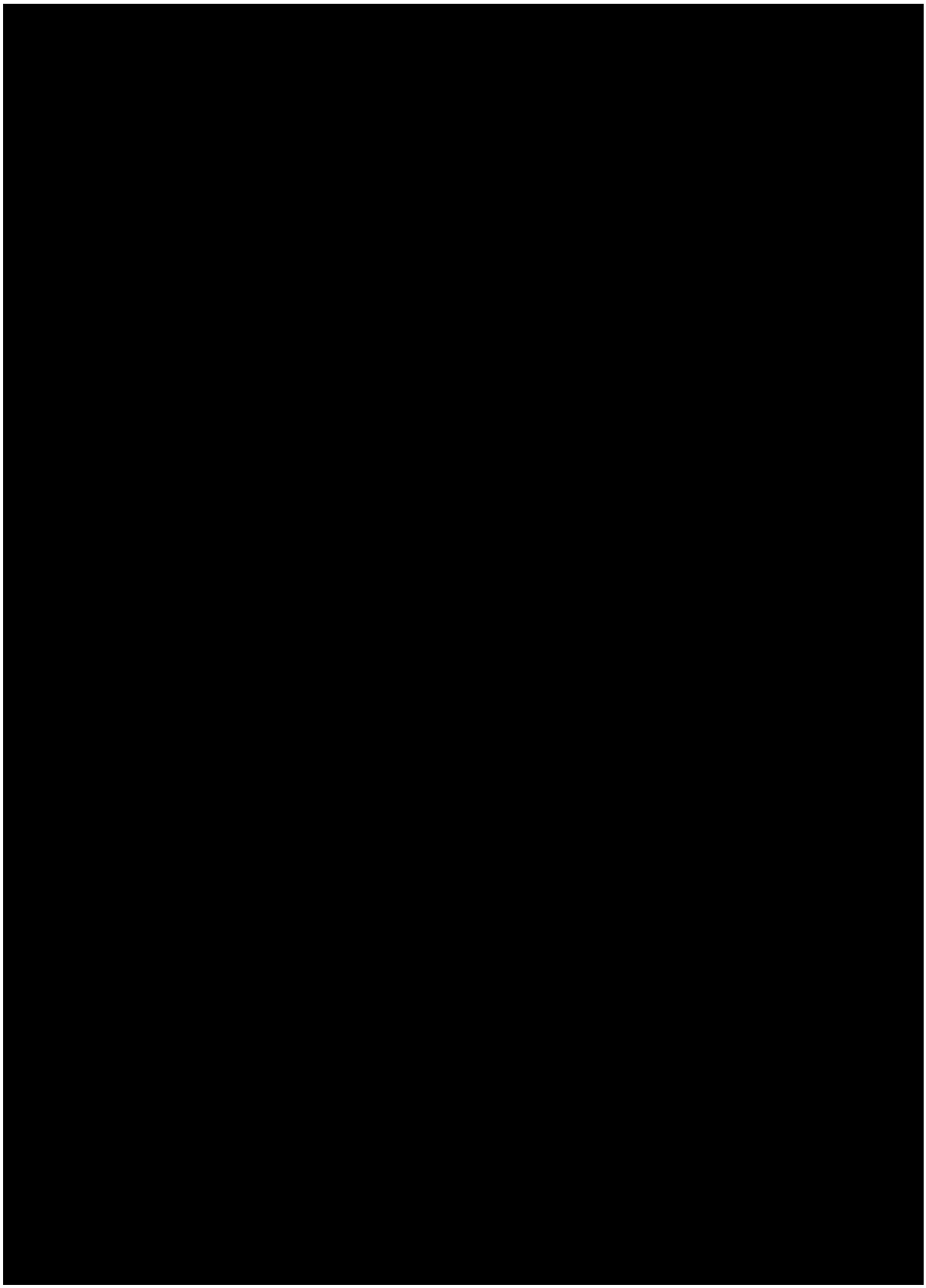
Current Disease Status	
n	
Severe Flare/New Disease	nn (xx.x%)
Limited Flare/New Disease	nn (xx.x%)
Persistent Severe Disease	nn (xx.x%)
Persistent Limited Disease	nn (xx.x%)
Remission	nn (xx.x%)
BVAS/WG PGA	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx.x–xx.x
PVAS Score	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx.x–xx.x
PVDI Score	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx.x–xx.x
PVDI Average School Absence (days)	
n	nn
=<1	nn (xx.x%)
>1 - 4	nn (xx.x%)
>4 - 10	nn (xx.x%)
>10	nn (xx.x%)

ID: DM002SP GPA / MPA History	**STREAM Template**: DMT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup. **Statistics and Calculation Methods:** For each variable, summary statistics are based on the number of patients in the corresponding "n" row. Major Renal Disease is taken from eCRF page, BVAS/ WG and PGA. If both hematuria and RBC casts are present, score only the RBC casts. Summaries are based on Medical history and Concomitant medication domains, and Screening records for other assessments. Most severe "Current Disease Status" is used for summary if patient has multiple disease status from Screening. Disease duration is from the start date of disease to start of study drug at baseline. **Numeric Precision and Formatting of Statistics:** See mockup.

	Rituximab (N=nnn)
Diagnosis	
n	nn
GPA Newly diagnosed	nn (xx.x%)
MPA Newly diagnosed	nn (xx.x%)
GPA relapsed	nn (xx.x%)
MPA relapsed	nn (xx.x%)
Disease duration (months)	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1 – Q3 (IQR)	xx.x – xx.x (xx.x)
Min–Max	xx–xx
Prior CYC therapy	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Major Renal Disease*	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)

* Major Renal Disease is taken from eCRF page, BVAS/ WG and PGA. If both hematuria and RBC casts are present, score only the RBC casts (the major item)





[redacted]

[redacted]

ID: DM003SP Listing of Patients who Discontinued from Study	**STREAM Template**: DSL02 **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Add a columns for "date of study discontinuation" and "study phase" to DSL02

ID: DS201SP Patient Disposition	**STREAM Template**: DST01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup.

Study	Rituximab (N = 25)
Completed 6 Month Remission Induction Phase	nn (xx.xx%)
Completed 18 Months on study	nn (xx.xx%)
Completed study from baseline to common-closeout*	nn (xx.xx%)
Entered extended safety follow-up+	nn (xx.xx%)
Discontinued Study	nn (xx.xx%)
Reason 1	nn (xx.xx%)
Reason 2	nn (xx.xx%)
Reason 3	nn (xx.xx%)
...	

*The common closeout date (10May2018) occurred 18 months after the enrollment of the last patient.
+patients whose B cells remain depleted below LLN for the population entered extended safety follow up.

ID: DS002SP Patients Discontinued from Study Treatment	**STREAM Template**: DST01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup

Status	Rituximab (N=25)
Completed Planned RTX Treatment	nn (xx.x%)
Discontinued Treatment During Study	nn (xx.x%)
Lost To Follow-Up	nn (xx.x%)
Patient Is Transitioning To Adult Care.	nn (xx.x%)
Transfer To Adult Services	nn (xx.x%)
Transfered To Adult Services And Upable To Stay In Follow Up Of Pi	nn (xx.x%)
Transferred To Adult Site	nn (xx.x%)
Transferring To Adult Services	nn (xx.x%)
Withdrawal By Subject	nn (xx.x%)

ID: CM001SP Listing of Concomitant Diseases other than MPA/GPA	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** See mockup. Concomitant Disease is defined as a disease started on or before baseline and continued after. Exclude MPA/GPA diseases from the listing.

Center/Patient ID - Age/Sex/Race Concurrent Disease MedDRA Preferred Term	Date of First Study Drug Administration	Start Date of Disease / Study Day of onset	Duration in Days	Outcome
[redacted] ANEAMIA NOS	[redacted]	[redacted] / -60	1	Resolved
APPETITE DECREASED	[redacted]	[redacted] / -91	2	Resolved
[redacted] DIARRHEA NOS	[redacted]	[redacted] / -425	2	Resolved

ID: CM002SP Listing of Previous Medications for GPA/MPA	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Include medications started and ended on or before baseline. See mockup.

Center/Patient ID - Age/Sex/Race Standardized Medication Name Reported Name of Drug, Medication or Therapy	Dose (unit)	Date of First Study Drug Administration	Start Date of Previous Medication / Study Day	Stop Date of Previous Medication / Study Day
[redacted]				
ANEAMIA NOS	xx	[redacted]	[redacted] / -34	[redacted] / -34
APPETITE DECREASED	xx	[redacted]	[redacted] / -122	[redacted] / -122
[redacted]	xx			
DIARRHEA NOS		[redacted]	[redacted] / -78	[redacted] / -78

ID: CM003SP Listing of Concomitant Medications for GPA/MPA	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Include medications started anytime (after, on or before baseline) and is ongoing during study. See mockup.

Center/Patient ID - Age/Sex/Race Standardized Medication Name Reported Name of Drug, Medication or Therapy	Dose (unit)	Date of First Study Drug Administration	Start Date of Concomitant Medication / Study Day	Stop Date of Concomitant Medication / Study Day
[redacted]				
ANEAMIA NOS	xx	[redacted]	[redacted] / -34	[redacted] -34
APPETITE DECREASED	xx	[redacted]	[redacted] / -122	[redacted] / -122
[redacted]	xx			
DIARRHEA NOS		[redacted]	[redacted] / -78	[redacted] / -78

ID: CM003.1SP Listing of Concomitant Medications for GPA/MPA Ongoing at Baseline	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Include medications started on or before baseline and is ongoing at baseline. See mockup CM003SP.

ID: CM003.2SP Listing of Concomitant Medications for non GPA/MPA Indications	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Include medications started anytime (after, on or before baseline) and is ongoing during study for non MPA/GPA indications. Exclude vaccines from the con meds if the start date is before day 1. See mockup for CM003SP.

