30 January 2020
EMA/CHMP/75432/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MabThera

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/000165/II/0162

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AAV	ANCA associated vasculitis
ADA	anti-drug antibody
ANCA	anti-neutrophil cytoplasmic antibodies
BSA	body surface area
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener's Granulomatosis
CARRA	North American Childhood Arthritis & Rheumatology Research Alliance
CCO	common closeout date
CHQ	Child Health Questionnaire
CHAQ	Childhood Health Assessment Questionnaire
EUVAS	European Vasculitis Study Group
GFR	glomerular filtration rate
GPA	granulomatosis with polyangiitis
IRR	Infusion-Related Reactions
IV	Intravascular
MPA	microscopic polyangiitis
MPO	myeloperoxidase
PD	pharmacodynamics
PGADA	Physician's Global Assessment of Disease Activity
PK	Pharmacokinetic
PR3	proteinase 3
PReS	Paediatric Rheumatology European Society
PRINTO	Paediatric Rheumatology International Trials Organization
PRO	patient-reported outcome
PVAS	Paediatric Vasculitis Activity Score
PVDI	Paediatric Vasculitis Damage Index
WG	Wegener's granulomatosis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 24 January 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of paediatric patients (aged ≥ 2 to <18 years old) with active polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA), for MA numbers EU/1/98/067/001-002 for MabThera; following efficacy and safety data from Clinical study report (CSR) WA25615 (also known as Paediatric Polyangiitis and Rituximab Study [PePRS]) which was conducted to fulfil the measure of the Paediatric Investigational Plan (PIP: EMEA-000308-PIP02-11-M01) agreed upon in the context of rituximab development for treatment of adult patients with GPA and MPA (RAVE study). The CSR for Study 1: WA 25615 was submitted on 30th Oct 2018 as the Post Approval Measure submission according to Article 46 requirement. Linked to this variation the final compliance check procedure to close the PIP has started 3rd January 2019.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 2, 3 and 4 of the Package Leaflet are updated accordingly. Furthermore, the PI is brought in line with the latest QRD template (version 10) and the opportunity is taken to combine the SmPC and PIL for 100mg and 500mg IV as they are identical except for strength specifications.
In addition, the applicant took the opportunity to implement minor editorial changes in the SmPC.

The RMP version 20.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0060/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0060/2016 was completed. However, the PIP P/128/2009 (and subsequent modifications thereof) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	24 January 2019
Start of procedure	1 March 2019
CHMP Co-Rapporteur's preliminary assessment report circulated on	25 April 2019
CHMP Rapporteur's preliminary assessment report circulated on	24 April 2019
PRAC Rapporteur's preliminary assessment report circulated on	2 May 2019
PRAC Rapporteur's updated assessment report circulated on	9 May 2019
PRAC RMP advice and assessment overview adopted by PRAC on	16 May 2019
Joint CHMP Rapporteurs' assessment report circulated on	23 May 2019
Request for supplementary information and extension of timetable adopted by the CHMP on	29 May 2019
MAH's responses submitted to the CHMP on	13 August 2019
Joint CHMP Rapporteurs' preliminary assessment report on the MAH's responses circulated on	26 September 2019
PRAC Rapporteurs' preliminary assessment report on the MAH's responses circulated on	25 September 2019
PRAC RMP advice and assessment overview adopted by PRAC on	3 October 2019
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on	11 October 2019
Second request for supplementary information and extension of timetable adopted by the CHMP on	17 October 2019
MAH's responses submitted to the CHMP on	7 November 2019
Joint CHMP Rapporteurs' preliminary assessment report on the MAH's responses circulated on	18 November 2019
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on	5 December 2019
Third request for supplementary information and extension of timetable adopted by the CHMP on	12 December 2019
MAH's responses submitted to the CHMP on	18 December 2019
Joint CHMP Rapporteurs' preliminary assessment report on the MAH's	15 January 2020

Timetable	Actual dates
responses circulated on	
CHMP opinion adopted on	30 January 2020

2. Scientific discussion

2.1. Introduction

Rituximab (MabThera) is a chimeric murine/human monoclonal antibody that binds to B-lymphocyte antigen CD20, a transmembrane protein that is present on B-lymphocytes which are implicated in lymphoma, leukemia and specific autoimmune diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis which include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The binding of rituximab to CD20 on B-lymphocytes promotes B-cell lysis via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.

Mabthera is currently registered in the following indications:

Non Hodgkin's lymphoma (NHL)

MabThera is indicated for the treatment of previously untreated patients with stage III IV follicular lymphoma in combination with chemotherapy.

MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabThera monotherapy is indicated for treatment of patients with stage III IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy.

See section 5.1 for further information.

Rheumatoid arthritis

MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying anti rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera has been shown to reduce the rate of progression of joint damage as measured by X ray and to improve physical function, when given in combination with methotrexate.

Granulomatosis with polyangiitis and microscopic polyangiitis

MabThera, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Pemphigus vulgaris

MabThera is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

Childhood- and adult-onset GPA and MPA are rare, potentially life- and organ-threatening systemic autoimmune diseases affecting small and medium-sized blood vessels. The most commonly affected organs in GPA and MPA include the upper respiratory tract (sinuses, nose, and trachea), kidneys, lungs and skin. Blood vessels in affected organs may become inflamed, and clusters of certain cells (granulomas) may occur. The onset of GPA or MPA may be slow with few symptoms, or rapid with severe progression. If untreated, GPA and MPA progress from limited disease processes (e.g., inflammation centred on the upper respiratory tract or lung) to a generalized phase characterized by multiple systemic or renal complications of small-vessel vasculitis.

Paediatric patients with GPA and MPA often present with clinical features of the disease similar to that of adult patients and share many signs and symptoms of the disease with adults (Calatroni et al. 2017). Childhood-onset GPA is associated with a higher prevalence of renal disease and nasal deformities at presentation and a higher overall incidence of subglottic stenosis over time than GPA in adults. In comparison to adult patients, paediatric patients are more likely to have multiple organ involvement, renal involvement, lower respiratory tract manifestations, and subglottic stenosis (Cabral et al. 2009, Akikusa et al. 2007).

Epidemiology

The incidence of GPA in paediatric patients in Europe ranged from 1.2 to 1.4 per million. The incidence of MPA in paediatric patients in Europe ranged from 1 to 1.4 per million. Within the US, the prevalence of GPA in paediatric patients ranged from 6.33 to 7.71 per million, and the prevalence of MPA in paediatric patients ranged from 2.73 to 3.51 per million. The evidence suggests that GPA and MPA are extremely rare in populations <18 years.

Current Treatment Options

In current adult practice, induction therapy typically consists of high dose glucocorticoids combined with either cyclophosphamide or rituximab, in order to rapidly reduce inflammation, ideally induce disease remission, and prevent permanent organ damage. In general, adverse effects of cyclophosphamide, including infertility, cytopenias, infections, bladder injury, and cancer, as well as the multiple adverse effects of lengthy courses of oral glucocorticoid treatment, are major causes of long-term morbidity and death.

Currently, there are no specific guidelines or recommendations for the treatment of paediatric GPA and MPA and treatment is adapted from available adult data with no clear guidance on dosage or duration of therapy in paediatric patients. Treatment decisions are based on clinical features of disease activity (as indicated by signs and symptoms of vasculitis) or remission, and corresponding laboratory tests including urinalysis for assessment of proteinuria, hematuria and worsening renal function.

Unmet medical need

There is a significant need to improve treatment options, as well as safety and efficacy outcomes, in paediatric GPA and MPA patients. Clinical trials and long-term outcome studies in paediatric vasculitis are lacking, except for retrospective analyses. As there are no guidelines for the treatment of paediatric patients with GPA or MPA, treatment of paediatric GPA or MPA relies on the studies performed in adults (Calatroni et al. 2017). The patients are often exposed to cytotoxic therapies for long periods along with high percentage of treatment failures and disease relapses. In clinical practice,

while paediatric patients respond to cyclophosphamide standard of care treatment, parents and caregivers frequently refuse treatment with cyclophosphamide and as a result, patients experience disease relapses and in some cases renal failure adding to the urgent need for acceptable alternative treatment options. Paediatric patients with GPA or MPA have limited treatment options and major unmet medical needs such as correct and early diagnosis, improved clinical remission rates, longer periods of disease control (prevention of disease flares), and reduction of toxicities associated with conventional glucocorticoids and current immunosuppressant therapies. These patients require access to safe and effective treatments that have been appropriately evaluated in the paediatric population within clinical trial settings.

Rituximab, already approved in adult patients with GPA and MPA for remission induction and as follow-up treatment to control disease activity/maintenance treatment, offers a therapy with a mode of action that could be associated with significant clinical benefits in paediatric patients with GPA and MPA.

Study WA25615 (also known as Paediatric Polyangiitis and Rituximab Study [PePRS]) was conducted to fullfil the measure of the Paediatric Investigational Plan (PIP: EMEA-000308-PIPO2-11) agreed upon in the context of rituximab development for treatment of adult patients with GPA and MPA (RAVE study). The PIP was initially agreed in 2012 with subsequent modification approved on 18 March 2016. The data supporting this application are based on the safety, PK/PD, and exploratory efficacy results from Study WA25615. In fulfillment of the Article 46 requirement, the MAH submitted the final CSR for study WA25615 via an Article 46 procedure P-46 97. The MAH then submitted the present application.

With this application, the MAH has sought the following indication:

MabThera, in combination with glucocorticoids, is indicated for the treatment of paediatric patients (aged ≥ 2 to < 18 years old) with active GPA (Wegener's) and MPA.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The pharmacologically active substance in MabThera, Rituximab, is a recombinant immunoglobulin-G monoclonal antibody with a molecular mass of approximately 145 kD. As an unaltered protein, Rituximab is predicted to be metabolised by regular proteinolysis in the patient and biodegraded in sewage treatment, as shown for other monoclonal antibodies. Also, the antibodies tested for acute ecotoxicity for labelling and classification purposes were not noticeably ecotoxic. Rituximab is unlikely to cause a significant risk to the environment and therefore does not need a formal ERA according to the EMA 2006 Guideline [EMEA/CHMP/SWP/4447/00 corr. 2].

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of rituximab.

Considering the above data, rituximab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The clinical data package for this variation consists of a single-arm open-label trial (WA25615) of remission induction using rituximab and corticosteroids, in paediatric patients older than 2 years of age with new onset or relapsing GPA or MPA, and of the post-marketing safety experience in paediatric patients older than 2 years of age, treated with rituximab for non-oncological conditions (off-label).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No. (Phase)	Study Title	Study Objectives	Population	Dose, Route, and Regimen	No. of Patients
Study WA25615 (Phase IIa)	A Phase IIa, international, multicenter, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4×375 mg/m^2 intravenous rituximab in paediatric patients with severe granulomatosis with polyangiitis (GPA) or microscopic	Primary Safety Objective To evaluate the safety and tolerability of rituximab in paediatric patients with severe GPA or MPA. Primary PK Objective To evaluate the PK parameters of rituximab in paediatric patients with severe GPA or MPA. Exploratory Efficacy Objective To assess the efficacy of rituximab for the induction of remission in paediatric patients with severe GPA or MPA.	Key Inclusion Criteria: Age at screening between ≥2 and <18 years Diagnosis of GPA (EULAR/PRINTO/PRES 2008, Ankara criteria for childhood WG [Özen et al. 2010]) or diagnosis of MPA (according to the Chapel Hill Consensus Conference [Jennette 1994]) 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	In the initial 6-month Remission Induction Phase of treatment, patients with newly diagnosed or relapsing GPA or MPA received 4 intravenous (IV) rituximab infusions of 375 mg/m^2 body surface area (BSA) on Days 1, 8, 15 and 22 with oral prednisolone or prednisone 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6. Patients were to receive 3 doses of methylprednisolone IV (30 mg/kg/day, max 1 g/day) prior to first rituximab infusion any time	25

	polyangiitis (MPA)	Other exploratory objectives for the study were : • PD parameters of rituximab in paediatric patients with GPA or MPA • The effect of rituximab on patient quality of life and disability/functioning, as assessed using the Child Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ), respectively.	more major BVAS/WG items per WA25615 Protocol or disease severe enough to require treatment with cyclophosphamide). Key Exclusion Criteria: Severe disease requiring mechanical ventilation due to alveolar hemorrhage. Requirement for plasmapheresis or dialysis at screening.	after screening, up to and including Day 1. After the 6 month Remission Induction Phase, patients entered the minimum 12-month Follow-Up Phase and could receive additional rituximab or other treatment for GPA/MPA in accordance with local standard of care, at the discretion of the investigator. Therefore all patients were followed for a minimum of 18 months in total.	

2.3.2. Pharmacokinetics

A primary objective of study WA25615 was to evaluate the PK parameters of rituximab in paediatric patients with severe GPA or MPA. Similar to the RAVE study in adults, the rituximab dosing regimen for induction of remission was 4 weekly IV doses of 375 mg/m2. The paediatric study included measurement of rituximab concentrations, anti-drug antibodies (ADAs), CD19+ B cells and also explored any potential relationship between rituximab exposure and safety or efficacy.

The PK data in paediatric population were analysed with those obtained in adults with GPA or MPA to confirm the suitability of the dosing regimen in paediatric patients and through extrapolation of the adult data, support a new indication for the treatment of paediatric patients with GPA or MPA.

The approved rituximab IV infusion drug was also used in Study WA25615. No change was made to the manufacturing process or formulation.

Validated enzyme-linked immunosorbent assays (ELISA) were used to measure drug levels in serum as well as measurements of serum ADA.

Pediatric study WA25615

Study WA25615 was a Phase IIa, multicenter, open-label, single-arm study where 25 pediatric patients, were enrolled with a median age of 14 years (range 6 to 17 years) across 11 sites in 6 countries. Children aged 2 to 11 years and adolescents aged 12 to < 18 years were eligible in the study, however, no children < 6 years of age were included in the study. An overview of demographic and baseline characteristics is provided in Table 1. The majority of patients were female (20 patients

[80%]), White (17 patients [68%]) and between 12 and 17 years of age (19 patients [76%]). The median body surface area was 1.45 m2 (range: 0.88-1.9 m2).