ID: MH001SP Immunization History	**STREAM Template**: DMT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup. **Statistics and Calculation Methods:** For each variable, summary statistics are based on the number of patients in the corresponding "n" row. **Numeric Precision and Formatting of Statistics:** See mockup

	Rituximab (N=nnn)
Tetanus Immunoglobulin	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Hepatitis B Immunoglobulin	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Hepatitis A Immunoglobulin	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Rabies Antiserum	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Varicella Zoster Immunoglobulin	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)
Other Immunoglobulin	
n	nn
Yes	nn (xx.x%)
No	nn (xx.x%)

ID: MH001_1SP Vaccination History	**STREAM Template**: DMT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup. **Statistics and Calculation Methods:** For each variable, summary statistics are based on the number of patients in the corresponding "n" row. Use CMCAT = "VACCITINATOIN" and CMOCCUR='Y'. **Numeric Precision and Formatting of Statistics:** See mockup

	Rituximab (N=nnn)
Tetanus Immunoglobulin	nn (xx.x%)
Hepatitis B Immunoglobulin	nn (xx.x%)
Hepatitis A Immunoglobulin	nn (xx.x%)
Rabies Antiserum	nn (xx.x%)

5. EXPOSURE TO STUDY MEDICATION

5.1 Exposure Output Specifications

The following data will be presented:

- Number (%) of patients receiving 1, 2, etc. infusions of RTX
- Cumulative dose of RTX by infusion number.
- Total dose, and the number of doses of methylprednisolone prior to first dose of RTX
- Oral corticosteroid treatment duration (months), summarized both descriptively and as number (%) of patients using the following duration categories:
  - Remission induction phase(1)
    - <1 month (<26 days)
    - 1 month - <2 months (<45 days)
    - 2 months - <4 months (<105 days)
    - 4 months - <6 months (<165 days)
    - 6 months (≥165 days)
  - Follow-up phase
    - 6 months - <12 months (<335 days)
    - 12 months - <18 months (<515 days)
    - 18 months - <2 years (<699 days)
    - 2 years - <3 years (<1067 days)
    - 3+ years (≥1067 days)
- Total dose of corticosteroid following first dose of RTX.
- duration (months) in the study phases over all patients, summarized as for Methylprednisolone, above

(1) *Total duration will be calculated as:*
1 + Study end date - Date rituximab *first administered*

where "study end date" is defined as:

1. For ealy discontinuation or completion patients: early withdrawal/discontinuation date or date patient completed study

2. For the rest of patients: minimum of common closeout date and last known alive date

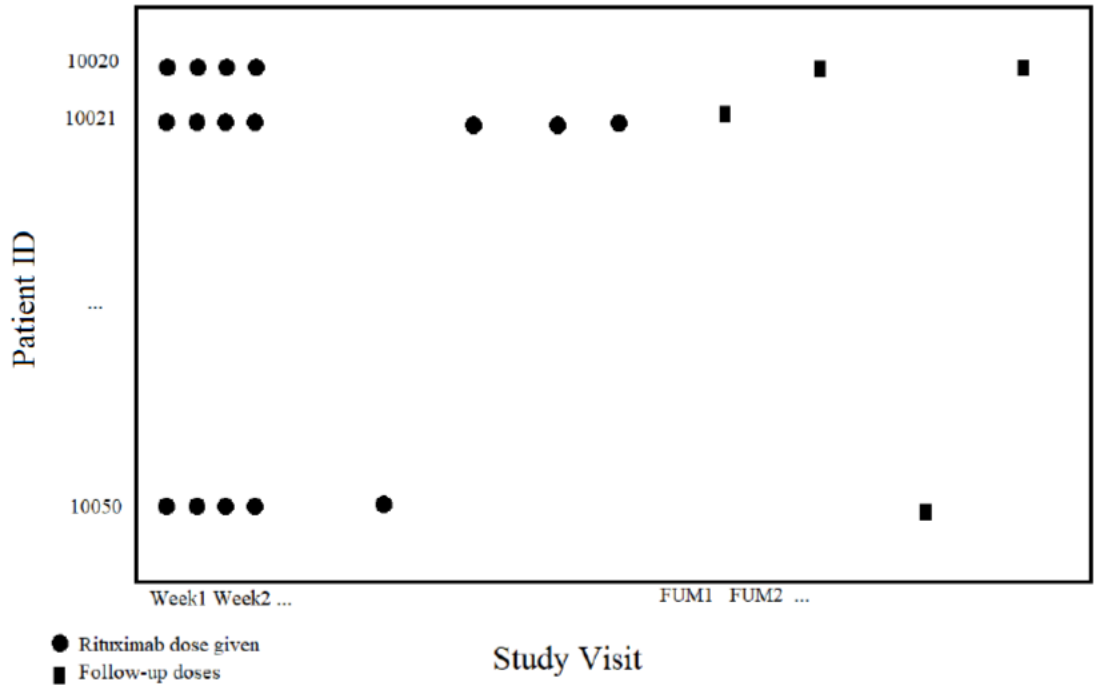
ID: EX001SP Rituximab Treatment Exposure by visit during Remission Induction Phase	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Number of infusions started, Number infusions completed without them being interrupted/modified, Number of patients with interrupted/modified infusions by infusion number, total dose of RTX. The number of infusions categories need to run from 1 (0 for number completed if necessary) to the maximum number of infusions started. Analysis visits to include are: Baseline, Weeks 1 to 3, Months 1, 2, 4, 6 **Statistics and Calculation Methods:** The Infusion Interrupted/Modified rows count the number of Yes's from the "Was the infusion interrupted/modified" question and the denominator for the %s will be the number of patients who started that infusion number and so will correspond to the appropriate row from "Number of infusions started". Percentages are based on: 1. for "Infusion started" section: based on n 2. for "Infusion Interrupted/Modified" section: based on nn*, where nn* is the number of infusions in corresponding visit.

Rituximab (N=nn)	
Infusions started	
n	nn
Baseline	nn* (xx.x%)
Week 1	nn* (xx.x%)
Week 2	nn* (xx.x%)
Week 3	nn* (xx.x%)
Month 1	nn* (xx.x%)
…	
Infusion Interrupted/Modified	
n	nn
Baseline	nn/nn* (xx.x%)
Week 1	nn/nn* (xx x%)
Week 2	nn/nn* (xx.x%)
Week 3	nn/nn* (xx.x%)
Month 1	nn/nn* (xx.x%)
…	
Total number of infusions completed	
n	nn
0	nn (xx.x%)
1	nn (xx.x%)
2	nn (xx.x%)
…	
Total cumulative dose(mg)	
n	nn
Mean (SD)	xxx.x (xx.x)
Median	xx.x
Q1 - Q3 (IQR)	xx.x- xx.x (xx.x)
Min - Max	xx - xxx

ID: EX001.1SP Summary of Rituximab Exposure	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mock. Percentages are based on n. Include data from Day 1 to common closeout date. *- study end date =* *1. For ealy discontinuation or completion patients: minimum of or early withdrawal/discontinuation or patient completed study* *2. For the rest of patients: minimum of common closout date and last known alive date* Duration of observation = *study end date – study start date + 1.* Date of last contact is the last available date of efficacy, complete medication start date, laboratory, adverse event assessments, early withdrawal visit, date of last contact or date of death.

```
Total number of Infusions administered
    n                                   nn
    Mean (SD)                       xxx.x (xx.x)
    Median                              xx.x
    Q1-Q3 (IQR)                     xx.x-xx.x(xx.x)
    Min - Max                       xx - xxx

Total cumulative dose(mg)
    n                                   nn
    Mean (SD)                       xxx.x (xx.x)
    Median                              xx.x
    Q1-Q3 (IQR)                     xx.x-xx.x(xx.x)
    Min - Max                       xx - xxx

Duration of Observation (Months)
    n                                   nn
    Mean (SD)                      xx.x (xx.x)
    Median                          xx.x
    Q1-Q3 (IQR)                    xx.x-xx.x(xx.x)
    Min - Max                      xx.x - xx.x


Duration of Observation (Months)
    n                                   nn
    Duration ≤ 6                        nn (xx.x%)
    6 < Duration ≤ 12                   nn (xx.x%)
    12 < Duration ≤ 18                  nn (xx.x%)
    18 < Duration ≤ 24                  nn (xx.x%)
    24 < Duration ≤ 36                  nn (xx.x%)
    36 < Duration ≤ 48                  nn (xx.x%)
    48 < Duration ≤ 60                  nn (xx.x%)
         Duration > 60                  nn (xx.x%)

    Total patient years of observation       xxx.xx
```

ID: EX001.2SP Rituximab Administration over Course of study	**STREAM Template:** None **Analysis Population:** Safety Evaluable Population **Plot of:** **Y-Axis:** Patient ID **X-Axis:** Study Visit See mockup.



ID: EX002SP Listing of Rituximab Administrations, Interruptions and Modifications	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Column Variables:** Include data from Day 1 to common closout date. Add "Dose Administered" column in "mg/m^2" calculating as follows: administered dose (mg/m^2) = dose administered (mg) / BSA (m^2), where *BSA = body surface area = sqrt [BW x Ht / 3600]* *BW = weight (kg)* *Ht = height (cm)* See mockup **Sorting:** Sort by center / patient ID and treatment administration day.

Center / Patient ID ASL.SITEID/AAE.PATNUM	Age/Sex/Race ASL.AGE/ ASL.SEX/ ASL.RACE	Height (cm) / Weight (kg)	Target Day	Study Day	Study Visit	Planned Dose (mg)	Dose Administered (mg)	Dose Administered (mg/m²)	Volume Administered (mL)	Infusion Interrupted / Modified	Reason for Modification
[redacted]	[redacted]	[redacted]	1	1	baseline	xxx	478.8	xxx	xxx	No	
			8	8	week 2	xxx	479.2	xxx	xxx	No	
			15	15	week 2	xxx	479.2	xxx	xxx	Yes	Medication Error
			22	22	month 1	xxx	482.5	xxx	xxx	No	
...											

ID: EX003SP Corticosteroid Treatment Exposure during Remission Induction Phase and Overall	**STREAM Template**: EXT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Oral steroids: duration of use and total dose. All steroids (all route) total use. This needs discussing with [redacted] as she has indicated that she will not be able to supply conversion factors for non-oral steroids. Percentages are based on n.

Phase: …

	Rituximab (N=25)
ORAL CORTICOSTEROID DRUGS	
Treatment duration (D)	
n	25
Mean (SD)	xxx.x (xx.x)
Median	xx.x
Q1 - Q3 (IQR)	xx.x - xx.x (xx.x)
Min - Max	xx - xxx
Treatment duration	
n	nn
<1 month (1-25 days)	nn (xx.x%)
1 - <2 months (26-44 days)	nn (xx.x%)
2 - <4 months (45-104 days)	nn (xx.x%)
4 - <6 months (105-164 days)	nn (xx.x%)
6 months (>=165 days)	nn (xx.x%)
Total cumulative oral dose(mg)	
n	nn
Mean (SD)	xxx.x (xx.x)
Median	xx.x
Q1 - Q3 (IQR)	xx.x - xx.x (xx.x)
Min - Max	xx - xxx
ALL CORTICOSTEROID DRUGS	
Total cumulative dose(mg)	
n	nn
Mean (SD)	xxx.x (xx.x)
Median	xx.x
Q1 - Q3 (IQR)	xx.x - xx.x (xx.x)
Min - Max	xx - xxx

ID: EX004SP Listing of Steroid Use	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** See mockup. **Sorting:** Sort by center / patient ID and treatment administration day.

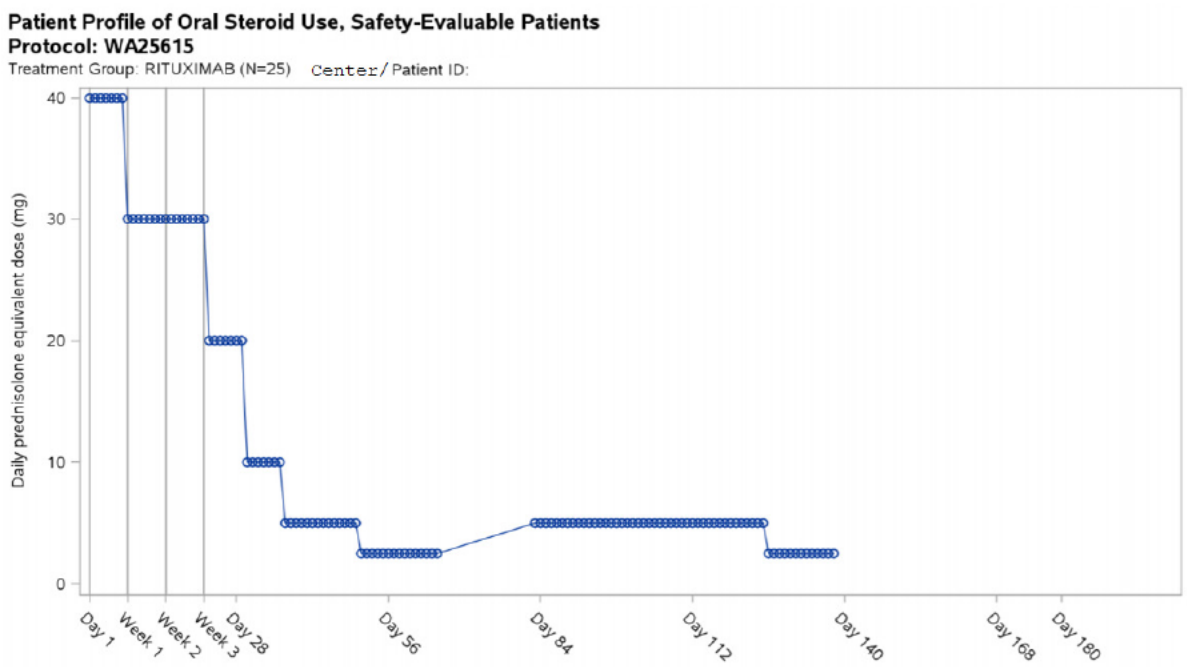
Center / Patient ID ASL.SITEID/AAE.PATNUM	Age/Sex/Race ASL.AGE/ ASL.SEX/ ASL.RACE	Height (cm) / Weight (kg)	Start Day	End Day	Medication	Dose Administered	Unit	Route
[redacted]	[redacted]	[redacted]	1	1	DEXAMETHASONE *	8	mg	Intravenous
			8	9		479.2		
			15	15		479.2		
			22	22		482.5		
[redacted]	[redacted]	[redacted]	1	1		322.5		
			8	8		322.5		
			15	15		322.5		

* GPA/MPA, PRE-RITUXIMAB INFUSION AND GLUCOCORTICOID CONCOMITANT MEDICATIONS

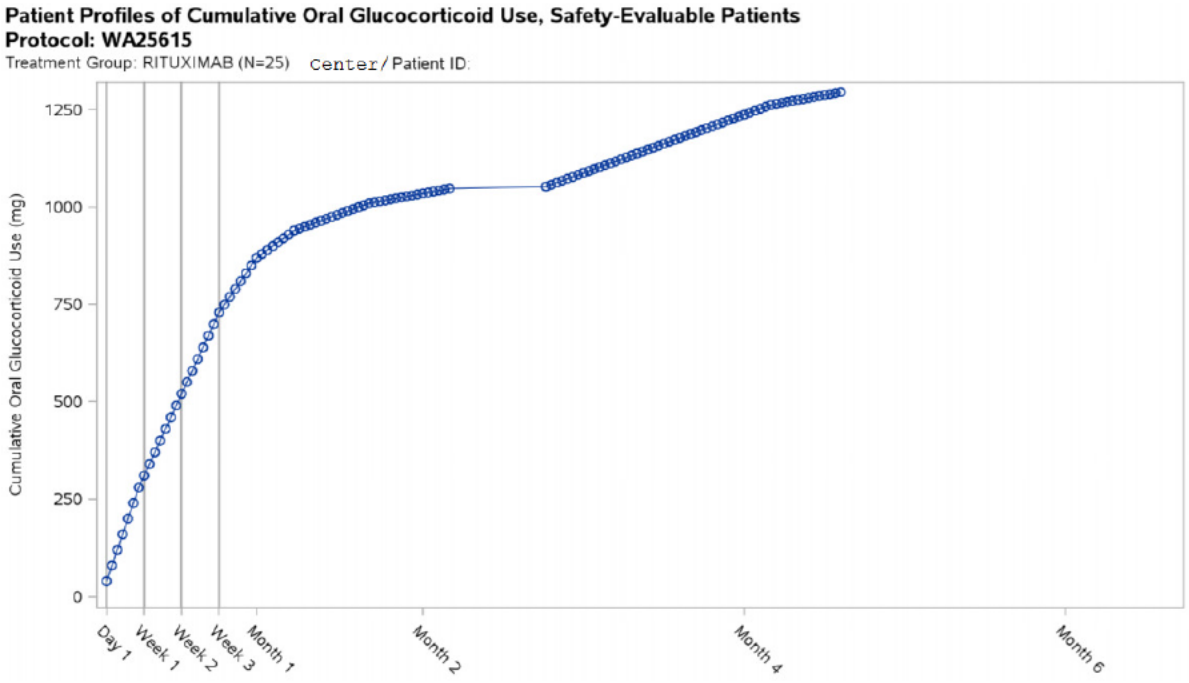
ID: EX006SP Methylprednisolone Treatment Exposure During Screening Period Prior to First Rituximab Infusion	**STREAM Template**: EXT01 **Analysis Population:** Safety Evaluable Population **Analusis Variables:** See mockup. Methylprednisolone (30 mg/kg, up to 1 g/day) include Methylprednisolone dose on or before Day 1 for the number of doses, include number anf percentage of patients having 1, 2, 3 and >3 doses. **Statistics and Calculation Methods:** Prcentages are based on n. **Sorting:** Sort by center / patient ID and treatment administration day.

	Rituximab (N=nnn)
Treatment duration (D)	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1-Q3 (IQR)	xx.x-xx.x (xx.x)
Min–max	xx–xx
Number of doses	
n	nn
1 dose	xx.x (xx.x%)
2 doses	xx.x (xx.x%)
3 doses	xx.x (xx.x%)
> 3 doses	xx.x (xx.x%)
Total cumulative dose (mg)	
n	nn
Mean (SD)	xx.x (xx.x)
Median	xx.x
Q1-Q3 (IQR)	xx.x-xx.x (xx.x)
Min–max	xx–xx

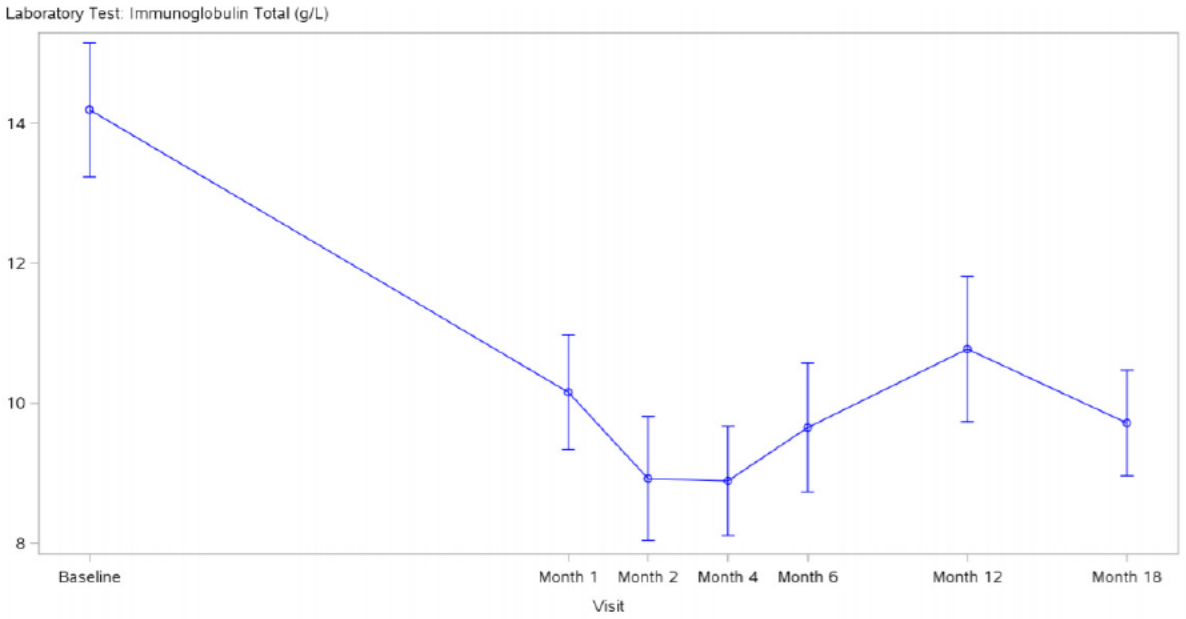
ID: EX007SP Patient Profile of Oral Steroid Use	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Plot of:** **Y-Axis**: Daily prednisolone equivalent dose (mg) **X-Axis**: Study Visit One plot for each patient. **Reference lines:** Draw reference lines through the x-axis on the days of RTX administration.



ID: EX007.1SP Patient Profiles of Cumulative Glucocorticoid Use	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Cumulative steroid (Oral and other types in one plot with different shapes/colors) use to Months Weeks 1 to 3 and Months 1, 2, 4, 6, 12 and 18. **Plot of:** **Y-Axis**: Cumulative prednisone equivalent dose (mg) to time-points given above. **X-Axis**: Study Visit One plot for each patient. **Reference lines:** Draw reference lines through the x-axis on the days of RTX administration. **Numeric Precision and Formatting of Statistics:** see mockup.



ID: EX007.2SP Median Glucocorticoid Use Over Time	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Median overall steroid use (Oral and other types in two separate plots in one output file) to Weeks 1 to 3 and Months 1, 2, 4, 6, 12 and 18. For IV, include screening period (day -28 to day 1) in the graph. **Plot of:** **Y-Axis**: Median overall prednisone equivalent dose (mg) to time-points given above. **X-Axis**: Study Visit **Error Bars:** Q1 and Q3. **Numeric Precision and Formatting of Statistics:** see mockup.



ID: EX007.3SP Glucocorticoid Use by Visit	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Glucocorticoid use to Screening, Weeks 1 to 3 and Months 1, 2, 4, 6, 12 and 18. **Numeric Precision and Formatting of Statistics:** see mockup.

Visit		Value at Visit
	n	nn
Screening	Median	xx.xx
	Q1 – Q3 (IQR)	xx.xx – xx.xx (xx.xx)
	Min - Max	xx.x – xx.x
Week 1	n	nn
	Median	xx.xx
	Q1 – Q3 (IQR)	xx.xx – xx.xx (xx.xx)
	Min - Max	xx.x – xx.x
...		

6. ADVERSE EVENTS

Adverse events will be considered TE (defined in Section 4) irrespective of the length of time since the first RTX infusion. Only TE adverse events will be included in summary tables. The current sponsor data safety standards will be used where available.