Table 1 Demographic and baseline characteristics patients in study WA25615

	Rituximab (N=25)
Age (yr)	
n	25
Mean (SD)	13.4 (2.9)
Median	14.0
Q1 - Q3 (IQR)	12.0 - 16.0 (4.0)
Min - Max	6 - 17
Age group (yr)	
n	25
2 to 11	6 (24.0%)
12 to 17	19 (76.0%)
Sex	
n	25
Male	5 (20.0%)
Female	20 (80.0%)
Race	
n	25
Asian	4 (16.0%)
Black or African American	1 (4.0%)
White	17 (68.0%)
Multiple	1 (4.0%)
Other	2 (8.0%)
Height (cm)	
n	25
Mean (SD)	153.22 (14.03)
Median	154.90
Q1 - Q3 (IQR)	146.00 - 161.00 (15.00)
Min - Max	120.0 - 175.2
Weight (kg)	
n	25
Mean (SD)	50.12 (15.25)
Median	50.90
Q1 - Q3 (IQR)	37.30 - 62.70 (25.40)
Min - Max	23.0 - 80.8
Body-mass index (kg/m2)	
n	25
Mean (SD)	20.95 (4.31)
Median	20.68
Q1 - Q3 (IQR)	18.03 - 22.32 (4.30)
Min - Max	15.7 - 32.2

Patients with newly diagnosed or relapsing GPA or MPA received 4 intravenous (IV) rituximab infusions of 375 mg/m2 BSA (at screening) on Days 1, 8, 15, and 22 with a tapering course of oral prednisolone or prednisone.

Serum samples for measurement of rituximab concentrations were collected prior to the first, second, third, and fourth infusions and after completion of the first and fourth infusions; and then subsequently on days 29 (Month [M]1), 60 (M2), 120 (M4), 180 (M6), 270 (M9), and 545 (M18).

Blood samples to determine ADAs were collected at baseline, M4, M6, M9, M18, and every 3 months following the M18 assessments.

Blood samples for CD19+ cell counts were collected at baseline, at Week 2, M4, M6, M9, M12, M15, and M18.

In the PK analysis population, non-linear mixed-effects modelling technique was used to analyse the PK data with the population PK model developed from adult patients with GPA and MPA in the RAVE study. The primary PK parameters were CL and volume of distribution. The secondary PK parameters (AUC0-inf, Cmax) were calculated for each patient. PK concentrations were summarized by visit. PK parameters were tabulated and summarized (i.e., by mean, SD, coefficient of variation, median, and minimum and maximum). PK exposure and response relationships were also explored graphically and for some parameters using logistic regression.

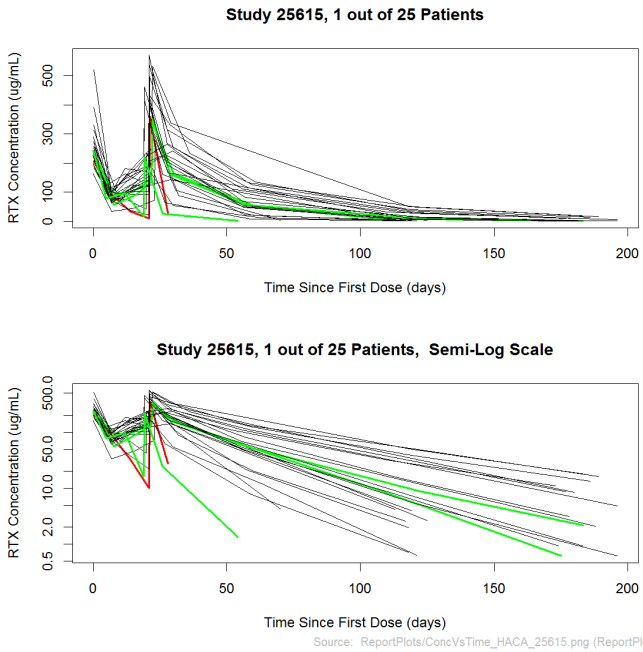
Results:

Main baseline covariates of paediatric patients are summarized in the table below:

Table 2 Summary of continuous covariates in paediatric patients

Covariate	Description	Median [Range] (N=25 patients)
AGE	Age (years)	14 [6 - 17]
BW	Weight(kg)	50.9 [23 - 80.8]
BSA	Body surface area (m^2)	1.45 [0.876 - 1.9]
BBCE	B Cell Count (10^6/L)	603 [197 - 2170]

Individual rituximab serum concentration profiles observed in paediatric patients following 4 weekly IV doses of 375 mg/m2 of rituximab are shown in Figure 1. Paediatric patients with ADA (N=4/25) are highlighted.



Observed serum concentrations (μg/mL) versus time after the first dose (days) for the one patient that did (**red**) or did not (**black**) have ADAs during the remission induction period (6M). Three more patients had ADA detected at Month 18 visit.

Figure 1 Observed Individual Serum Concentrations for Paediatric Patients with and without ADAs in first 6 months

Summary statistics of predicted Cmax and Cmin after each of the 4 rituximab doses are shown in Table 4. Summary Statistics of Rituximab PK Parameters from paediatric patients see table 3 (Final popPK model).

Table 3 Summary of individual PK parameters, study WA25615

Parameter Definition	Geometric Mean (CV%) (N=25 patients)
Clearance (CL) (mL/day)	204 (0.414)
Central volume of distribution (V_C) (mL)	2220 (0.212)
Volume of distribution at steady-state (V_{ss}) (mL)	4870 (0.244)
Effective half-life ($t_{1/2,eff}$) (day)	16.5 (0.7)

Table 4 Summary of predicted maximum (Cmax) and minimal (Cmin) serum concentrations in paediatric patients with GPA/MPA following 1st, 2nd, 3rd and 4th IV dose of rituximab 375 mg/m2 (study WA25615)

Rituximab IV dosing	1st dose	2nd dose	3rd dose	4th dose*
Cmax (µg/mL)	230 (0.166)	305 (0.181)	353 (0.183)	378 (0.174)
Cmin (µg/mL)	79.4 (0.297)	116 (0.35)	147 (0.343)	168 (0.354)

Population PK analysis report No 1090451

In the Pop PK analyses, rituximab clinical pharmacology in pediatric patients with GPA or MPA, from the WA25615 study were combined with the data from the RAVE study (adult patients with ANCA-Associated Vasculitis (Study ITN021AI)).

A total of 204 PK serum concentrations from the Remission Induction Phase of Study WA25615 were pooled with 487 serum concentrations from 97 adult patients from the RAVE. As not all patients received further rituximab doses after the Remission Induction Phase, the PK analysis was restricted to induction only. In total, 691 samples from 122 patients with GPA or MPA who received at least 4 weekly IV doses of 375 mg/m2 of rituximab were included in a population PK analysis (Table 5).

Table 5 Summary of Studies Used in Population PK Analysis

Study # (name)	Populations	Design	RTX treatment	# Patients contributing PK	# PK Samples
WA26615 (PePRS)	Paediatric GPA/MPA	Open label, uncontrolled single arm	375 mg/m^2 once weekly X 4	25	204
ITN021AI (RAVE)	Adult GPA/MPA	Double-blind, placebo controlled	375 mg/m^2 once weekly X 4	97	487

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; PK=pharmacokinetic; RTX = rituximab.

A summary of key patient characteristics by study and overall is provided in Table 6.

Table 6 Summary of Key Baseline Characteristics in Paediatric and Adult Studies

Covariate	Description	Overall	Paediatric Study (PePRS)	Adult Study (RAVE)
	Number of patients	122	25	97
AGE	Age [range] (years)	50 [6-92]	14 [6 - 17]	55 [16-92]
BW	Weight [range] (kg)	73.9 [23-128]	50.9 [23 - 80.8]	80.5 [47.3-128]
BSA	Body surface area [range] (m^2)	1.84 [0.88-2.45]	1.45 [0.88 - 1.9]	1.9 [1.43-2.45]
BBCE	B Cell Count [range] (10^6/L)	273 [9.72-2320]	603 [197 - 2170]	221 [9.72-2320]
SEX	Male number (%)	50 (41%)	5 (20%)	45 (46.4%)
	Female number (%)	72 (59%)	20 (80%)	52 (53.6%)

BBCE=B-cell count; BSA=body surface area; BW=body weight. Results of continuous covariates are presented as median (range). For categorical covariates, results are N(%).

Samples for rituximab concentration levels taken after the end of the first treatment period (37 non-BLQ concentrations from 17 paediatric patients) and samples below limit of quantification (BLQ) taken before the first dose were excluded from the analysis and from all summaries. There were 258 (27.2% of all observations) post-dose BLQ samples. A large fraction of BLQ observations is due to the

extensive sampling during times where concentrations are expected to be BLQ (up to 4 years post-dose). Specifically, among 258 BLQ samples 43 were within 180 days post-dose (or less) while 155 were collected at post-dose time points exceeding 1 year.

Model development

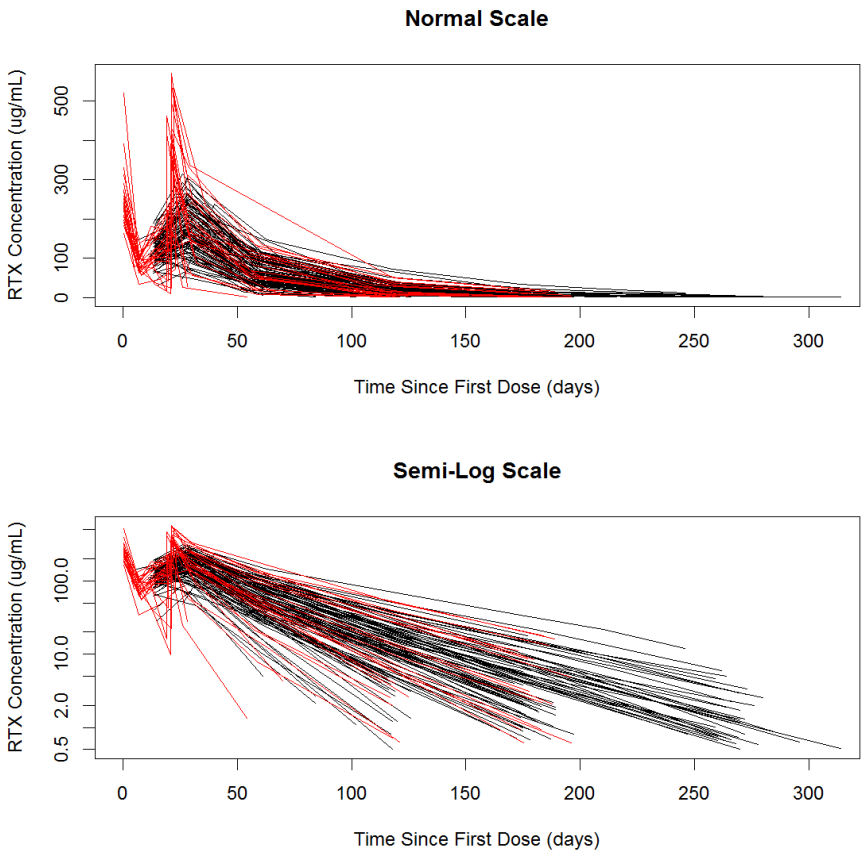
The population PK analysis was conducted via nonlinear mixed-effects modelling with the NONMEM software, Version 7.4.1 (ICON Development Solutions). Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R for Windows (R project, http://www.r-project.org/). The first-order conditional estimation with INTERACTION option (FOCEI) method in NONMEM was employed for all model runs.

In adult GPA and MPA patients from the RAVE study, rituximab pharmacokinetics was described by a two-compartment linear model. Sex and ADA were significant covariates on rituximab clearance, while sex and BSA were impacting central volume of distribution. Therefore, the two-compartment linear model was used in the current pooled analysis.

Structural model refinement was driven by the data and was based on various goodness-of-fit indicators, including visual inspection of diagnostic scatter plots (observed vs. predicted concentration, conditional weighted residual vs. predicted concentration or time, histograms of individual random effects, etc.), plausibility of parameter estimates, precision of the parameter estimates, the minimum objective function value (OF) and the number of estimated parameters.

Potential covariate-parameter relationships were identified based on scientific interest, mechanistic plausibility, and exploratory graphics, and added to the full model. Interpretation and refinement of the covariate model were based on point estimates, confidence intervals, diagnostic plots of the covariate effects, and on the objective function value. Covariate effects not supported by the data (effects close to null value, with high relative standard error and with the 95% confidence intervals [CI] that included the null value) were excluded.

Individual rituximab serum concentration profiles observed in paediatric and in adult GPA or MPA patients following 4 weekly IV doses of 375 mg/m2 of rituximab are shown in the figure below:



Observed serum concentrations (μg/mL) versus time after the first dose (days) for patients from Study WA25615 (**paediatric in red**) or Study ITN021A (**adults in black**).

Figure 2 Observed Individual Serum Concentrations for Paediatric and Adult Patients

Rituximab serum concentrations were in both children adults described by a 2-compartment PK model with linear elimination. In the population PK model previously developed in adults with GPA or MPA, sex and ADA were significant covariates on rituximab clearance, while sex and BSA were impacting central volume of distribution. In this updated analysis, model parameters were similar to the ones from the RAVE population PK model. The final model is described in the Table below.

Table 7 Parameter Estimates for the Final Model

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage (%)
CL (mL/day)	θ_1	258	4.22	236 - 279		
V_C (mL)	θ_2	3070	9.3	2510 - 3630		
V_P (mL)	θ_3	4160	3.59	3870 - 4450		
Q (mL/day)	θ_4	317	4.85	287 - 347		
CL, V_C ~ BSA	θ_5	0.952	19.6	0.587 - 1.32		
CL~ ADA	θ_6	1.38	9.9	1.11 - 1.65		
Q, V_p ~ BSA	θ_7	1.48	12.7	1.12 - 1.85		
ω^2_{CL}	Ω(1,1)	0.126	15.4	0.0881 - 0.164	CV=35.5%	2.1%
ω^2_{Vc}	Ω(2,2)	0.0402	50.4	0.000504 - 0.0799	CV=20.1%	60.7%
ω^2_{Vp}	Ω(3,3)	0.0553	18.6	0.0352 - 0.0754	CV=23.5%	16.4%
σ^2	Σ(1,1)	0.0393	2.7	0.0372 - 0.0414	CV=19.8%	15.8%
$t_{1/2,term}$ (day)		25.6				

ADAs=anti-drug antibodies; BSA=body surface area; CL=clearance; CV=coefficient of variance; RSE= relative standard error; Q= intercompartmental clearance; V_C=central volume of distribution; V_P = peripheral volume of distribution.

Model parameters for a typical patient (BSA=1.9 m2 and absence of ADA), i.e., clearance (258 mL/day), inter-compartment clearance (317 mL/day), central volume (3070 mL), peripheral volume (4160 mL), and terminal half-life (25.6 days) were in the typical range for monoclonal antibodies.

The visual predictive check plots (Figure 3) and NPDE plots (Figure 4) indicate a good agreement between the simulated and observed data during the first treatment period and the absence of any covariate trends. After accounting for covariate dependencies, the model correctly predicts the central trend of the data for both studies. Variability seems to be slightly higher in observed data for the paediatric Study WA25615 but this could be related to the small sample size of this study. Result of model evaluation indicated that the final model (Model 014) provided a good description of data observed during the remission induction phase, and it can be used to predict rituximab exposure for the exposure response analyses.

For the adult study, the lines show median (red), and the 10th and 90th percentiles (blue) of the observed concentrations. For the pediatric study, the lines show median (red), and the 25th and 75th percentiles (blue) of the observed concentrations. The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 500 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.

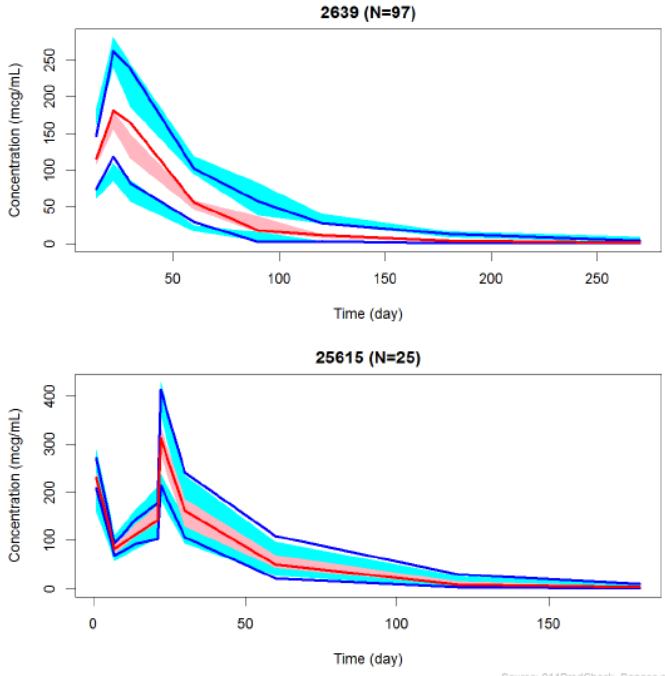


Figure 3 Visual predictive check for model 014, by study: original scale

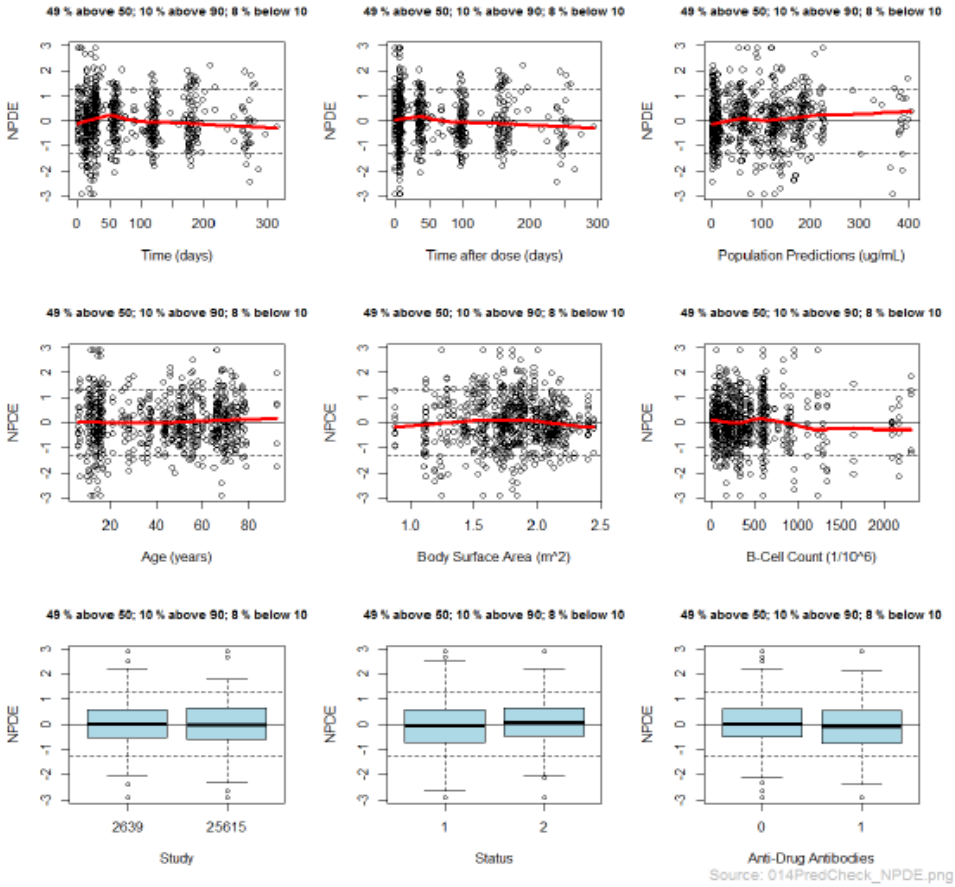


Figure 4 NPDE versus Time, Time after Dose, Population Predictions, and Covariates, Model 014

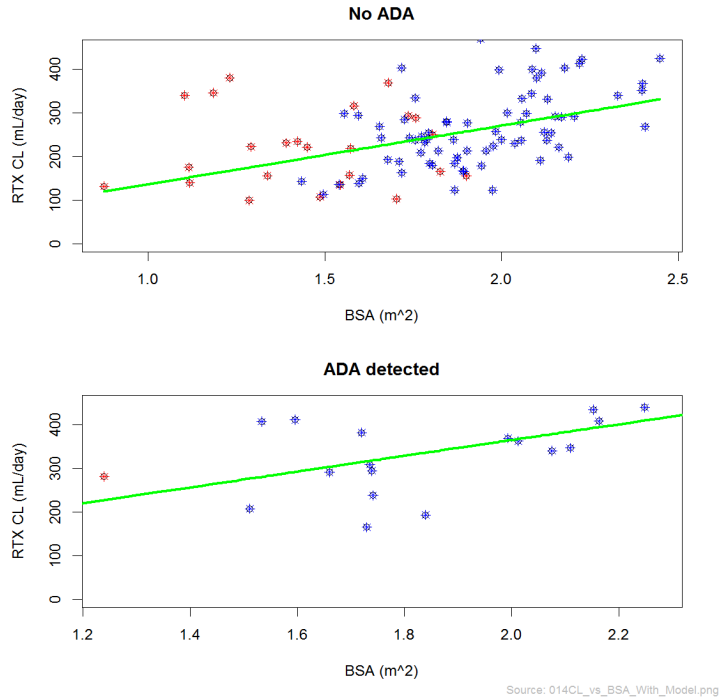
Impact of Body Surface Area and ADA on rituximab PK

Body surface area (BSA) and presence of anti-drug antibodies (ADA) were the only two significant covariates impacting rituximab exposure.

Clearance (CL), and central volume of distribution (VC) values were 39.5% lower for BSA of 1.12 m2 and 24.9% higher for BSA of 2.4 m2 compared to the respective values of patients with BSA=1.9 m2. Patients with detected ADA had 38.2% higher clearance resulting in 27.6% lower AUC.

As a consequence of the BSA effect on rituximab PK parameters, the clearance of paediatric patients was lower than for adult patients; but the exposures of paediatric and adult patients were similar. As the dose administered to each patient was proportional to BSA, it was lower in the paediatric patients, compensating for lower clearance.

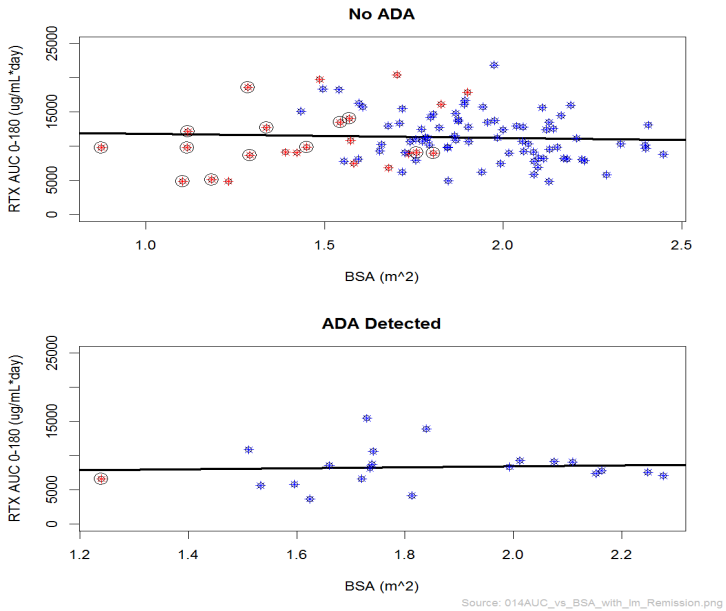
Rituximab clearance increase with BSA, as shown in figure 3 for the overall (i.e. paediatric and adult) antibody positive and antibody negative populations is described by the following relationship: CL= θ_{CL} X (BSA/1.9) $^{0.952}$ X 1.38*ADA where θ_{CL} is a typical value of clearance in milliliters per day (mL/day) for a typical patient (i.e., Body Surface Area [BSA] of 1.9 m^2 and absence of anti-rituximab antibodies [ADAs]) and is equal to 258 mL/day). The strong relationship between BSA and CL can also be seen in the exponent value of 0.952, which describes the BSA CL relationship.



CL=rituximab clearance. **Red**: predicted individual CL values for paediatric study; **Blue**: predicted individual CL values for adult study; **Green line**: model prediction of CL. All four patients considered ADAs positive in the entire study included. CL= θCL X (BSA/1.9) 0.952 X 1.38*ADA with θCL, the typical value of clearance in (mL/day) for a typical patient (i.e., BSA of 1.9 m^2 and absence of ADA) and is equal to 258 mL/day)

Figure 5 Relationships of Rituximab Clearance with Body Surface Area in Paediatrics and Adults, by ADA Detection Categories

While rituximab clearance increases with BSA, since rituximab is administered based on mg/m^2, the exposure is the same across the entire range of BSA values, as shown in the figure below.



AUC_{180}=rituximab AUC over the first 180 days. **Red**: predicted individual AUC_{180} values for paediatric study; **Blue**: predicted individual AUC_{180} values for adult study; **Black**: linear regression lines. Paediatric patients in remission by Month 6 are shown by larger circles.

Figure 6 Relationships of Rituximab AUC with Body Surface Area in Paediatrics and Adults, by ADA Detection Categories

The CHMP noted that as in adults, BSA has a significantly impact on volume of distribution and clearance in paediatric subjects. Rituximab CL and volume of distribution were lower in paediatric patients than in adults.

The lower BSA in paediatric subjects compared to adult subjects is compensated for by the BSA-adjusted dosing regimen. Therefore, the BSA-adjusted dosing regimen of 4 weekly IV doses of rituximab 375 mg/m2 ensured similar exposure between adult and paediatric patients with GPA or MPA.

The Pop PK model has adequately confirmed that a similar rituximab dosing regimen result in similar paediatric and adult rituximab exposure.

Comparison of rituximab pharmacokinetics in paediatric and adult patients with GPA/MPA

Summary statistics of rituximab PK parameters from paediatric and adult patients (Final popPK Model) are shown in the table below.

Table 8 Summary of Predicted Individual Exposures by Study

Parameter	Statistic	Study	
		Paediatric Study (PePRS)	Adult Study (RAVE)
N	Number of patients	25	97
C_{max} (µg/ml)	Mean (SD)	390.4 (68.5)	376.3 (42.1)
	Median (Range)	382.8 (270.6-513.6)	372.6 (252.3-533.5)
	Geometric Mean (CV)	384.5 (0.18)	374 (0.11)
C_{180} (µg/mL)	Mean (SD)	3.8 (5.5)	3.9 (4.9)
	Median (Range)	0.9 (0-17.7)	2.1 (0-29.3)
	Geometric Mean (CV)	0.9 (2.09)	1.4 (1.9)
AUC_{180} (µg/mL*day)	Mean (SD)	10996 (4594)	10720 (3494)
	Median (Range)	9787 (4838-20446)	10302 (3653-21874)
	Geometric Mean (CV)	10120 (0.42)	10143 (0.34)

AUC_{180} =cumulative exposure from day 0 to day 180; C_{max} =maximum serum concentration of rituximab during the first 180 days; C_{180} = rituximab concentration at the day 180.
CV was computed as standard deviation of the log-transformed data.

The PK parameters in paediatric patients and in adults are summarized in the table below. Consistent with the relationship between the PK parameters and BSA, rituximab CL and volume of distribution (Vc and steady-state volume of distribution [Vss]) were lower in paediatric patients than in adults, with a similar terminal elimination t1/2 in both paediatric population and adults.