Summaries of TE adverse events will be produced by study phase. Summaries will be produced of the numbers of patients (%) experiencing the following TE adverse events:

Summaries will be produced of the following TE adverse events:

- Summary profile of TE adverse events
- Overview of adverse events
- All events
- All events by most extreme toxicity grade(*)
- Events other than IRR occurring during or within 24 hours of a RTX Infusion by relationship to treatment (count multiple occurrences as one event)
- Events leading to death
- SAEs
- SAEs assessed as related to the study drug
- Events leading to discontinuation of study medication
- Events leading to a study medication dose modification
  - Infections
    - MedDRA SOC infections and infestations
  - Serious Infections
    - serious events in MedDRA SOC infections and infestations (include non-serious infections treated with IV anti-infective)
  - Opportunistic Infection
    - from Roche standard AEGT Opportunistic Infections
  - Infusion Related Reactions (IRRs)
    - events that occur during or within 24 hours of an infusion and fall within Roche standard AEGT Infusion Related Reactions + Hypersensitivity
    - Count multiple symptoms as one IRR for each infusion.
  - Cardiac events
    - MedDRA SOC “Cardiac Events” MedDRA SOC “Cardiac Events”
  - Malignancies
    - preferred terms in the Malignant or Unspecified Tumors SMQ (Wide)
- CTCAE grade 3 and grade 4 events
- Non-serious events reported by ≥ 5% patients (CTg requirement, not for CSR)
- Common Adverse Events reported by ≥ 10% patients

(*) Most extreme toxicity grade is recorded on the eCRF. If most extreme toxicity grade is not recorded then initial toxicity grade will be used; if neither grade is given then an unknown category will be used. The grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.

Adverse Event Output Specifications

ID: AE001SP Overview of Adverse Events during Remission Induction Phase and Overall	**STREAM Template**: AET01 **Analysis Population**: Safety Evaluable Population **Analysis Variables**: See mockup **Statistics and Calculation Methods**: Percentages are of the number of patients in SE population. For "Total number of events" rows, multiple occurrences of the same AE are counted separately. For the frequency counts by preferred term, multiple occurrences of the same AE in one individual are counted only once. For the severe AEs (at greatest intensity), consider AEs with NCI-CTCAE grade >= 3. **Numeric Precision and Formatting of Statistics**: see mockup.

Phase: …

	Rituximab (N=nnn)
Total number of adverse events	nn
Total number of serious adverse events	nn
Total number of deaths	nn
Total number of patients with at least one	nn
Adverse event	nn (xx.x%)
Severe adverse event (at greatest intensity)	nn (xx.x%)
Adverse event assessed as related to study drug by investigator	nn (xx.x%)
Serious adverse event	nn (xx.x%)
Serious adverse event assessed as related to study drug by investigator	nn (xx.x%)
Adverse event leading to discontinuation from study treatment	nn (xx.x%)
Specific AEs	
Infection	nn (xx.x%)
Serious infection	nn (xx.x%)
Opportunistic infection	nn (xx.x%)
Infusion related reaction	nn (xx.x%)
Cardiac event	nn (xx.x%)
Malignancies	nn (xx.x%)

ID: AE002SP Adverse Events during Remission Induction Phase and Overall	**STREAM Template**: AET02 **Analysis Population**: Safety Evaluable Population **Analysis Variables**: See mockup. **Statistics and Calculation Methods**: For "Total number of AEs" rows, multiple occurrences of the same AE are counted separately. For the frequency counts by preferred term, multiple occurrences of the same AE in one individual are counted only once. Percentages are based on N. **Numeric Precision and Formatting of Statistics**: See mockup.

Phase: …

System Organ Class Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	22 (88.0%)
Overall total number of AEs	301
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	16 (64.0%)
Total number of AEs	63
UPPER RESPIRATORY TRACT INFECTION	10 (40.0%)
LOWER RESPIRATORY TRACT INFECTION	4 (16.0%)

ID: AE002.2SP Summary of Infusion Related Reactions (IRRs) by Visit	**STREAM Template**: DMT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** See mockup. **Column Variables**: Infusion numbers. **Statistics and Calculation Methods:** Include two tables in one output file: 1. For remission induction phase. 2. Foroveral period, Day 1 to common closeout date. Infusion Related Reactions (IRRs) are defined as: • events that occur during or within 24 hours of an infusion and fall within Roche standard AEGT Infusion Related Reactions + Hypersensitivity Count multiple symptoms as one IRR for each infusion. Percentages are based on n. Visits to be included: Baseline, Week 1 to 3, month 6, 12 and 18. Symptom of IRR = Reported term. **Numeric Precision and Formatting of Statistics:** See mockup

	Rituximab (N=57)				
Preferred Term/ Symptom of IRR	Infusion 1 ...	Infusion 4	Infusion 5	Infusion 8	Infusion 10
Number of patients who had an infusion (n)	57	56	56	54	54
Infusion related reaction*					
Total No. of patients with events	5 (8.8%)	1 (1.8%)	2 (3.6%)	1 (1.9%)	0
bronchospasm	1 (1.8%)	0	0	0	0
cough	1 (1.8%)	0	0	0	0
exanthema	0	0	0	1 (1.9%)	0
metallic taste, tingling at the back of the throat	0	1 (1.8%)	0	0	0
pruritus	1 (1.8%)	0	0	0	0
skin rash	1 (1.8%)	0	0	0	0
tightness in the throat	0	0	1 (1.8%)	0	0
tingling at the back of the throat during the	0	0	1 (1.8%)	0	0

ID: AE004SP
to
ID: AE020SP

Adverse Event Subsets during Remission Induction Phase and Overall

STREAM Template: AET02

Analysis Population: Safety Evaluable Population

Subset: Same table contents and format, except use the following subsets (see also the beginning of this section):

ID	Subset
AE005SP	Events resulting to death (**Stream Template:** AET07)
AE006SP	SAEs
AE007SP	SAEs assessed as related to the study drug
AE008SP	Events leading to discontinuation of study medication
AE009SP	Events leading to a study medication dose modification
AE010SP	Infections • MedDRA SOC infections and infestations
AE011SP	Serious Infections • serious events in MedDRA SOC infections and infestations
AE012SP	Opportunistic Infection • from Roche standard AEGT Opportunistic Infections
AE014SP	Cardiac events MedDRA SOC "Cardiac Disorders"
AE015SP	Malignancies • preferred terms in the Malignant or Unspecified Tumors SMQ (Wide)
AE016SP	NCI CTCAE grade 3 and 4 events, using separate sections for each grade
AE018SP	Events other than IRR occurring during or within 24 hours of a rituximab Infusion by relationship to treatment

Statistics and Calculation Methods: Percentages are of the number of patients in SE population (N). For "Total number of AEs" rows, multiple occurrences of the same AE are counted separately. For the frequency counts by preferred term, multiple occurrences of the same AE in one individual are counted only once.

For AE016SP, flag grade 4 events with "*".

ID: AE021SP Adverse Events by Highest NCI CTCAE Grade	**STREAM Template**: AET04 **Analysis Population**: Safety Evaluable Population **Analysis Variables**: See mockup. Include all AEs with an onset from first dose of study treatment through common closeout date **Statistics and Calculation Methods**: Percentages are based on the number of patients in SE population (N). Multiple occurrences of the same AE in one individual are counted once at the greatest intensity/highest grade for this preferred term. **Sort by:** Sort alphabetically by SOC, then within a SOC, sort by decreasing frequency of PT. **Numeric Precision and Formatting of Statistics**: See mockup.

MedDRA System Organ Class MedDRA Preferred Term	Grade	Dose 1 (N=14)	Dose 2 (N=6)	All Patients (N=20)
- Any adverse events -	any	14 (100.0%)	6 (100.0%)	20 (100.0%)
	5	2 (14.3%)	1 (16.7%)	3 (15.0%)
	4	2 (14.3%)	1 (16.7%)	3 (15.0%)
	3	4 (28.6%)	4 (66.7%)	8 (40.0%)
	2	4 (28.6%)	0	4 (20.0%)
	1	2 (14.3%)	0	2 (10.0%)
GASTROINTESTINAL DISORDERS				
- Overall -	any	13 (92.9%)	6 (100.0%)	19 (95.0%)
	3	2 (14.3%)	0	2 (10.0%)
	2	4 (28.6%)	1 (16.7%)	5 (25.0%)
	1	7 (50.0%)	5 (83.3%)	12 (60.0%)
DIARRHOEA	any	10 (71.4%)	4 (66.7%)	14 (70.0%)
	3	1 (7.1%)	0	1 (5.0%)
	2	4 (28.6%)	0	4 (20.0%)
	1	5 (35.7%)	4 (66.7%)	9 (45.0%)
VOMITING	any	9 (64.3%)	3 (50.0%)	12 (60.0%)
	2	1 (7.1%)	1 (16.7%)	2 (10.0%)
	1	8 (57.1%)	2 (33.3%)	10 (50.0%)
NAUSEA	any	7 (50.0%)	4 (66.7%)	11 (55.0%)
	2	1 (7.1%)	1 (16.7%)	2 (10.0%)
	1	6 (42.9%)	3 (50.0%)	9 (45.0%)
DRY MOUTH	any	2 (14.3%)	1 (16.7%)	3 (15.0%)
	1	2 (14.3%)	1 (16.7%)	3 (15.0%)
RETCHING	any	2 (14.3%)	1 (16.7%)	3 (15.0%)
	1	2 (14.3%)	1 (16.7%)	3 (15.0%)
CONSTIPATION	any	1 (7.1%)	1 (16.7%)	2 (10.0%)
	1	1 (7.1%)	1 (16.7%)	2 (10.0%)
DYSPEPSIA	any	1 (7.1%)	1 (16.7%)	2 (10.0%)
	1	1 (7.1%)	1 (16.7%)	2 (10.0%)
ABDOMINAL PAIN	any	1 (7.1%)	0	1 (5.0%)
	1	1 (7.1%)	0	1 (5.0%)

ID: AE022SP Listing of Patients with Dose Modification or Interruption Due to Adverse Events during Remission Induction Phase and Overall	**STREAM Template**: AEL02 **Analysis Population**: Safety Evaluable Population **Variables Displayed:** Add a new column to AEL02 for "The start date of AE leading to dose modification/interruption". **Numeric Precision and Formatting of Statistics**: See mockup.

ID: AE023SP Non-Serious Adverse Events Reported in >= 5% of Patients	**STREAM Template**: EUDRAT01 **Analysis Population**: Safety Evaluable Population **Analysis Variables**: This table will be used to fulfill EudraCT and clintrials.gov disclosure requirements. It summarizes, for each treatment group, the number of patients, and the number of events, for non-serious AEs occurring in ≥ 5% of patients. Results will be displayed by SOC and PT within each SOC. Number of events at the SOC level is not displayed. **Statistics and Calculation Methods**: Percentages are based on N in column heading. For each preferred term, multiple occurrences of the same AE in an individual are counted only once for the number of patients, and counted separately for the number of events. **Sort by:** Display the data alphabetically by SOC, and by PT alphabetically within a SOC . **Numeric Precision and Formatting of Statistics**: See mockup.

	rituximab (N=98)	
MedDRA System Organ Class MedDRA Preferred Term	Patients	Events
Total number of patients with at least one non-serious adverse event occurring at relative frequency >=5% and number of events	95	1742
Blood And Lymphatic System Disorders		
Anaemia	21	34
Leukopenia	10	17
Neutropenia	32	58
Thrombocytopenia	11	22
Eye Disorders		
Lacrimation Increased	9	9
Vision Blurred	5	5
Gastrointestinal Disorders		
Abdominal Pain	17	27
Abdominal Pain Upper	9	13
Diarrhoea	54	123
Dyspepsia	14	16
…		

NOTE: Number of events includes all occurrences.

ID: AE023.2SE Serious Adverse Events, Fatal SAEs and SAEs Related to Study Medication	**STREAM Template**: EUDRAT02 **Analysis Population**: SE Population **Analysis Variables**: See mockup. This table will be used to fulfill EudraCT disclosure requirements. It summarizes, by treatment group, by SOC and preferred term, the following: • Number of patients with serious adverse events (SAEs) • Number of SAEs • Number of patients with fatal SAEs • Number of SAEs resulting in death (fatal) • Number of SAEs related to study medication • Number of SAEs related to study medication and resulting in death Number of events at the SOC level is not displayed. **Statistics and Calculation Methods**: Percentages are based on N in column headings. For each preferred term, multiple occurrences of the same AE (that meet the relevant filter) in an individual are counted only once for the number of patients, and counted separately for the number of events. **Sort by:** Display the data alphabetically by SOC, and by PT alphabetically within a SOC .

NOTE: Number of events includes all occurrences.

MedDRA System Organ Class MedDRA Preferred Term	Patients (All)	Events (All)	Patients (Fatal)	Events (Fatal)	Events (Related)	Events (Fatal and Related)
Blood And Lymphatic System Disorders						
Anaemia	nnn	nnn	nnn	nnn	nnn	nnn
Coagulopathy	nnn	nnn	nnn	nnn	nnn	nnn
Febrile Neutropenia	nnn	nnn	nnn	nnn	nnn	nnn
Cardiac Disorders						
Acute Myocardial Infarction	nnn	nnn	nnn	nnn	nnn	nnn
Atrial Fibrillation	nnn	nnn	nnn	nnn	nnn	nnn
…						

NOTE: Number of events includes all occurrences.

ID: AE024SP Common Adverse Events Reported in >= 10% of Patients during Remission Induction Phase and Overall	**STREAM Template**: None **Analysis Population**: Safety Evaluable Population **Analysis Variables**: Table of AEs grouped by System Organ Class (SOC) and listed by Preferred Term (PT) that occurred at a frequency ≥10% for each phase. Note: "with at least one AE " means "with at least one AE which occurred for >=10% of patients". **Numeric Precision and Formatting of Statistics**: See mockup.

MedDRA System Organ Class	RITUXIMAB (N=25)
Total number of patients with at least one AE	24 (96.0%)
UPPER RESPIRATORY TRACT INFECTION	11 (44.0%)
HEADACHE	10 (40.0%)
DIARRHOEA	8 (32.0%)
EPISTAXIS	7 (28.0%)
ARTHRALGIA	6 (24.0%)
CHEST PAIN	5 (20.0%)
CONJUNCTIVITIS	5 (20.0%)
COUGH	5 (20.0%)
GRANULOMATOSIS WITH POLYANGIITIS	5 (20.0%)
NAUSEA	5 (20.0%)
PYREXIA	5 (20.0%)
HYPOGAMMAGLOBULINAEMIA	3 (12.0%)
MIGRAINE	3 (12.0%)
NASOPHARYNGITIS	3 (12.0%)
PHARYNGITIS	3 (12.0%)
RHINITIS	3 (12.0%)
TREMOR	3 (12.0%)
URINARY TRACT INFECTION	3 (12.0%)
VIRAL INFECTION	3 (12.0%)
VOMITING	3 (12.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
Table includes only AEs occurring in >=10% of patients in at least one treatment group.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

7. SAFETY LABORATORY ANALYSES

7.1 Safety Laboratory Analyses

Safety hematology and serum chemistry laboratory samples are taken during each planned study visit.

Treatment-emergent clinically relevant laboratory test abnormalities are to be reported as adverse events on the Adverse Event eCRF and so will be reported as AEs. This is required for planned samples taken at study visits and also for any unscheduled samples taken.

For hematology and chemistry parameters, following summaries will be produced:

- Descriptive summaries, including changes from baseline, of values at baseline and throughout the study.
- The number of patients with values outside the normal upper and lower limit at each visit.

7.2 Acute-phase Reactants

Samples for measurement of erythrocyte sedimentation rate and C-reactive protein are taken during each study visit for analysis by the site's local laboratory. The parameters values and their changes from baseline will be summarized descriptively by visit and study phase.

7.3 Immunologic and Antibody Assessments

B- and T-cell populations are measured at baseline and each subsequent visit.

Samples for measurement of IgA, IgG, IgM and total immunoglobulins are taken at screening, baseline and then at each visit from Month 1 onwards. These will be summarized descriptively by visit and study phase and as changes from baseline.

7.4 Laboratory Output Specifications

ID: LB001SP Laboratory Test results and Change from Baseline by Visit	**STREAM Template**: LBT01 **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Single output file with separate page for each lab parameter as required by the protocol. Create tables for: • Hematology: hematocrit, hemoglobin, red blood cells and indices (mean corpuscular volume, mean cell hemoglobin, mean corpuscular hemoglobin concentration), white blood cells, absolute differential [neutrophils, lymphocytes, monocytes, basophils], and platelet counts • Serum chemistry: ALT/SGPT, alkaline phosphatase, AST/SGOT, calcium, chloride, creatinine, glycosylated hemoglobin (HbA_{1c}), phosphate, potassium, sodium, total bilirubin (direct and indirect will be performed if total bilirubin is greater than the ULN), total protein, urea, uric acid Sort order for tables: alphabetical by lab test (within hematology and chemistry) **Statistics and Calculation Methods:** Per standard display. Analysis visits to include are: Baseline, Weeks 1 to 3, Months 1, 2, 4, 6, 12 and 18. Values at visits to include only patients for whom a baseline value is included. **Numeric Precision and Formatting of Statistics:** See mockup

```
Laboratory Test: SGPT/ALT (U/L)
_____________________________________________

                        Rituximab
                          (N=25)
                 ____________________________

                                  Change from
Visit         Value at Visit       Baseline
_____________________________________________

Baseline
  n                  24
  Mean (SD)    25.54 (22.20)
  Median             17.00
  Q1 - Q3 (IQR)     xx.x - xx.x (xx.x)
  Min - Max       7.0 - 79.0
Week 1
  n                  21                  20
  Mean (SD)    27.43 (21.50)       1.75 (12.47)
  Median             17.00                4.00
  Q1 - Q3 (IQR) xx.x - xx.x (xx.x)     xx.x - xx.x (xx.x)
  Min - Max       7.0 - 95.0        -34.0 - 19.0
…
```

ID: LB004SP Laboratory Abnormalities by Visit and Baseline Status	**STREAM Template:** None **Analysis Population:** Safety Evaluable Population **Mock format:** See below for specific example with 4 extra columns. **Analysis Variables:** See LB001SP for parameters to be included and the appropriate analysis visits. **Statistics and Calculation Methods**: Use the normal ranges given within the data. For each lab test and visit, include the following rows: (a) For Baseline, should have rows for Low, Normal, and High. (Always display all 3, even if count is 0.) (b) For Post-baseline visits, should have rows for Low – Change from Baseline Low – Sustained Low – Baseline Missing Normal High – Change from Baseline High – Sustained High – Baseline Missing For post-baseline visits, only display the "Low – Baseline Missing" and "High – Baseline Missing" rows when they have a non-zero count. For all other rows, always display, even if count is 0. **ALB.BASE1, ALB.RANGEB1, ALB.RANGE** Analysis visits to include are: Baseline, Weeks 1 to 3, Months 1, 2, 4, 6, 12 and 18. Percentages are based on n. **Numeric Precision and Formatting of Statistics:** See mockup (although we have just the one treatment group) – noting request above for rows to be presented.

Key Laboratory Assessments with Values Outside the Normal Limits
Safety-Evaluable Patients

Lab Test	Visit		Placebo (N=66)	Lab 37.5 mg (N=64)	Lab 125 mg (N=62)	Lab 250 mg (N=66)	All Lab (N=192)
Alanine Aminotransferase	Baseline	n	66	64	62	66	192
		Normal	59 (89.4%)	59 (92.2%)	53 (85.5%)	58 (87.9%)	170 (88.5%)
		High	7 (10.6%)	5 (7.8%)	9 (14.5%)	8 (12.1%)	22 (11.5%)
	Week 4	n	60	53	55	60	168
		Normal	55 (91.7%)	51 (96.2%)	51 (92.7%)	55 (91.7%)	157 (93.5%)
		High - Change from Baseline	1 (1.7%)	1 (1.9%)	1 (1.8%)	1 (1.7%)	3 (1.8%)
		High - Sustained	4 (6.7%)	1 (1.9%)	3 (5.5%)	4 (6.7%)	8 (4.8%)
	Week 8	n	52	52	54	50	156
		Normal	48 (92.3%)	50 (96.2%)	50 (92.6%)	43 (86.0%)	143 (91.7%)
		High - Change from Baseline	1 (1.9%)	2 (3.8%)	1 (1.9%)	3 (6.0%)	6 (3.8%)
		High - Sustained	3 (5.8%)	(0.0%)	3 (5.6%)	4 (8.0%)	7 (4.5%)
	Week 12	n	48	44	43	47	134
		Normal	43 (89.6%)	43 (97.7%)	41 (95.3%)	41 (87.2%)	125 (93.3%)
		High - Change from Baseline	1 (2.1%)	1 (2.3%)	(0.0%)	4 (8.5%)	5 (3.7%)
		High - Sustained	4 (8.3%)	(0.0%)	2 (4.7%)	2 (4.3%)	4 (3.0%)
	Week 16	n	43	41	39	42	122
		Normal	38 (88.4%)	40 (97.6%)	39 (100.0%)	35 (83.3%)	114 (93.4%)
		High - Change from Baseline	2 (4.7%)	1 (2.4%)	(0.0%)	3 (7.1%)	4 (3.3%)
		High - Sustained	3 (7.0%)	(0.0%)	(0.0%)	4 (9.5%)	4 (3.3%)
	Week 20	n	37	36	37	36	109
		Normal	32 (86.5%)	33 (91.7%)	33 (89.2%)	31 (86.1%)	97 (89.0%)
		High - Change from Baseline	4 (10.8%)	3 (8.3%)	3 (8.1%)	3 (8.3%)	9 (8.3%)
		High - Sustained	1 (2.7%)	(0.0%)	1 (2.7%)	2 (5.6%)	3 (2.8%)

High: >ULN; Low: <LLN.
Low @ Change from Baseline: Normal or high at baseline, but low post-baseline.
Low @ Sustained: Low at baseline, and low post-baseline.
Normal: Normal at visit.
High @ Change from Baseline: Normal or low at baseline, but high post-baseline.
High @ Sustained: High at baseline, and high post-baseline.

Source: Biostatistics [redacted] pgm(/allergy/ilr/gb27862/final/programs/t_lab_shift)
Database (LOCKED) Datasets (asl alb)
: Generated 09JAN14 07:40 Page 1 of 66

<table>
<tr>
<td>ID: LB005SP

Laboratory Test Shift Table: Highest NCI CTCAE Grade Post-Baseline: [High / Low] Hematology</td>
<td>
STREAM Template: LBT14

Analysis Population: Safety Evaluable Population

Mock format: See mockup below.