Table 9 Summary of Predicted Individual PK Parameters by Study

Parameter [model estimate]	Statistic	Study	
		Paediatric (WA25615)	Adult (ITN021AI)
N	Number of patients	25	97
CL (mL/day) [155]	Mean (SD)	221 (87.2)	295 (112)
	Median (Range)	222 (99.6-381)	279 (113-653)
	Geometric Mean (CV)	204 (0.414)	275 (0.381)
V_C (mL) [3049]	Mean (SD)	2270 (468)	3110 (354)
	Median (Range)	2280 (1430-3170)	3120 (2420-3910)
	Geometric Mean (CV)	2220 (0.212)	3090 (0.116)
V_{SS} (L) [6071]	Mean (SD)	5000 (1180)	7510 (1470)
	Median (Range)	5040 (2710-7840)	7590 (4290-10900)
	Geometric Mean (CV)	4870 (0.244)	7360 (0.201)
$t_{1/2,term}$ (day) [29.6]	Mean (SD)	24.3 (8.8)	26.6 (8.6)
	Median (Range)	21.6 (11.3-41.5)	25.3 (10.7-51.7)
	Geometric Mean (CV)	22.8 (0.36)	25.1 (0.34)
$t_{1/2,eff}$ (day) [27.1]	Mean (SD)	18.3 (8.7)	20.1 (7.9)
	Median (Range)	15.3 (7-36.7)	18.8 (6.1-45.4)
	Geometric Mean (CV)	16.5 (0.47)	18.5 (0.41)

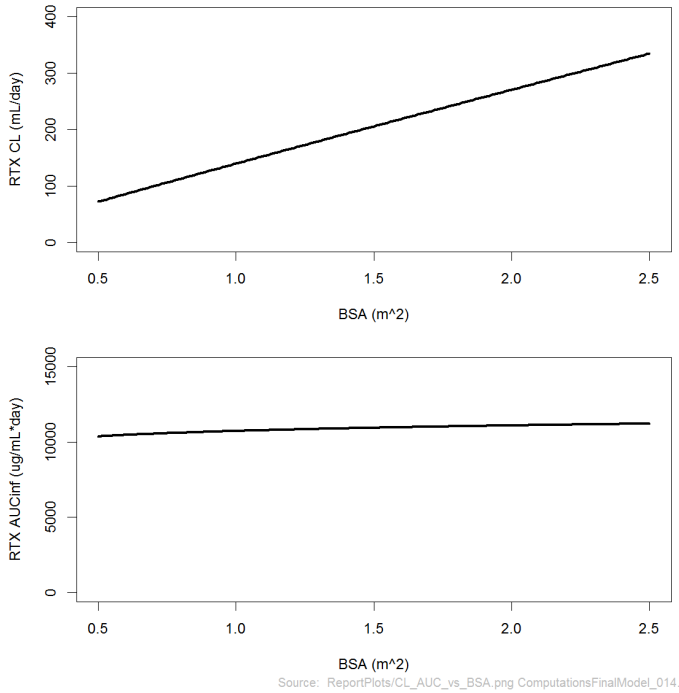
CL=clearance; V_C=central volume of distribution; V_{ss}= steady-state volume of distribution; $t_{1/2}$= half-life.
Source: 014_Ind_by_STUD.csv
Patients' individual PK parameters estimated from Model 014 were used for the summary.
CV was computed as standard deviation of the log-transformed data.

Since rituximab is administered based on BSA, the dosing results in matching exposure when comparing the pediatric and adult populations with median AUC_{0-180} of 9787 and 10302 μg/mL·day for the pediatric and adult populations, respectively. The variability in exposure was similar across the BSA range, further supporting the matching exposure in pediatric population and adults, when rituximab is dosed based on BSA. Therefore, matching the pediatric and the adult exposure is achieved with the 375 mg/m^2 once weekly x 4 regimen according to the MAH.

The CHMP noted that as in adults, BSA has a significant impact on volume of distribution and clearance in pediatric subjects. Rituximab CL and volume of distribution were lower in pediatric patients than in adults. The lower BSA in pediatric subjects compared to adult subjects is compensated for by the BSA-adjusted dosing regimen. Therefore, the BSA-adjusted dosing regimen of 4 weekly IV doses of rituximab 375 mg/m2 ensured similar exposure between adult and pediatric patients with GPA or MPA. The Pop PK model has adequately confirmed that a similar rituximab dosing regimen result in similar pediatric and adult rituximab exposure.

Extrapolation of PK and dose recommendation to children 2 - 6 years of age

Although the paediatric study enrolled patients of ≥6 years of age, and the lowest BSA was 0.876, based on the fact that BSA and rituximab clearance are strongly correlated (exponent of 0.952 in the power model describing BSA and CL), it is expected that the slope of the BSA CL relationship is the same in paediatric patients ≥2 to <6 years of age as in older/larger paediatric patients, as shown in the figure below.



CL = rituximab clearance; AUC_{inf} = rituximab AUC from zero to infinity following four 375 mg/m^2 doses. CL= θ_{CL} X (BSA/1.9) $^{0.952}$ X 1.38*ADA with θ_{CL}, the typical value of clearance in (mL/day) for a typical patient (i.e., BSA of 1.9 m^2 and absence of ADA) and is equal to 258 mL/day)

Figure 7 Relationships of Rituximab Clearance and AUC with Body Surface Area: Model Predictions

Therefore, according to the MAH, administration of 375 mg/m2 weekly x 4 in paediatric patients ≥2 to <6 years of age is expected to result in similar exposure as in the ≥ 6 year old paediatric patients. This is supported by the fact that the FcRn receptor, responsible for the long half-life of IgGs (Ghetie and Ward, 2002, Roopenian and Akilesh, 2007), as well as rituximab (half-life of approximately 22-25 days), can be found in fetuses, infants, children and adults and thus the elimination half-life is expected to be the same in paediatric patients ≥2 to <6 years of age as in the older paediatric patients (Israel EJ et al, 1997, Shah U et al, 2003).

At the CHMP's request, the MAH submitted rituximab PK data in paediatric patients (3 to 17 years old) with non-Hodgkin lymphoma to support the proposed dosing regimen in the younger age group. PK data from 35 paediatric subjects in the age range 3-17 years are available including 9 children 3 to 6 years of age. AUC and Cmin were similar across the BSA range 0.5 to 2 m2. A trend toward higher Cmax was seen for lower BSA values, but still within a range seen in adults. The pharmacokinetic data in paediatric patients with non-Hodgkin lymphoma, demonstrated that the pharmacokinetics of rituximab was not different in 3-5 years old compared to 6-18 year old paediatric patients.

2.3.3. Pharmacodynamics

Mechanism of action

There is strong evidence of 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) and the number of activated B cells has been shown to correlate with the extent of active disease (Popa et al. 1999). Similar to adults, short-lived plasma cells in paediatric patients are thought to be the primary source of pathogenic autoantibodies such as ANCAs to PR3 and MPO. 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).

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions that mediate B cell lysis. Possible mechanisms of effector mediated cell lysis include complement dependent cytotoxicity, and antibody dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In adult patients with GPA or MPA, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m2, and remained at that level in most patients up to the 6 month time point. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

Primary and secondary pharmacology

B-cell levels

Treatment with rituximab resulted in complete and sustained CD19+ peripheral B-cell depletion which persisted until at least Month 6, and in the majority of cases throughout the duration of follow-up, in which repeat rituximab infusions could be administered (Figure below). By Month 18, CD19 levels had increased but still remained below baseline levels with a median (min-max) of 58 (0.0 – 600)/µL.

Patients in the age group of ≥2 to <12 years (n=6), had baseline CD19 counts in the same range as paediatric patients aged ≥12 to ≤17 years [n=19]) and depleted similarly to 0 cells/µl after rituximab treatment.

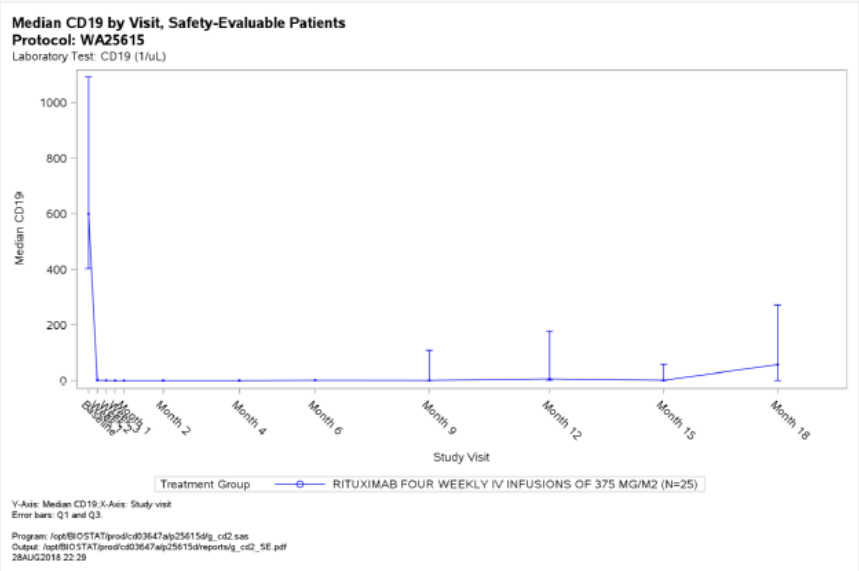


Figure 8 Median CD19 B cell levels by visit, safety-evaluable patients

Auto-antibody levels

At baseline (Month 0), 7 out of 25 patients (28%) were reported to be MPO-ANCA positive. This proportion had decreased to 5 out of 25 patients (20%) at Month 1, 1 out of 25 patients (4%) at Month 6 and 0 out of 24 patients at Month 12. At Month 18, 2 out of 23 patients (8.7%) were reported to be MPO-ANCA positive.

At baseline, 14 out of 25 patients (56%) were PR3-ANCA positive. This proportion had decreased to 13 out of 25 patients (52%) at Month 1, 8 out of 25 patients (32%) at Month 6 and 5 out of 24 patients (20.8%) at Month 12. At Month 18, 6 out of 23 patients (26.1%) were reported to be PR3-ANCA positive.

Immunogenicity

No paediatric patients in study WA25615 tested positive for anti-drug antibodies to rituximab at baseline. A total of 4 out of 21 evaluable patients (19%) developed treatment-induced ADA during the study period: one patient first tested positive for ADA at Month 4 and continued to have positive titres at subsequent study visits (Months, 6, 9 and 18). Three additional patients first tested positive for ADA at Month 18.

Individual rituximab serum concentration profiles observed in paediatric patients following 4 weekly IV doses of 375 mg/m2 of rituximab are shown in Figure 2. Paediatric patients with ADA (N=4/25) are highlighted.

In the adult study, 20 out of 97 subjects were ADA positive (Figure below).

Observed serum concentrations (ug/mL) versus time after the first dose (days) for patients that did (**red**) or did not (**black**) have ADA detected.

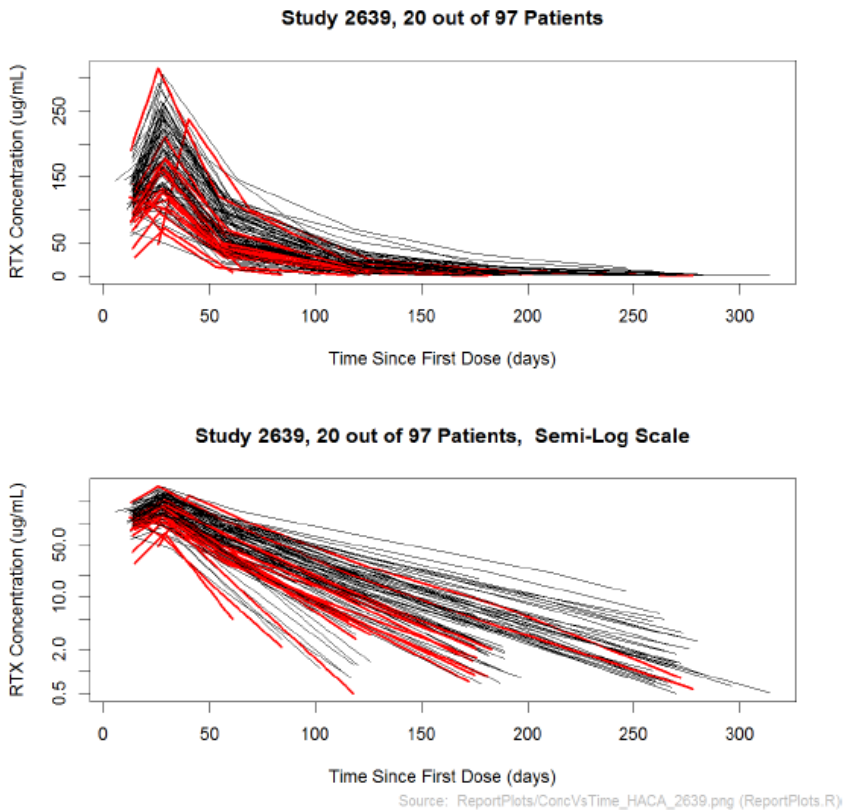


Figure 9 Observed individual serum concentration for patients with and without ADA study U2639s

The CHMP noted that the Pop PK analysis, patients with detected ADA had 38.2% higher clearance resulting in 27.6% lower AUC. Four paediatric patients out of 21 were ADA positive in the paediatric study. One patient with ADAs had fast decline in rituximab concentration indication higher clearance. No obvious difference in the individual serum concentrations of the three additional subjects with ADAs indicate major differences in exposure between ADA positive and negative subjects, but numbers are small. Development of ADAs has been shown in the Pop PK analyses to cause higher clearance and lower exposure which may have an impact on efficacy. In the RAVE study, 20 of 97 adult subjects were

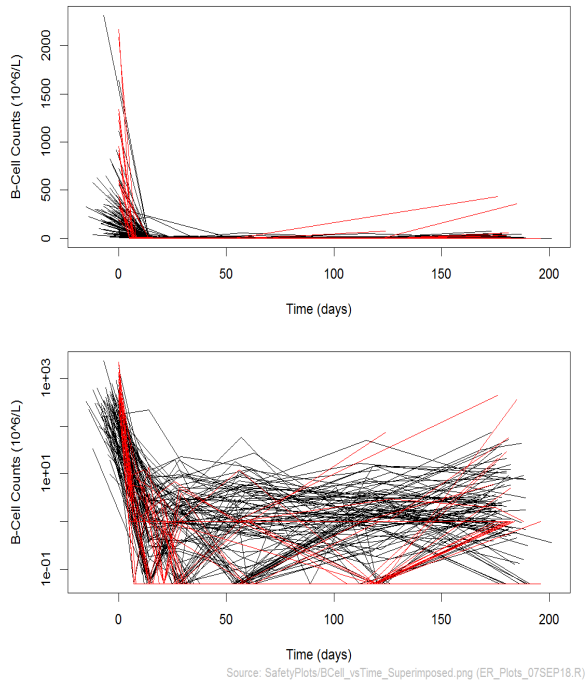
ADA positive. There is no apparent differences between adult and paediatric subjects in immunogenicity.