Analysis Variables: See LB001SP for parameters to be included and the appropriate analysis visits.

Include patients with a missing baseline value.

Statistics and Calculation Methods: Use CTCAE grades, as appropriate. Use all available post-baseline data, not just windowed (analysis visit) results.

Percentages are based on n.

Numeric Precision and Formatting of Statistics: See mockup (although we have just the one treatment group) – noting request above for rows to be presented.

Additional Outputs:

A similar output will be provided for the following safety lab categories:
<table>
<tr><td>ID</td><td>Lab Category</td></tr>
<tr><td>LB006SP</td><td>Chemistry</td></tr>
<tr><td>LB007SP</td><td>Urinalysis</td></tr>
</table>
</td>
</tr>
</table>

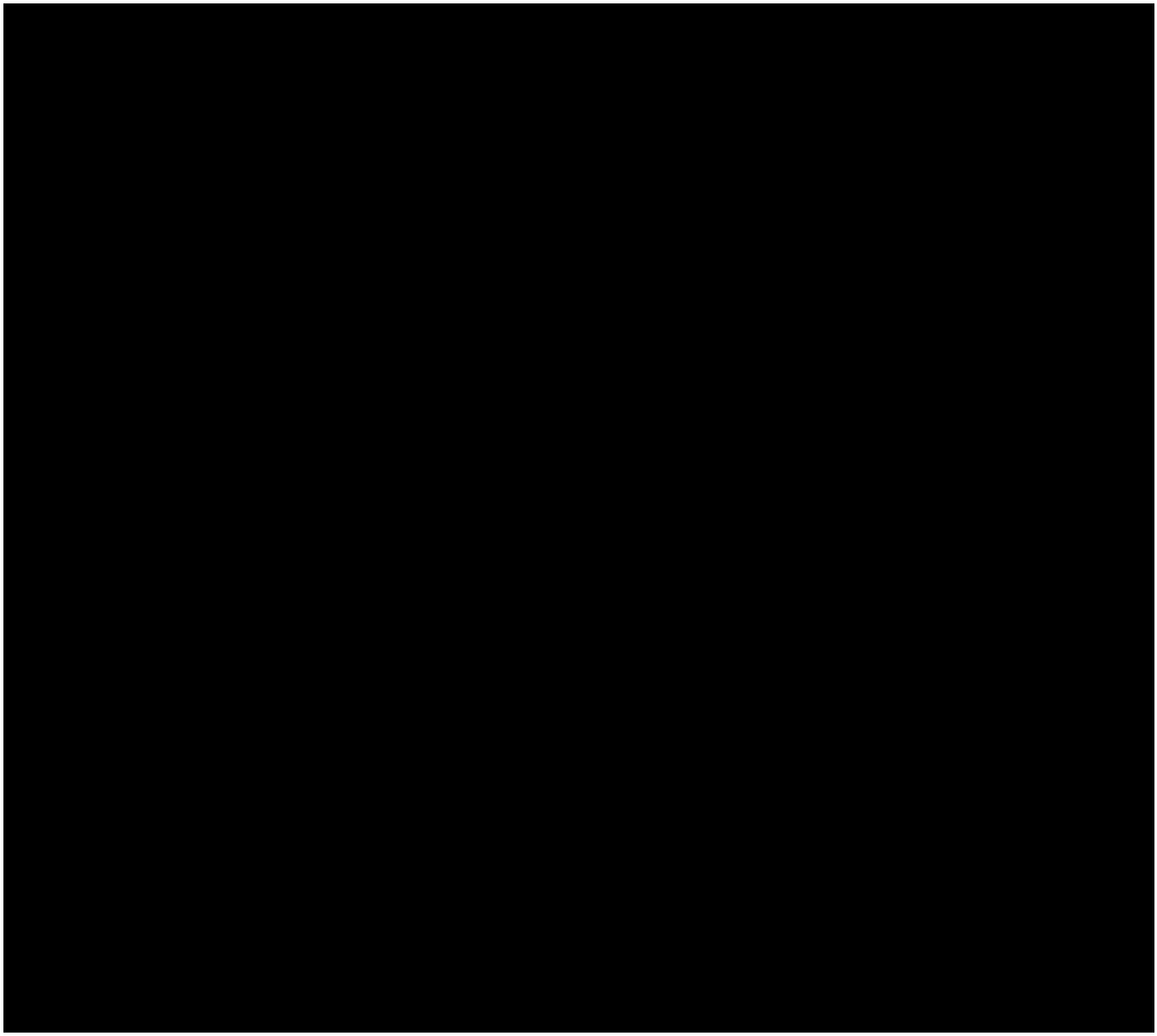
Absolute neutrophil count

Post-baseline NCI-CTCAE Grade	Baseline NCI-CTCAE Grade	Rituximab (N = nnn)
0	Total (n)	nn
	1	nn (xx.x%)
	2	nn (xx.x%)
	3	nn (xx.x%)
	4	nn (xx.x%)
	Missing	nn (xx.x%)
1	Total (n)	nn
	1	nn (xx.x%)
	2	nn (xx.x%)
	3	nn (xx.x%)
	4	nn (xx.x%)
	Missing	nn (xx.x%)
...		

ID: LB004SP Listing of Normal Ranges for Laboratory Tests	**STREAM Template:** None **Analysis Population:** Safety Evaluable Population **Variables Displayed:** Name of Lab test, Lab ranges Low-High under Lab Parameters (with unit), grouped by age and gender. **Numeric Precision and Formatting of Statistics:** See mockup

Lab Test	Lower Lab Range				Upper Lab Range				Unit
	Age		Gender		Age		Gender		
	<12	>=12	Female	Male	<12	>=12	Female	Male	
<Lab Test>	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx
	xx	xx	xx	xx	xx	xx	xx	xx	xx

ID: LB004.1SP Listing of lab abnormalities	**STREAM Template:** LBL02A **Analysis Population:** Safety Evaluable Population **Numeric Precision and Formatting of Statistics:** Add a column for "date of first drug administration" to LBL02A.



8. VITAL SIGNS OUTPUT SPECIFICATIONS

During treatment visits, vital signs (temperature, pulse and BP) are measured immediately prior to the infusion, then every 15 minutes during the infusion until one hour, followed by every 30 minutes until the end of the infusion; a further reading is taken at least one hour after completion of the infusion. These data will be summarized within each visit by planned assessment time-point and also as changes from the within-visit pre-infusion value.

Additionally, vital signs plus height and weight will be summarized descriptively by visit (using pre-infusion values when appropriate), including changes from the baseline pre-infusion value.

8.1 Vital Signs Output Specifications

ID: VS001SP Vital Sign Results and Change from Pre-infusion by Infusion Number in Remission Induction Phase	**STREAM Template**: VST01 **Analysis Population:** Safety Evaluable Population **Column Variables:** Value after infusion and Change from Pre-infusion. **Analysis Variables:** Separate tables in one file for each of: pulse rate (display as "heart rate" in the output), systolic blood pressure, and diastolic blood pressure. Use pre-infusion values only. Include planned infusions (in the remission induction phase). **Statistics and Calculation Methods:** Time-points to include are: pre-infusion and 0.25, 0.5, 0.75, 1, 1.5, 2, … 6 hours post-infusion. **Numeric Precision and Formatting of Statistics:** See mockup

Time-point Relative to Infusion Start		Value at Time-point	Change from Pre-infusion
Infusion 1			
Pre-infusion	n	nn	
	Mean (SD)	xxx.x (xx.x)	
	Median	xxx.x	
	Q1 – Q3 (IQR)	xx.x-xx.x(xx.x)	
	Min-Max	xxx.x-xxx.x	
0.25 hours Post	n	nn	nn
	Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
	Median	xxx.x	xxx.x
	Q1 – Q3 (IQR)	xx.x-xx.x(xx.x)	xx.x-xx.x(xx.x)
	Min-Max	xxx.x-xxx.x	xxx.x-xxx.x
Infusion 2 …			

ID: VS002SP Vital Sign Results and Change from Baseline by Visit	**STREAM Template**: VST01 **Analysis Population:** Safety Evaluable Population **Column Variables:** Value at visit and Change from Baseline. **Statistics and Calculation Methods:** Analysis visits to include are: Baseline, Weeks 1 to 3, Months 1, 2, 4, 6, 9, 12, 15 and 18. Values at visits to include only patients for whom a baseline value is included. **Numeric Precision and Formatting of Statistics:** See mockup

Visit		Value at Visit	Change from Baseline
Day 1 (Baseline)	n	nn	
	Mean (SD)	xxx.x (xx.x)	
	Median	xxx.x	
	Q1 – Q3 (IQR)	xx.x-xx.x(xx.x)	
	Min-Max	xxx.x-xxx.x	
Week 1	n	nn	nn
	Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
	Median	xxx.x	xxx.x
	Q1 – Q3 (IQR)	xx.x-xx.x(xx.x)	xx.x-xx.x(xx.x)
	Min-Max	xxx.x-xxx.x	xxx.x-xxx.x
Week 2	n	nn	nn
	Mean (SD)	xxx.x (xx.x)	xxx.x (xx.x)
	Median	xxx.x	xxx.x
	Q1 – Q3 (IQR)	xx.x-xx.x(xx.x)	xx.x-xx.x(xx.x)
	Min-Max	xxx.x-xxx.x	xxx.x-xxx.x
…			

ID: VS003SP Vital Sign Results and Changes from Baseline Above and Below Specified Limits by Visit	**STREAM Template**: None **Analysis Population:** Safety Evaluable Population **Analysis Variables:** Separate tables in one file for each of: pulse rate (display as "heart rate" in the output), systolic blood pressure, and diastolic blood pressure. **Statistics and Calculation Methods:** Use pre-infusion values only.Analysis visits to include are: Baseline, Weeks 1 to 3, Months 1, 2, 4, 6, 9, 12, 15 and 18. Values at visits to include only patients for whom a baseline value is included. Cut-off for each of the vital sign parameters are as follows:

		Value at Visit		Change from Baseline	
Vital Sign	Units	Low	High	Decrease	Increase
Pulse rate	beats/min	<50	>100	≥20	≥20
Systolic blood pressure	mmHg	≤90	≥140	≥20	≥20
Diastolic blood pressure	mmHg	≤50	≥90	≥15	≥15

As well as by-visit summaries, also summarise the number of patients who are low or high, or have a decrease/increase, at any post-baseline time-point. This will include <u>all</u> post-baseline data included in this analysis. A patient may count at most once towards the count on none, one or more of the 4 categories (see mockup).

Percentages are based on n.

Numeric Precision and Formatting of Statistics: See mockup

Visit		Rituximab (N = nnn)
Day 1 (Baseline)	n	nn
Value at Visit	<50	nn (xx.x%)
	≥50 to ≤100	nn (xx.x%)
	>100	nn (xx.x%)
Week 1	n	nn
Value at Visit	<50	nn (xx.x%)
	≥50 to ≤100	nn (xx.x%)
	>100	nn (xx.x%)
Change from Baseline	Decrease ≥20	nn (xx.x%)
	Increase ≥20	nn (xx.x%)
…		
Month 6	n	nn
Value at Visit	<50	nn (xx.x%)
	…	
Change from Baseline	…	
Any Post-baseline Value	n	nn
Values at Visits	<50	nn (xx.x%)
	>100	nn (xx.x%)
Changes from Baseline	Decrease ≥20	nn (xx.x%)
	Increase ≥20	nn (xx.x%)

ID: VS004SP Listing of Vital Sign Abnormalities	**STREAM Template**: LBL02A* (see mock) **Analysis Population:** Safety Evaluable Population **Numeric Precision and Formatting of Statistics:** See mockup Include patients with at least one post-baseline "abnormal" VS test. Flag high (H) and low (L) results.

Vital Sign Test (Unit)	Center / Patient ID	Age/Sex	Study Day	Date	Result	Normal Range
<Vital Sign Test> (<unit>)	xxxx/xxx	xx	xx	ddMMMYY	xx L	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx L	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx H	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx L	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx	xx–xx
	xxxx/xxx	xx	xx	ddMMMYY	xx H	xx–xx

9. EFFICACY ANALYSES

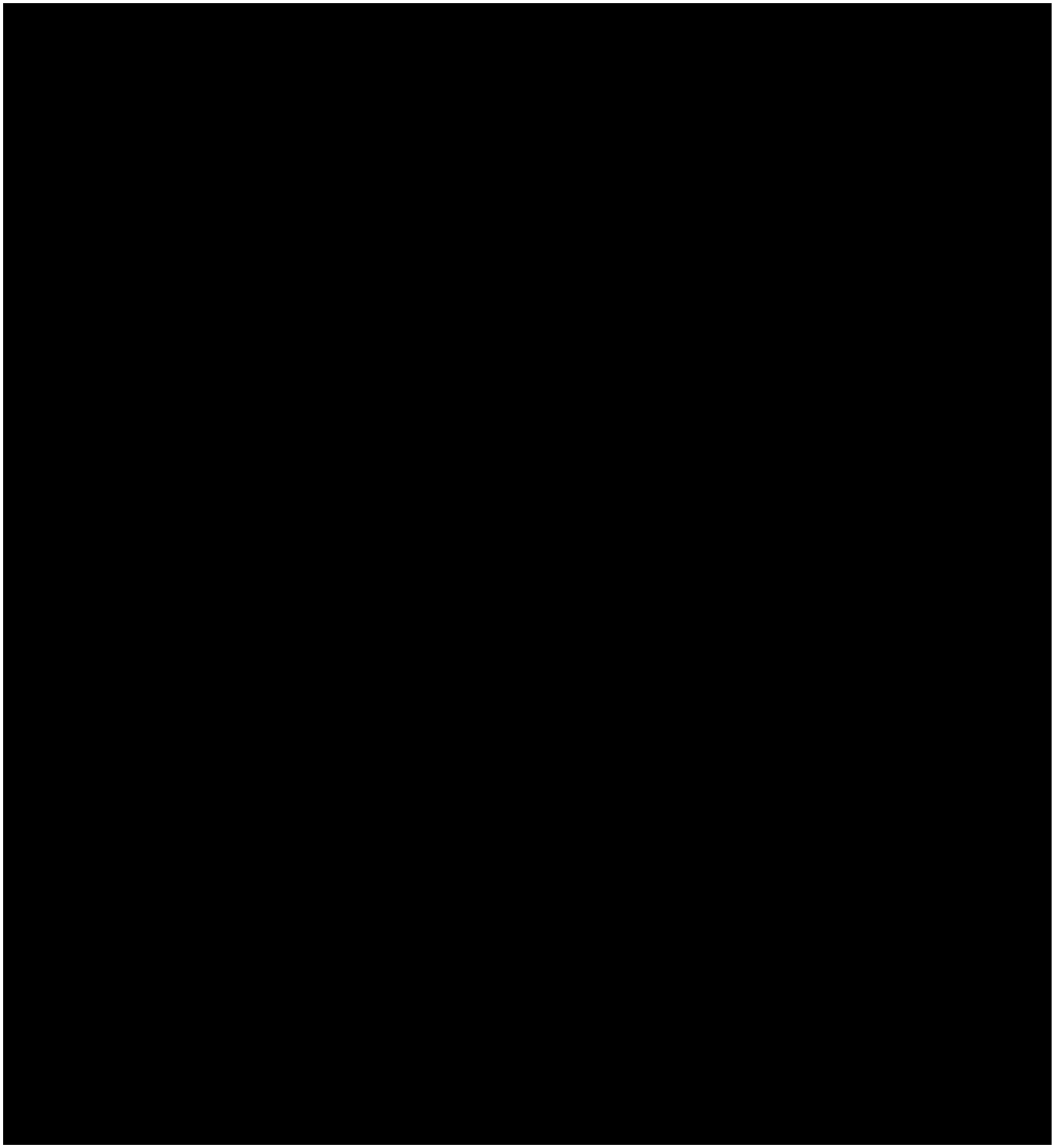
[redacted]

[redacted]

9.1 Efficacy Output Specifications

[redacted]

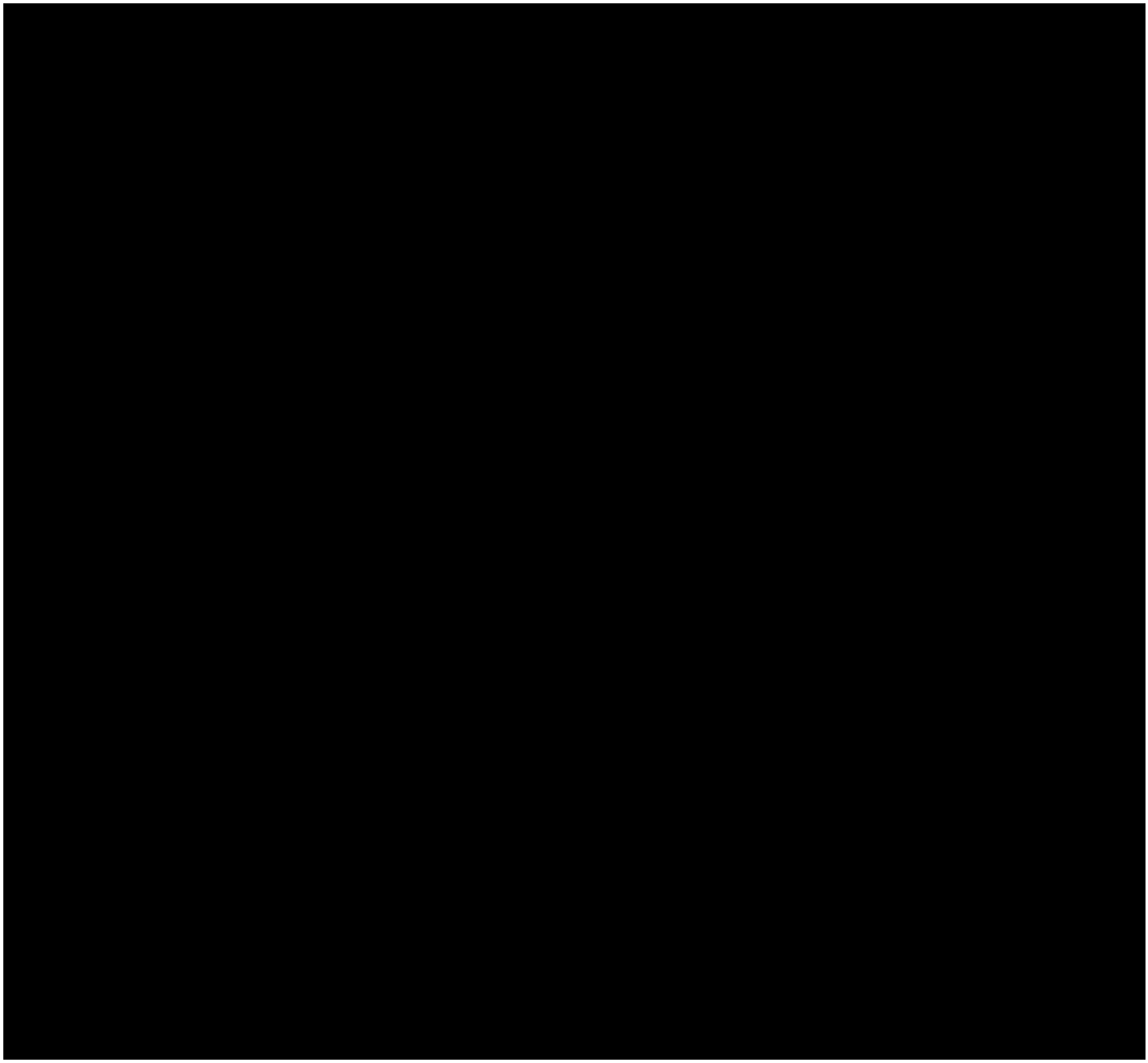
[redacted]