2.3.4. PK/PD modelling

Four different individual exposure measures were predicted by simulations from the final PK model using patients' actual dosing history over the first 180 days and individual PK parameters: CMAX, C180, AUC180, and AUCinf. All exposure measures were highly correlated, AUC180 was used for the graphical exposure-response analysis. Exposure categories were defined by the values of AUC180. Low (high) exposure category included 13 (12) patients with AUC180 less or equal (greater) than the median of AUC180 values in patients of Study WA25615 (equal to 9787 µg*day/mL).

$CD19^+$ B cells in Paediatrics and adult Patients with GPA and MPA

Graphical analyses demonstrated that rituximab administration in paediatric and adult patients induced rapid and prolonged peripheral $CD19^+$ B-cell depletion which persisted until at least Month 6, and there were no differences in B-cell depletion or start of time to repletion between adult and paediatric patients, as shown in the figure below.



Note: Red lines show B-cell counts over time for paediatric patients. B-cell counts equal to zero are assigned value 0.05 on the semi-log scale plots. Note: The data are presented for first 6 months.

Figure 9 Observed B-Cell Counts over Time in Paediatrics (top graph) and Adults Superimposed (bottom graph)

The CHMP noted that B-cell depletion is fast and remain for most paediatric subjects until month 6.

The time-course of observed B-cell counts by exposure categories in paediatric patients is shown in the figure below. Visually, there were no differences between B-cell time course of patients in low and high exposure categories, but a longer B-cell suppression was observed in patients with higher exposures. Similar results were observed in adults.

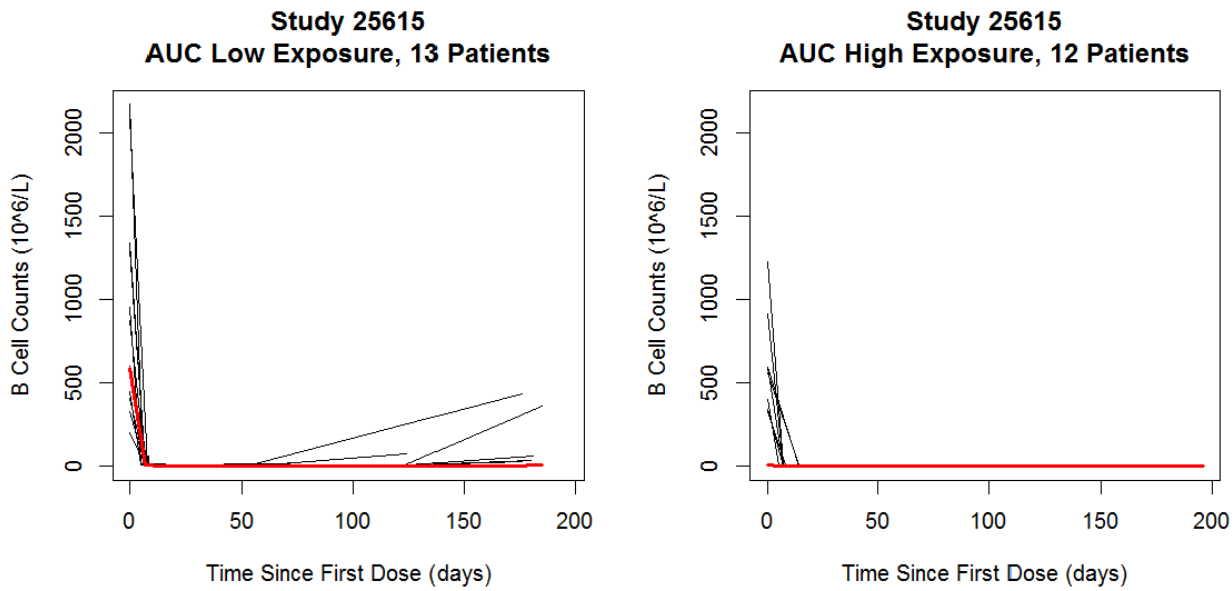


Figure 10 Observed B-cell counts over time for low and high exposure categories in paediatric patients with PGA/MPA Red lines: lowess (local regression smoother) trend lines.

Exposure-response relationship in paediatric patients

Four different individual exposure measures were predicted by simulations from the final PK model using patients' actual dosing history over the first 180 days and individual PK parameters: CMAX, C180, AUC180, and AUCinf. Patients from each study separately and from the two studies combined were categorized to low or high exposure group compared to median exposure. All exposure measures were highly correlated and did not depend on study, sex, age, weight, or BSA.

Efficacy

In the paediatric population, the efficacy parameters included in the analysis were:

- Paediatric Vasculitis Activity Score (PVAS) remission at Month 6,
- PVAS remission by Month 6,
- cumulative number of PVAS flares,
- cumulative glucocorticoids dose, and
- levels of MPO- antineutrophil cytoplasmic antibody (ANCA) and PR3-ANCA auto-antibodies.

Relationships between rituximab exposure and paediatric vasculitis score

The figure below illustrates distributions of PVAS scores at baseline and at 6 months. The median PVAS score decreased from about 9 at baseline to about 1 at 6 months. The plots suggested that PVAS significantly improved during the study (WA25615) without appreciable differences between the exposure groups.

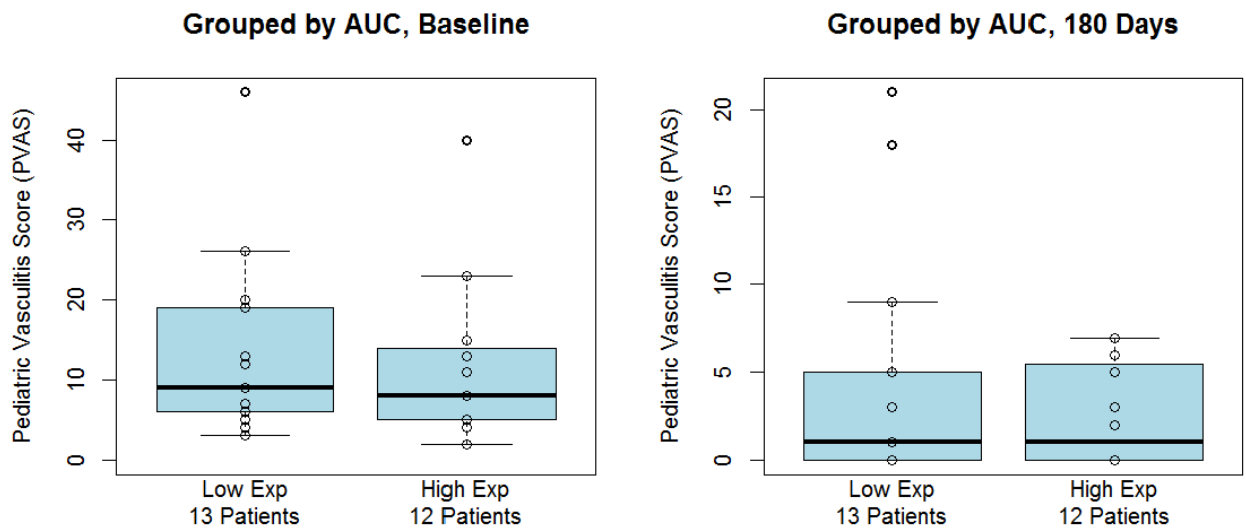


Figure 11 Distributions of observed PVAS score at baseline and Day 180 by exposure categories
The individual observed PVAS score values are plotted versus an exposure category using a box and whisker plot. Median values of the scores are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

There was only 1 patient with flares in the high exposure group, while 5 patients in the low exposure group experienced at least one flare during the study. The exposure of patients with flares was lower than in patients without flares. However, there were no obvious relationships between exposure and probability of flares events in the logistic regression models (p-values > 0.1).

The individual exposure values (AUC_{180}) are plotted versus an event category using a box and whisker plot. Median exposure values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

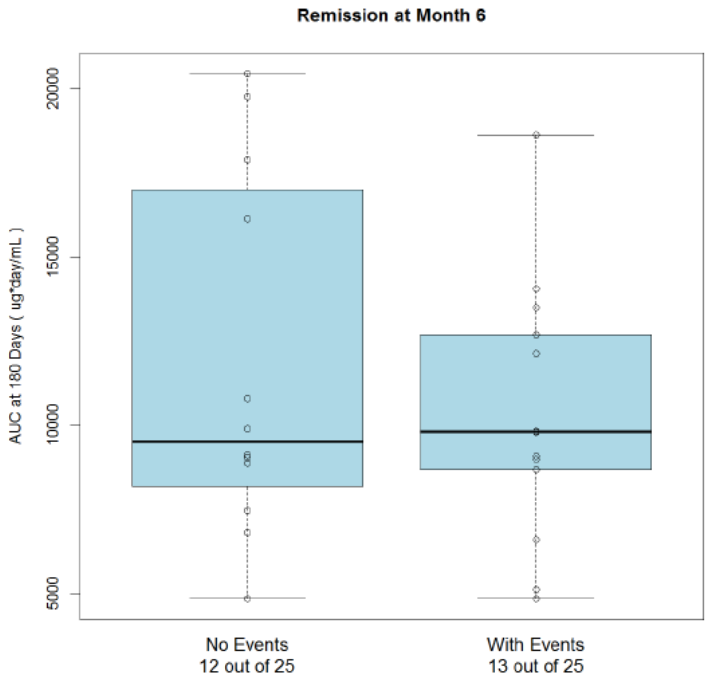


Figure 12 Relationship between remission at month 6 and exposure study WA25615

Safety

The relationship between rituximab exposure and safety was assessed for the following events: serious adverse events (SAEs), Grade ≥3 AEs, serious infections, infusion related reactions (IRRs), laboratory abnormalities of prolonged hypogammaglobulinemia (table below).

While the sample size was small (N=25), there were no increases in the occurrence of any of these AEs when comparing patients with lower rituximab exposure (i.e., AUC0–180 less than the median) to those with higher exposure (i.e., AUC0–180 greater than the median). The observed rituximab concentrations were also similar for patients with and without each type of AEs. When using logistic regressions, the occurrence of any of these AEs did not show any significant relationships with exposure (p-values >0.05).

Table 10 Occurrences of AEs, study WA25615

Event Type	Number (%) of Patients with AEs		
	AUC_{180} ≤ 9787 µg*day/mL (N=13)	AUC_{180} > 9787 µg*day/mL (N=12)	All Patients (N=25)
Serious Adverse Event (SAE)	3/13 (23.1%)	4/12 (33.3%)	7/25 (28%)
Adverse Event of Grade ≥ 3 (AE3)	3/13 (23.1%)	4/12 (33.3%)	7/25 (28%)
Serious Infection (SI)	1/13 (7.7%)	2/12 (16.7%)	3/25 (12%)
Infusion Related Reaction (IRR)	8/13 (61.5%)	7/12 (58.3%)	15/25 (60%)
Infusion Related Reaction of Grade ≥ 2 (IRR2)	5/13 (38.5%)	3/12 (25%)	8/25 (32%)
Laboratory Abnormality of Prolonged Low IgG (hypogammaglobulinemia)*	6/13 (46.2%)	7/12 (58.3%)	13/25 (52%)

Source: AESummary.csv

*defined as IgG <LLN (low limit of normal) for a 4 month period where a month is defined as 28 days.

The CHMP noted that the exposure-response analysis did not identify an exposure-response relationship for either efficacy or safety, but numbers are small. The rituximab exposure in paediatric subjects was adequate to induce rapid and prolonged B-cell depletion, confirming suitability of the BSA-adjusted dosing regimen of weekly IV doses of rituximab 375 mg/m2 to treat both adult and paediatric patients with GPA or MPA from 6 years of age.

2.3.5. Discussion on clinical pharmacology

This application is based on results from one study WA25615 in paediatric patients with severe granulomatosis with GPA/MPA. Although efficacy and safety data are collected in paediatric patients with GPA/MPA, because of the limited number of patients, the role of the pharmacokinetics in this application is to show comparable rituximab pharmacokinetics in paediatric patients 2-18 years of age with the pharmacokinetics in adults in order to bridge the efficacy and safety from adults with GPA/MPA of age to children 2-18 years of age. For that purpose, an updated popPK analysis is presented combining pharmacokinetic data in paediatric and adult patients with GPA/MPA. In addition, exploratory exposure-effect analysis for CD19 B-cell suppression, paediatric vasculitis activity score and safety were submitted.

Rituximab pharmacokinetics was described by a two-compartment linear model. In this updated analysis, model parameters for adult patients were similar to the ones from the RAVE population PK model. The popPK analysis predicted the exposures in paediatric and adult patients well. Clearance of rituximab was lower in paediatric patients than for adult patients. As the dose administered to each patient was proportional to BSA, the dose administered was lower in the paediatric patients resulting in

comparable exposures in paediatric and adult patients. Predicted rituximab exposure parameters AUC0-180 days, Cmax and C180 days were comparable in paediatric and adult patients following once weekly administration x4 of 375 mg/m2 rituximab.