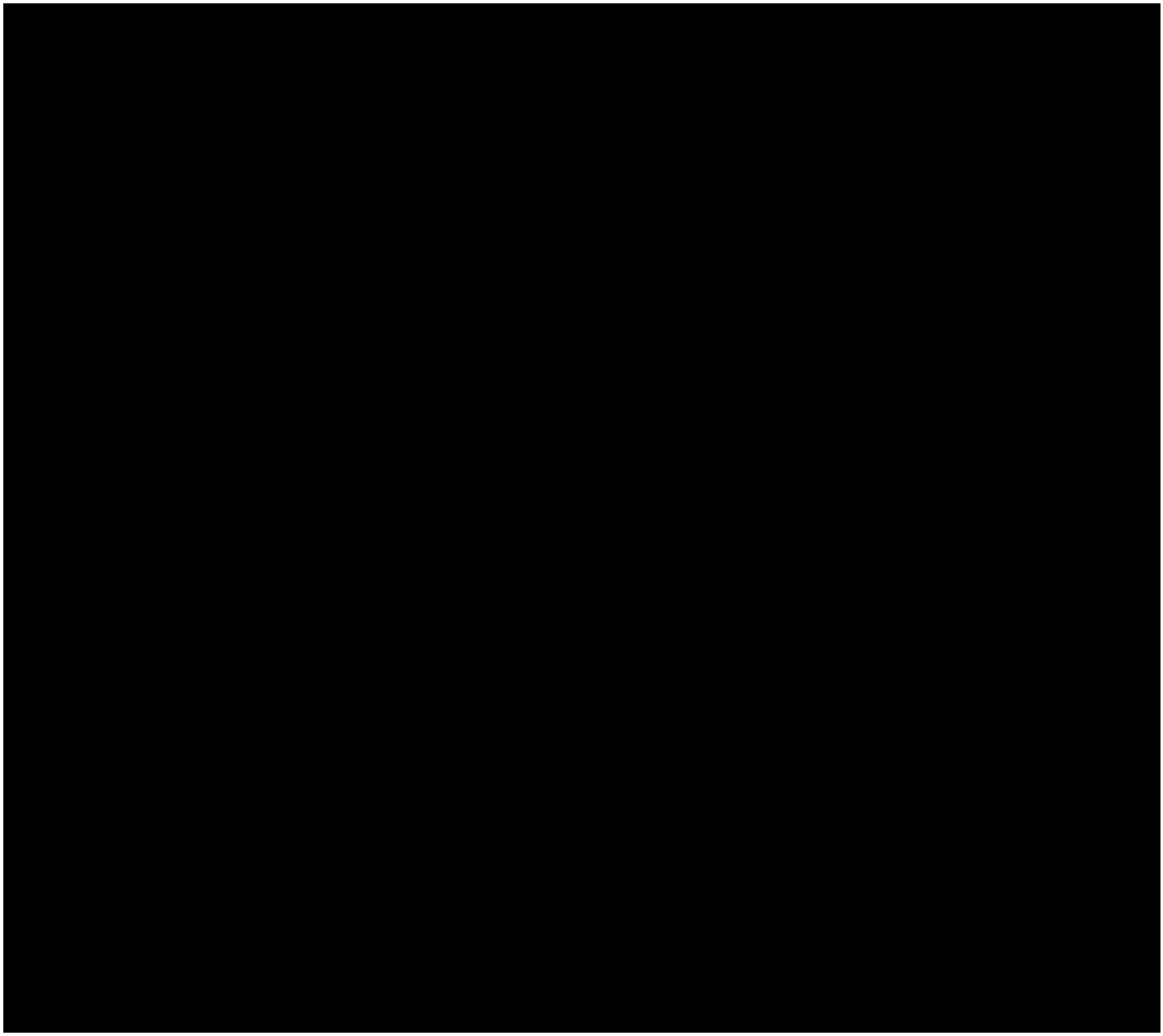


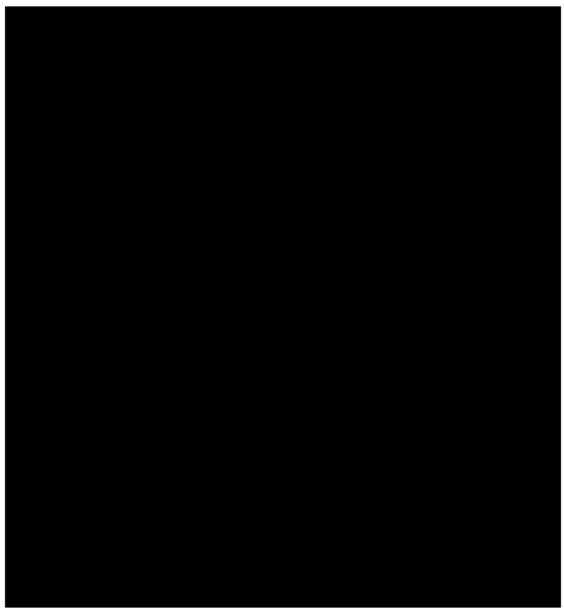
10. PHARMACODYNAMIC ANALYSES

[redacted]

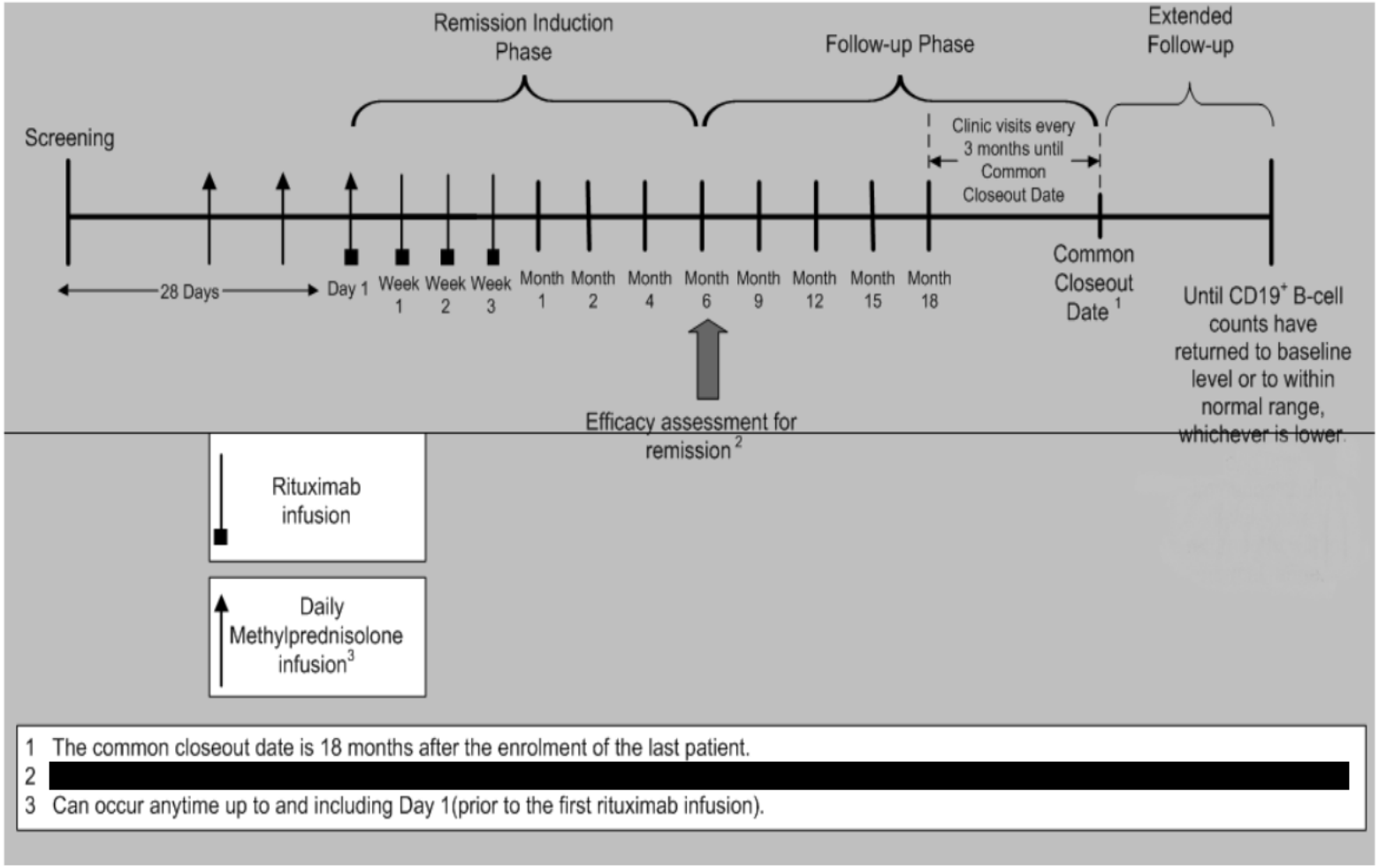
[redacted]







Appendix 1
Study Design



Appendix 2
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 2
Schedule of Assessments (cont.)

		Week				Month								Follow-Up		
Visit [a]	Screen [b]	BL [c]	1	2	3	1	2	4	6	9	12	15	18	Every 3 Months after Month 18 [d]	WD	Extended Follow-Up [e]
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 2
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.

[a] For visit windows, please refer to protocol 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.

[o] [redacted]

[p] [redacted]

[q] CD19 B-cell samples to be obtained prior to infusion of rituximab.

[r] [redacted]

[s] Fasting is not required.

[t] After screening, only if clinically indicated.

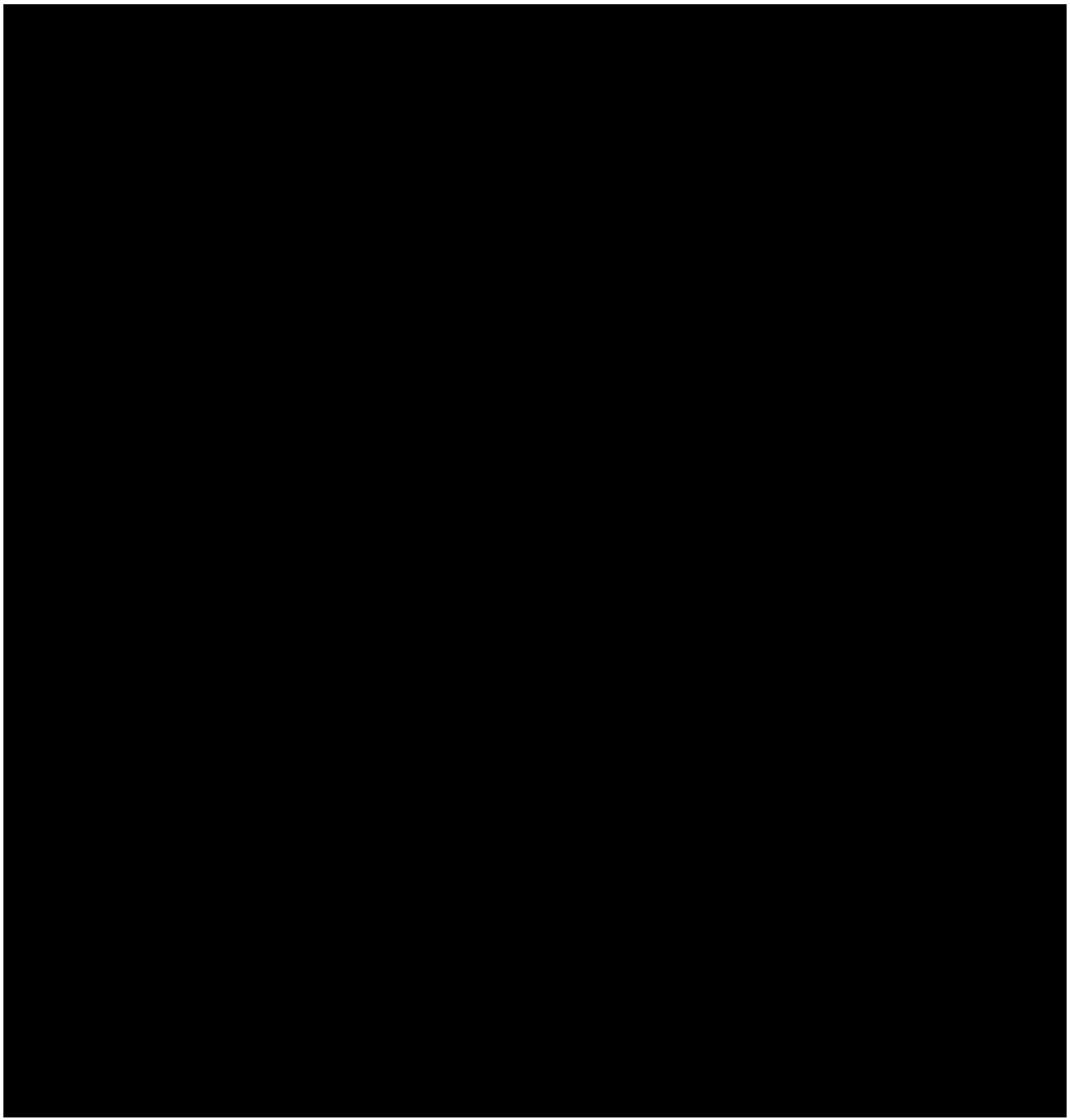
[u] After the Month 18 visit, samples should be taken every 6 months thereafter.

[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.



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