Based on the population pharmacokinetic analysis of 25 children (6-17 years old) with GPA and MPA who received 375 mg/m2 MabThera once weekly for four doses, the estimated median terminal elimination half life was 22 days (range, 11 to 42 days). Rituximab mean clearance and volume of distribution were 0.221 L/day (range, 0. 0996 to 0.381 L/day) and 2.27 L (range 1.43 to 3.17 L), respectively. Maximum concentration during the first 180 days (Cmax), minimum concentration at Day 180 (C180) and cumulative area under the curve over 180 days (AUC180) were (median [range]) 382.8 (270.6-513.6) µg/mL, 0.9 (0-17.7) µg/mL and 9787 (4838-20446) µg/mL*day, respectively.

The rituximab dose employed for paediatric patients in study WA25615 was 375 mg/m2 iv given once weekly, for 4 consecutive weeks. This is the same dose as approved for adults with GPA and MPA, that was used in the pivotal RAVE study. In RAVE, a population PK analysis showed that body surface area (BSA), gender and presence of anti-drug antibodies (ADAs) influenced rituximab pharmacokinetics. Therefore, it was expected that BSA-adjusted dosing would provide similar exposure in adult and paediatric patients. In adult patients with GPA or MPA in the RAVE study, a 375 mg/m2 dose regimen achieved uniform pharmacokinetic (PK) exposures across a wide range of body weights or BSA. The allometric scaling method indicated that 375 mg/m2 would be adequate in paediatric patients.

Study WA25615 was not designed to evaluate rituximab in the maintenance setting, but only the induction of remission. Maintenance treatment and repeat remission-induction treatment with rituximab, as has been established in adult patients has not been studied in the paediatric patients but was given at the discretion of the investigator, per their clinical judgement (including dose and treatment regimen) based on disease activity, previous response to treatment, and the investigator's assessment of the benefit/risk of additional rituximab treatment. Approximately 68% (17/25) received additional rituximab treatment post month 6. However, this was at the discretion of the physician, and different doses and treatment regimens were used. Furthermore, in the majority of the cases, the intention was to induce remission, not to maintain a response. The MAH also provided a post-hoc analysis PVAS in patients only receiving induction treatment vs. those patients who also received treatment beyond month 6. In this analysis, no major differences are seen. However, no firm conclusions can be based on such small number of patients.

Rituximab exposure following the 4 weekly IV infusions of 375 mg/m2 rituximab regimen induced rapid and prolonged B-cell depletion in paediatric patients. This was reached with one course of remission-induction. The depletion (B-cell count < $5x10^6$ cells/L) appeared to last longer in patients with higher exposure. Similar effects were observed in adult patients.

The median PVAS score decreased from about 9 at baseline to about 1 at 6 months. A similar reduction was observed in paediatric patients with low or high rituximab exposure. Rituximab exposure of patients with flares appeared to be lower than in patients without flares. However, there were no obvious relationships between exposure and probability of flares events in the logistic regression models (p-values > 0.1). Overall, no association between rituximab exposure and clinical efficacy or safety was observed. Similar findings were reported for adults with GPA or MPA from the RAVE trial.

Pharmacokinetics of rituximab showed a comparable exposure in adult and paediatric patients, supporting the dosing regimen. It appears that the MAH had not set criteria for similarity in exposure between paediatric and adults to allow bridging to efficacy and safety established in adult patients. Since mean/median rituximab exposures and variability in paediatric patients and adults was comparable as was B-cell depletion, this issue was not pursued by CHMP.

Only patients ≥ 6 years of age were enrolled in the study. Hence pharmacokinetics of rituximab in patients ≥2 years of age and < 6 years of age are missing. Simulations of rituximab exposure in ≥ 2 to < 6 years old children and older patients with GPA or MPA with different methods to estimate PK parameters indicated similar exposure across age groups. This was further supported by rituximab PK data in paediatric patients (3 to 17 years old) with non-Hodgkin lymphoma. PK data from 35 paediatric subjects in the age range 3-17 years are available including 9 children 3 to 6 years of age. AUC and Cmin were similar across the BSA range 0.5 to 2 m2. A trend toward higher Cmax was seen for lower BSA values, but still within a range seen in adults. The pharmacokinetic data in paediatric patients with non-Hodgkin lymphoma, demonstrated that the pharmacokinetics of rituximab was not different in 3-5 years old compared to 6-18 year old paediatric patients. Therefore, the CHMP considered that it has been adequately justified that a body size based dosing regimen in GPA/MPA will provide similar and acceptable exposure in the youngest children ≥ 2 to < 6 years of age even though no clinical data in this age group are available.

The CHMP noted that the Pop PK analysis, patients with detected ADA had 38.2% higher clearance resulting in 27.6% lower AUC. Four paediatric patients out of 25 were ADA positive in the paediatric study. One patient with ADAs had fast decline in rituximab concentration indication higher clearance. No obvious difference in the individual serum concentrations of the three additional subjects with ADAs indicate major differences in exposure between ADA positive and negative subjects, but numbers are small. Development of ADAs has been shown in the Pop PK analyses to cause higher clearance and lower exposure which may have an impact on efficacy. In the RAVE study, 20 of 97 adult subjects were ADA positive. There are no apparent differences between adult and paediatric subjects in immunogenicity.

2.3.6. Conclusions on clinical pharmacology

The PK parameters of rituximab in paediatric patients with GPA or MPA were similar to those in adults with GPA or MPA, once taking into account the BSA effect on clearance and volume of distribution parameters.

The CHMP concluded that the body size body regimen was adequate for children from 2 years onwards in GPA/MPA. Section 4.2 of the SmPC therefore recommends a dosage of MabThera for the treatment of paediatric patients with severe, active GPA or MPA is 375 mg/m2 BSA, administered as an IV infusion once weekly for 4 weeks..

Limited data shows there was no trend observed in the adverse reactions reported in ADA positive patients. There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the paediatric GPA and MPA clinical trials.

2.4. Clinical efficacy

2.4.1. Dose response study

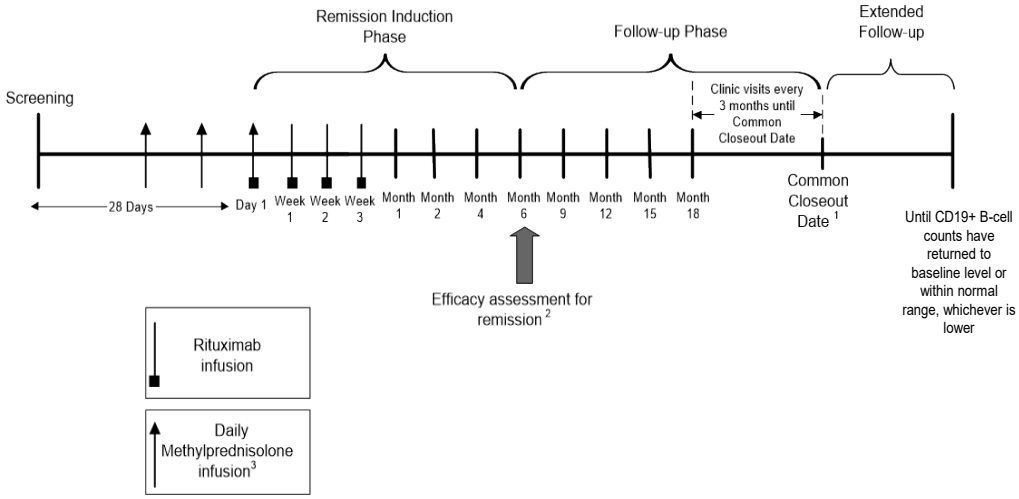
Not applicable, a dose-response study has not been performed.

2.4.2. Main study

- **Study WA25615**

Study WA25615 is a Phase IIa, international, multicenter, open-label, single-arm uncontrolled study. The overall design consisted of a 28-day screening period, an initial 6-month Remission Induction

Phase, followed by a minimum 12 month Follow-Up Phase. After Month 18, patients were followed at study visits every 3 months until the CCO.



1 The common closeout date is 18 months after enrolment of the last patient.
2 Remission is defined by a BVAS/WG or PVAS of 0 and tapering of glucocorticoids to a minimum of 0.2 mg/kg/day (or 10 mg, whichever is lowest).
3 Can occur anytime up to and including Day 1 (prior to the first rituximab infusion).

BVAS = Birmingham Vasculitis Activity Score; PVAS = Paediatric Vasculitis Activity Score; WG = Wegener's granulomatosis

Figure 13 Study WA25615 Design

Methods

Study participants

Eligible patients were children aged 2 to 11 years and adolescents aged 12 to <18 years with newly diagnosed or relapsing active GPA or MPA (new onset or recurrence of potentially organ- or life-threatening disease (i.e., one or more major BVAS/WG items or disease severe enough to require treatment with immunosuppressive therapy, e.g. cyclophosphamide).

The main inclusion criteria were:

- Age at screening ≥2 and <18 years
- Diagnosis of GPA (EULAR/PRINTO/PRES 2008, Ankara criteria for childhood WG [Özen et al. 2010]) *or* diagnosis of MPA (according to the Chapel Hill Consensus Conference [Jennette 1994])
- Newly diagnosed patients *or* patients with relapsing disease (recurrence or new onset of potentially organ- or life-threatening disease (major BVAS/WG items) or disease severe enough to require treatment with cyclophosphamide).

Main exclusion criteria were:

1. *Limited* disease that would not normally be treated with cyclophosphamide
2. *Severe* disease requiring mechanical ventilation due to alveolar hemorrhage
3. Requirement for plasmapheresis or dialysis at screening

4. Treatment 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

5. Previous treatment with other cell-depleting therapies

Treatments

Rituximab

Rituximab was given as an IV infusion of 375 mg/m2 once a week for 4 consecutive weeks, starting at the baseline visit. The dose for rituximab was calculated according to the patient's body surface area (BSA) at the screening visit after the patient's eligibility had been established, and remained the same for all four infusions. Each patient'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) was used to calculate a patient's BSA according to the Dubois formula.

Patients were to be medicated pre-infusion with paracetamol/acetaminophen and cetirizine hydrochloride (or similar antihistamine), both according to locally approved age-related doses, which were 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 could be administered at least 30 minutes prior to infusion of rituximab (but not prior to clinical assessments) if the patient had experienced an IRR with a previous rituximab infusion.

Facilities for immediate emergency intervention, including resuscitation in case of an anaphylactic reaction, were to be available. Vital signs (i.e., pulse rate, systolic and diastolic blood pressure, and temperature) were taken pre-infusion. During the infusions, vital signs were to 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 was available on site. Rituximab was not to be administered as an IV push or bolus due to the possibility of occurrence of hypersensitivity reactions. After infusion, the IV line was to remain in the patient for at least 1 hour to enable the administration of any necessary medication, as applicable.

Methylprednisolone

Patients were to 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 could 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) could be given by IV infusion. No more than six doses of methylprednisolone in total were to be given. All methylprednisolone doses had to be completed prior to the first rituximab infusion. The first rituximab infusion had to occur no longer than 14 days after the final IV glucocorticoid dose; the final IV glucocorticoid dose could be given on Day 1 (prior to the first rituximab infusion). Compliance was assessed according to completion of a glucocorticoid log.

Prednisolone or Prednisone

On Day 1 and following completion of IV glucocorticoids, all patients were to receive concomitant oral prednisolone or prednisone (1 mg/kg/day or up to 60 mg/day or equivalent, whichever was lower), the dose of which was to be tapered to a minimum of 0.2 mg/kg/day (or 10 mg/day, whichever was lowest) no later than Month 6. The general guidance on the suggested oral steroid dose-tapering schedule was 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 was lowest), which was to be reached no later than Month 6. Oral prednisone (used in some non-UK sites) could be substituted for prednisolone at the same dose as long as there was no hepatic impairment. The steroid-tapering practice was specific to a particular patient and as such was to be tailored individually for each patient at the time of study entry, at the discretion of the investigator.

Objectives

Primary objectives

The primary safety objective of this study was to evaluate the safety and tolerability of rituximab in paediatric patients with severe GPA or MPA. The primary PK objective of this study was to evaluate the PK parameters of rituximab in paediatric patients with severe GPA or MPA.

Exploratory objectives

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

Other exploratory objectives for this study were as follows:

1. To explore the PD parameters of rituximab in paediatric patients with GPA or MPA
2. To explore the effect of rituximab on patient quality of life and disability/functioning, as assessed using the Child Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ), respectively.

Outcomes/endpoints (efficacy)

Exploratory efficacy endpoint:

PVAS (Paediatric Vasculitis Activity Score):

- Proportion of patients in PVAS remission by Month 6, 12 and 18: defined as a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) or a PVAS of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose.
- Proportion of patients in remission at Month 6: defined as a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower).
- Duration of remission (equivalent to 'time to flare after remission'): defined as a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) until the time to major or minor PVAS relapse/flare after remission or until the end of the main study (common closeout date) or early study withdrawal, whichever came first.
- Proportion of patients in remission: defined by PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) at Months 12 and 18.
- Proportion of patients in partial remission: defined as a 0<PVAS ≤2 with no new or worse items and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg, whichever was lower) at Months 6, 12, and 18.
- Number of major or minor PVAS relapses/flares at Months 6, 12, and 18.
- Number (proportion) of patients with PVAS disease progression prior to remission by Month 6.

BVAS (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis)

- Proportion of patients in BVAS/WG remission by Month 6: defined as a BVAS/WG of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) or a BVAS/WG of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose.
- Proportion of patients in remission at Month 6: defined as a BVAS/WG of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower).

- Proportion of patients in remission: defined as BVAS/WG of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) at Months 12 and 18.
- Duration of remission (equivalent to 'time to flare after remission'): defined by a BVAS/WG of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) until the time to major or minor BVAS/WG relapse/flare after remission or until the end of the main study (common closeout date) or early study withdrawal, whichever came first.
- Proportion of patients in partial remission: defined as a 0<BVAS/WG ≤2 with no new or worse items and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) at Months 6, 12, and 18.
- Number of major or minor BVAS/WG relapses/flares at Months 6, 12, and 18.
- Number (proportion) of patients with BVAS/WG disease progression prior to remission by Month 6

Other Efficacy Endpoints

The following efficacy endpoints were summarized descriptively:

1. The cumulative glucocorticoid dose for patients at Months 6, 12, and 18.
2. The change from baseline in the estimated glomerular filtration rate (calculated using the Schwartz formula) to Month 6.
3. The PGADA, which was completed at screening, baseline and then at each visit starting from Month 1.
4. The PVDI (Paediatric Vasculitis Damage Index), which was assessed at screening, baseline and then six-monthly until the end of the Follow-Up Phase, or at early withdrawal. PVDI evaluated cumulative organ damage (persisting for ≥ 3 months) for any item developing since the onset of vasculitis. The total PVDI score was the number of symptoms present from a list of 72 symptoms divided into 10 categories (there was also a separate four-category scale regarding days of school absence). At baseline, missing individual PVDI scores were replaced by the corresponding screening value, when given. At all visits, if any of the sets of symptoms were not assessed, including any missing at both baseline and screening, then it was assumed that the symptoms were not present. The total PVDI scores and their changes from baseline were summarized descriptively by 6-monthly intervals. The days of school absence scale were cross-tabulated as counts at baseline versus each 6- monthly assessment score.

The CHMP noted that MAH has defined multiple clinically relevant endpoints. Since these are all exploratory endpoints, there is no adjustment for multiplicity. Although the efficacy objective is declared as exploratory by the MAH, it is implied that PVAS remission at month 6 is the outcome of main interest, which is agreed. PVAS remission was defined as a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower) or a PVAS of 0 on two consecutive readings at least 4 weeks apart irrespective of glucocorticoid dose. This is endorsed as a clinical relevant outcome in children's GPA and MPA. Though not finally validated, PVAS is considered to have face validity and it can be relied on the validity and acceptance of the BVAS/WG in GPA/MPA. Results on BVAS/WG remission as defined for in adults can be used for robustness. The Physician's Global Assessment of Disease Activity (PDGA), Cumulative glucocorticoid dose, Children's Stanford Health Assessment Questionnaire (CHAQ) disability index, are especially useful to support clinical relevance and robustness of findings on PVAS. While the efficacy outcomes are also assessed after month 6 (months 12 and 18), it is more difficult to interpret their value, because follow-up treatment was at the discretion of the treating physician (patients and families).

Sample size

Study WA25615 was an open-label, single-arm study, with the primary objective of evaluating safety and PK of rituximab in paediatric patients with severe GPA or MPA. PD and efficacy were exploratory endpoints. There was no formal statistical hypothesis testing for any of the study endpoints.

The planned sample size of 25 patients was determined on the basis of the occurrence paediatric GPA and MPA and on information from existing patient cohorts. The number of paediatric patients that would be eligible for treatment with rituximab and that could be expected to be enrolled within a reasonable timeframe was taken into account. The planned sample size was considered to 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. The planned sample size should have ensured a 95% probability of observing at least one AE when the underlying incidence of that event is ≥ 11%. The planned sample size was also chosen to allow estimation of the percentage of patients in remission at 6 months to lie within 20% of the point estimate (the distance from the point estimate to the upper or lower limit of a 95% CI).

The CHMP noted that the planned sample size seems to be driven by the time frame and prevalence available. The MAH describes the precision that can be obtained with this sample size. In fact, 95%-CI for the estimated standard deviation (SD) of a PK parameters (on log scale) would be from 0.78*SD to 1.39*SD, so a relative precision of 22%. Also, the 95%-CI for the percentage (perc) of responder would be typically from perc -20% to perc +20% (this is what probably is meant by the uninterpretable formulation "estimation of the percentage of patients in remission at 6 months to lie within 20% of the point estimate (the distance from the point estimate to the upper or lower limit of a 95% CI).") This somehow limits the comparison between adult and pediatric data.

Randomisation

Randomisation was not applied, it was a single-arm study.

Blinding (masking)

The clinical assessors were not blinded, it was an open-label study.

Statistical methods

Study WA25615 was an open-label, single-arm study, with the primary objective of evaluating safety and PK of rituximab in paediatric patients with severe GPA or MPA. PD and efficacy were exploratory endpoints. There was no formal statistical hypothesis testing for any of the study endpoints, the Data Analysis Plan was finalized prior to final analysis.

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.

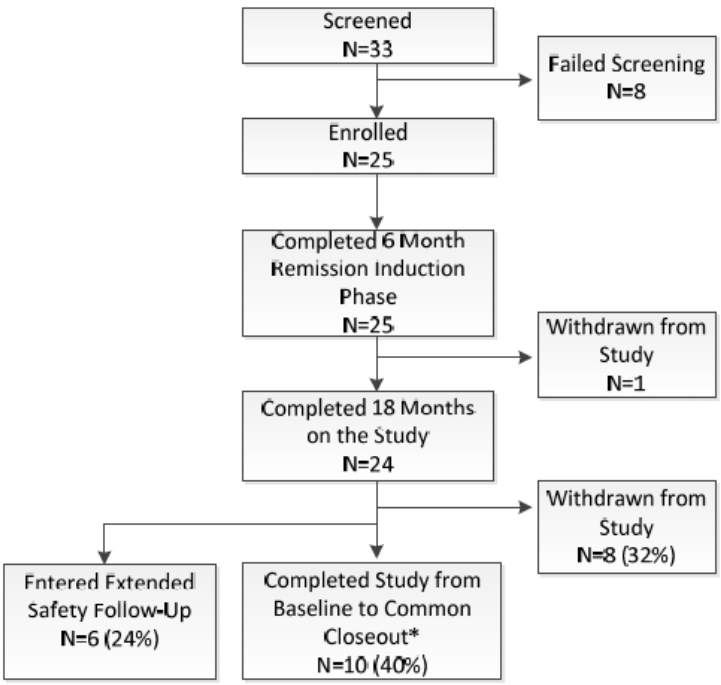
Primary analysis will be done once all of the data, up until the follow-up visit subsequent to the common closeout date (the Withdrawal visit), has been entered into the study database, cleaned and the database locked for editing. A final analysis will be reported once the extended follow-up for all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

Descriptive statistics will be used. The proportions of patients in remission and partial remission, according to the various definitions will be summarized as counts and percentages, together with 95%-CI based on the binomial distribution.

The CHMP noted that in the absence of pre-specification of tests, the efficacy endpoints and in particular their 95%-CI can only be interpreted descriptively. Also, no order of importance of the efficacy endpoints was planned. The interim analysis was not planned to stop the study and not of influence on multiple testing as no testing was performed in this study. It is reassuring that the interim was after the most relevant part of the study. As discussed for the sample size above, the precision in this study is limited.

Results

Participant flow



*Common Closeout (CCO) occurred on 10 May 2018, 18 months after the enrollment of the last patient.

Figure 14 Participants flow

Table 11 Patient disposition, safety-evaluable patients

Protocol: WA25615

Status	Rituximab (N=25)
Completed 6 Month Remission Induction Phase	25 (100.0%)
Completed 18 Months on study	24 (96.0%)
Completed study from baseline to common-closeout*	10 (40.0%)
Entered extended safety follow-up+	6 (24.0%)
Discontinued Study	9 (36.0%)
Other: Patient Transferring Back To Local Hospital Will No Longer Be Under The Pi Care	1 (4.0%)
Other: Physician And Family Decision Due To Family Circumstances	1 (4.0%)
Other: Transfer To Adult Services	1 (4.0%)
Other: Transferring To Adult Services	3 (12.0%)
Other: Transferring To Adult Services And Unable To Obtain Further Information. Also Patient And Family Unable To Attend Two Different Places Due To Illness, Committment Too Heavy.	1 (4.0%)
Physician Decision	1 (4.0%)
Withdrawal By Subject	1 (4.0%)

"*" = 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.

Recruitment

A total of 25 patients were enrolled into the study. The first patient was enrolled in May 2013 and last patient was enrolled in November 2016. Patients were enrolled at 11 investigational sites across 6 countries, over a 3.5 year period. A total of 17 patients (68%) were enrolled in Europe and 8 patients (32%) in North America. A majority of 13 patients (52%) was enrolled at 3 sites in the United Kingdom.

Conduct of the study

Protocol deviations

Four patients (16%) had a total of 4 major protocol deviations during the study. A per-protocol analysis was not performed for this open-label study. Major deviations were primarily related to concomitant medications (3 patients), which included 1 patient not receiving methylprednisolone doses prior to rituximab treatment per protocol; 1 patient not receiving pre-medications prior to rituximab infusion; and 1 patient continuing to receive a prohibited concomitant medication (mycophenolate mofetil) for their pre-existing severe chronic renal disease as suspension of the treatment, in the Investigator's opinion could have exposed the patient to a risk of potential renal damage. In addition, one major deviation for a patient fulfilling an exclusion criterion (IgM below LLN at baseline) was reported. These deviations were not considered to have any significant impact on overall interpretation of safety or efficacy results of the study.

Table 12 Major protocol deviations, safety-evaluable patients

Protocol: WA25615

Category Description	Rituximab (N=25)
Total number of patients with at least one major protocol deviation	4 (16.0%)
Total number of major protocol deviations	4
EXCLUSION CRITERIA	
LEVEL OF IGM BELOW LLN OF AGE-SPECIFIC REFERENCE RANGE	1 (4.0%)
MEDICATION	
NO METHYLPRED X3 30 MG/KG (UP TO 1 G/DAY) PRIOR TO DAY 1 BASELINE	1 (4.0%)
PATIENT DID NOT RECEIVE PRE-INFUSION MEDICATION PER PROTOCOL	1 (4.0%)
RECEIVED PROHIBITED CONCOMITANT MEDICATION	1 (4.0%)

Changes in Conduct of study

There were four protocol amendments to the original Protocol WA25615 Version 1, which was released on 2 July 2012.

Protocol Version 2

Study protocol WA25615 Version 2 was released on 13 October 2012. The main changes to the protocol were as follows:

1. The tool used for the exploratory endpoint of the measurement of childhood primary vasculitis from the Vasculitis Damage Index (VDI) was changed to the Paediatric Vasculitis Damage Index (PVDI), which had just become available. The tool was modified from the existing adult version and considered more relevant to paediatric patients and enabled collection of more relevant patient data.
2. The quality of life (QOL) instrument the Child Health Questionnaire (CHQ) was added to the exploratory outcome measures in order to assess both QOL and disability/functioning. The description of the Childhood Health Assessment Questionnaire (CHAQ), an instrument for disability/functioning, was corrected since it was previously incorrectly described as an instrument for QOL assessment.

Protocol Version 3

Study protocol WA25615 Version 3 was released on 31 May 2013. The main changes to the protocol were as follows:

- New safety information was provided on severe skin reactions (e.g., Toxic Epidermal Necrolysis and Stevens-Johnson syndrome) based on up-to-date information in the context of the use of rituximab.
- The exclusion limit of ALT or AST levels was increased in order to align the inclusion criteria with the RAVE study.
- Definitions of progressive disease, disease relapse/flare, and major and minor items for Birmingham Vasculitis Activity Score (BVAS) for Wegener's granulomatosis (WG) BVAS/WG and Paediatric Vasculitis Activity Score (PVAS) were provided to facilitate more robust data analysis. Additional exploratory efficacy outcome measures/endpoints were included and clarifications provided.
- Two additional exploratory endpoints were added to provide a more stringent definition for investigation of remission, if remission was sustained for ≥4 weeks:
- Proportion of patients in remission by Month 6, defined as a BVAS/WG of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose.
- Proportion of patients in remission by Month 6, defined as a PVAS of 0 ontwo consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose.

Protocol Version 4

Study protocol WA25615 Version 3 was released on 27 March 2015. The main changes to the protocol were as follows:

- Further information on posterior reversible encephalopathy syndrome (PRES) in the Disease Background Section (Section 1.1) was added. These changes were made to provide additional information about this serious condition and to refer physicians to the information already available in the IB and SmPC.

Protocol Version 5

Study protocol WA25615 Version 5 was released on 26 April 2016. The main changes to the protocol were as follows:

- The exclusion criteria relating to general health, prior medications and laboratory findings were modified. Changes were made to extend the possibility of entry into the study to a wider range

of suitable GPA and MPA patients, who would otherwise have limited treatment options. The changes to exclusion criteria required the treating physician to assess benefit/risk, prior to patient study entry. The changes allowed a small proportion of patients who were not previously eligible the opportunity to participate in this study.

Changes in Data Analysis Plan

Exploratory PVAS remission by Month 12 and 18 were added to provide alignment with the assessment of other efficacy endpoints at the same study visits.

The CHMP noted that there were 4 protocol amendments during the conduct of the study, but none of the amendments are considered critical with regards to study design and conduct of the study.

Baseline data

Table 13 Demographic and baseline characteristics, safety-evaluable patients

	Rituximab (N=25)
Age (yr)	
n	25
Mean (SD)	13.4 (2.9)
Median	14.0
Q1 - Q3 (IQR)	12.0 - 16.0 (4.0)
Min - Max	6 - 17
Age group (yr)	
n	25
2 to 11	6 (24.0%)
12 to 17	19 (76.0%)
Sex	
n	25
Male	5 (20.0%)
Female	20 (80.0%)
Race	
n	25
Asian	4 (16.0%)
Black or African American	1 (4.0%)
White	17 (68.0%)
Multiple	1 (4.0%)
Other	2 (8.0%)
Height (cm)	
n	25
Mean (SD)	153.22 (14.03)
Median	154.90
Q1 - Q3 (IQR)	146.00 - 161.00 (15.00)
Min - Max	120.0 - 175.2
Weight (kg)	
n	25
Mean (SD)	50.12 (15.25)
Median	50.90
Q1 - Q3 (IQR)	37.30 - 62.70 (25.40)
Min - Max	23.0 - 80.8
Body-mass index (kg/m2)	
n	25
Mean (SD)	20.95 (4.31)
Median	20.68
Q1 - Q3 (IQR)	18.03 - 22.32 (4.30)
Min - Max	15.7 - 32.2
Concomitant Diseases (continuing at Baseline)	
n	24
No concomitant diseases	0
1 concomitant disease	6 (25.0%)
2 concomitant diseases	2 (8.3%)
>=3 concomitant diseases	16 (66.7%)
Estimated GFR (Schwartz formula) (mL/min/1.73 m2)	
n	25
Mean (SD)	140.26 (36.75)
Median	137.78
Q1 - Q3 (IQR)	120.31 - 156.81 (36.50)
Min - Max	79.9 - 260.7
Immunofluorescence (IF) ANCA status	
Negative	3 (12.0%)
cANCA	12 (48.0%)
pANCA	4 (16.0%)
MPO	8 (32.0%)
PR3	14 (56.0%)

BVAS/WG Score	
n	25
Mean (SD)	6.80 (4.43)
Median	7.00
Q1 - Q3 (IQR)	3.00 - 9.00 (6.00)
Min - Max	1.0 - 18.0
Current Disease Status	
n	25
Severe Flare/New Diseases	14 (56.0%)
Limited Flare/New Disease	5 (20.0%)
Persistent Severe Disease	4 (16.0%)
Persistent Limited Disease	2 (8.0%)
Remission	0
BVAS/WG PGA	
n	25
Mean (SD)	47.40 (24.72)
Median	46.00
Q1 - Q3 (IQR)	29.00 - 71.00 (42.00)
Min - Max	6.0 - 95.0
PVAS Score	
n	25
Mean (SD)	12.72 (11.14)
Median	8.00
Q1 - Q3 (IQR)	5.00 - 15.00 (10.00)
Min - Max	2.0 - 46.0
PVDI Score	
n	25
Mean (SD)	2.64 (5.94)
Median	0.00
Q1 - Q3 (IQR)	0.00 - 3.00 (3.00)
Min - Max	0.0 - 29.0
PVDI Average School Absence (days)	
n	25
=<1	12 (48.0%)
>1 - 4	5 (20.0%)
>4 - 10	5 (20.0%)
>10	3 (12.0%)

SD = Standard Deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range, GFR = Glomerular Filtration Rate, ANCA = Anti-Neutrophil Cytoplasmic Antibodies, pANCA = Perinuclear Anti-Neutrophil Cytoplasmic Antibodies, cANCA = Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies, PGA = Physician Global Assessment, PVDI = Pediatric Vasculitis Damage Index; PVAS = Pediatric Vasculitis Activity Score; BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis

Most severe "Current Disease Status" is used for summary if patient has multiple disease status from Screening.

Concomitant Disease is defined as a disease started before baseline and continued after.

Percentages are based on n.

ANCA positivity determined by indirect immunofluorescence (IF) microscopy staining pattern.

Table 14 GPA / MPA history, safety-evaluable patients

Protocol: WA25615

	Rituximab (N=25)
Diagnosis	
n	25
GPA Newly diagnosed	13 (52.0%)
MPA Newly diagnosed	5 (20.0%)
GPA relapsed	6 (24.0%)
MPA relapsed	1 (4.0%)
Disease duration (months)	
n	24
Mean (SD)	9.40 (19.00)
Median	0.50
Q1 - Q3 (IQR)	0.33 - 8.07 (7.74)
Min - Max	0.2 - 72.1
Prior CYC therapy	
n	25
Yes	2 (8.0%)
No	23 (92.0%)
Major Renal Disease*	
n	25
Yes	4 (16.0%)
No	21 (84.0%)

* Major Renal Disease is taken from eCRF page, BVAS and PGA. If both hematuria and RBC casts are present, score only the RBC casts.
SD = Standard Deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range, CYC = Cyclophosphamide, PGA = Physician Global Assessment.
Summaries are based on Medical history and Concomitant medication domains, and Screening records for other assessments.
Disease duration is from the start date of disease to start of study drug at baseline.
Percentages are based on n.

Table 15 PVAS baseline disease characteristics, safety-evaluable patients

Protocol: WA25615

	Rituximab (N=25)
General	
n	25
None	9 (36.0%)
Arthralgia or Arthritis	16 (64.0%)
Fever >= 38.0 C	8 (32.0%)
Myalgia	8 (32.0%)
Weight Loss >= 5% Body Weight	7 (28.0%)
Cutaneous	
n	25
None	11 (44.0%)
Gangrene	1 (4.0%)
Livedo	2 (8.0%)
Other Skin Vasculitis	5 (20.0%)
Polymorphous Exanthema	3 (12.0%)
Purpura	10 (40.0%)
Skin Nodules	3 (12.0%)
Ulcer	3 (12.0%)
Mucous Membranes/Eyes	
n	25
None	17 (68.0%)
Conjunctivitis/Blepharitis/Keratitis	3 (12.0%)
Mouth Ulcers/Granulomata	4 (16.0%)
Red Eye (Epi)scleritis	3 (12.0%)
Significant Proptosis	1 (4.0%)
Uveitis	1 (4.0%)
ENT	
n	25
None	7 (28.0%)
Conductive Hearing Loss	4 (16.0%)
Nasal Discharge/Crusts/Ulcers/Granuloma	14 (56.0%)
Paranasal Sinus Involvement	6 (24.0%)
Sensorineural Hearing Loss	1 (4.0%)
Subglottic Stenosis/Hoarseness/Stridor	3 (12.0%)
Chest	
n	25
None	14 (56.0%)
Endobronchial/Endotracheal Involvement	1 (4.0%)
Infiltrate	3 (12.0%)
Massive Haemoptysis/Alveolar Haemorrhage	2 (8.0%)
Nodules or Cavities	6 (24.0%)
Pleural Effusion/Pleurisy	1 (4.0%)
Wheeze or Expiratory Dyspnea	2 (8.0%)
Cardiovascular	
n	25
None	24 (96.0%)
Pericarditis	1 (4.0%)
Abdominal	
n	25
None	20 (80.0%)
Abdominal Pain	4 (16.0%)
Blood in Stools or Bloody Diarrhoea	1 (4.0%)
Renal	
n	25
None	10 (40.0%)
GFR 50-80ml/min/1.73 m2	2 (8.0%)
Hematuria >=2+ or 5 rbc/hpf or rc casts	13 (52.0%)
Hypertension >95th Centile	3 (12.0%)
Proteinuria >0.3 g/24h,>20mmol/mg creat	7 (28.0%)
Rise in Creatinine >10% or GFR Fall >25%	1 (4.0%)
Nervous System	
n	25
None	21 (84.0%)
Headache	3 (12.0%)
Organic Confusion/Cognitive Dysfunction	1 (4.0%)
Seizures (Not Hypertensive)	1 (4.0%)
Sensory Peripheral Neuropathy	1 (4.0%)
Stroke	1 (4.0%)
Other	
n	18
None	18 (72.0%)

ENT = Ear, Nose and Throat; GFR = Glomerular Filtration Rate
The characteristic is considered to be "Active" only if abnormality due to active vasculitis is newly present or worse over the last 4 weeks or persists for less than 3 months. If there are no abnormalities in a system, it is considered as "None".
Percentages are based on N.

Previous and Concurrent Diseases (Other than GPA / MPA) and previous medication

For the 24 patients (96%) who had their previous/concurrent disease status recorded at baseline, all patients had at least 1 concomitant disease other than GPA or MPA (see summary of previous medical history). Sixteen patients (67%) had 3 or more concurrent conditions at baseline. The majority of concomitant diseases, excluding underlying vascular diseases (GPA or MPA), were gastrointestinal (GI) disorders (9 patients [36%]), respiratory, thoracic and mediastinal disorders (9 patients [36%]), and musculoskeletal and connective tissue disorders (7 patients [28%]).

The majority of patients did not have history of passive immunization (immunoglobulin) for tetanus, hepatitis B, hepatitis A, rabies or varicella zoster (see summary). A summary of vaccination history, including active immunizations, is additionally provided. The most commonly reported active vaccinations at baseline were typical of those received in childhood and included tetanus (18 patients [72%]), measles, mumps, rubella and diphtheria (each reported in 17 patients [68%]). The vaccination compliance overall reflected that in the real world being <100%.

Table 16 Medical history, safety-evaluable patients

Previous Medical History, Safety-Evaluable Patients
Protocol: WA25615

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Total number of patients with at least one condition	24 (96.0%)
Overall total number of conditions	146
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one condition	6 (24.0%)
Total number of conditions	7
ANAEMIA	5 (20.0%)
LYMPHADENOPATHY	1 (4.0%)
CARDIAC DISORDERS	
Total number of patients with at least one condition	2 (8.0%)
Total number of conditions	2
PERICARDIAL EFFUSION	1 (4.0%)
PULMONARY VALVE STENOSIS	1 (4.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	
Total number of patients with at least one condition	3 (12.0%)
Total number of conditions	3
ANAL ATRESIA	1 (4.0%)
ANOMALY OF MIDDLE EAR CONGENITAL	1 (4.0%)
SICKLE CELL DISEASE	1 (4.0%)
EAR AND LABYRINTH DISORDERS	
Total number of patients with at least one condition	1 (4.0%)
Total number of conditions	2
AURAL POLYP	1 (4.0%)
DEAFNESS UNILATERAL	1 (4.0%)
ENDOCRINE DISORDERS	
Total number of patients with at least one condition	2 (8.0%)
Total number of conditions	2
BASEDOW'S DISEASE	1 (4.0%)
GOITRE	1 (4.0%)
EYE DISORDERS	
Total number of patients with at least one condition	1 (4.0%)
Total number of conditions	1
EYELID OEDEMA	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one condition	9 (36.0%)
Total number of conditions	15
CONSTIPATION	5 (20.0%)
ABDOMINAL PAIN	2 (8.0%)
PANCREATITIS	2 (8.0%)
CHRONIC GASTRITIS	1 (4.0%)
CROHN'S DISEASE	1 (4.0%)
GASTRITIS	1 (4.0%)
HAEMATOCHEZIA	1 (4.0%)
NAUSEA	1 (4.0%)
SMALL INTESTINAL HAEMORRHAGE	1 (4.0%)

Investigator text for medical history conditions is coded using MedDRA version 20.1.
Percentages are based on N (number of patients in SE population).

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_mh.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_mh_SE.out
01AUG2018 19:02

Previous Medical History, Safety-Evaluable Patients
Protocol: WA25615

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Total number of patients with at least one condition	5 (20.0%)
Total number of conditions	6
CHEST PAIN	1 (4.0%)
CYST	1 (4.0%)
ILL-DEFINED DISORDER	1 (4.0%)
PAIN	1 (4.0%)
PERIPHERAL SWELLING	1 (4.0%)
PYREXIA	1 (4.0%)
HEPATOBILIARY DISORDERS	
Total number of patients with at least one condition	1 (4.0%)
Total number of conditions	1
HEPATITIS	1 (4.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one condition	1 (4.0%)
Total number of conditions	3
DRUG HYPERSENSITIVITY	1 (4.0%)
DUST ALLERGY	1 (4.0%)
SEASONAL ALLERGY	1 (4.0%)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one condition	5 (20.0%)
Total number of conditions	10
CAMPYLOBACTER GASTROENTERITIS	1 (4.0%)
CONJUNCTIVITIS	1 (4.0%)
EAR INFECTION	1 (4.0%)
EYE INFECTION	1 (4.0%)
ORAL CANDIDIASIS	1 (4.0%)
PNEUMONIA VIRAL	1 (4.0%)
RHINITIS	1 (4.0%)
SEPSIS	1 (4.0%)
URINARY TRACT INFECTION	1 (4.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one condition	3 (12.0%)
Total number of conditions	3
ANAPHYLACTIC TRANSFUSION REACTION	1 (4.0%)
SCAR	1 (4.0%)
SUBARACHNOID HAEMORRHAGE	1 (4.0%)
INVESTIGATIONS	
Total number of patients with at least one condition	6 (24.0%)
Total number of conditions	6
ATYPICAL MYCOBACTERIUM TEST POSITIVE	1 (4.0%)
CARDIAC MURMUR	1 (4.0%)
PLATELET COUNT INCREASED	1 (4.0%)
PULMONARY FUNCTION TEST DECREASED	1 (4.0%)
TRANSAMINASES INCREASED	1 (4.0%)
VITAMIN D DECREASED	1 (4.0%)

Investigator text for medical history conditions is coded using MedDRA version 20.1.
Percentages are based on N (number of patients in SE population).

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_mh.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_mh_SE.out
01AUG2018 19:02

Previous Medical History, Safety-Evaluable Patients
Protocol: WA25615

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
METABOLISM AND NUTRITION DISORDERS	
Total number of patients with at least one condition	3 (12.0%)
Total number of conditions	3
FAILURE TO THRIVE	1 (4.0%)
IRON DEFICIENCY	1 (4.0%)
OBESITY	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one condition	7 (28.0%)
Total number of conditions	11
BONE LESION	2 (8.0%)
JOINT SWELLING	2 (8.0%)
ARTHRALGIA	1 (4.0%)
ARTHRITIS	1 (4.0%)
BACK PAIN	1 (4.0%)
CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDER	1 (4.0%)
OSTEONECROSIS	1 (4.0%)
OSTEOPOROSIS	1 (4.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Total number of patients with at least one condition	2 (8.0%)
Total number of conditions	5
INFLAMMATORY PSEUDOTUMOUR	1 (4.0%)
MASTOCYTOMA	1 (4.0%)
NEOPLASM	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one condition	5 (20.0%)
Total number of conditions	8
EPILEPSY	2 (8.0%)
HEADACHE	2 (8.0%)
CEREBRAL DISORDER	1 (4.0%)
CEREBRAL INFARCTION	1 (4.0%)
SEIZURE	1 (4.0%)
SYNCOPE	1 (4.0%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one condition	1 (4.0%)
Total number of conditions	2
ANXIETY	1 (4.0%)
FEAR OF INJECTION	1 (4.0%)
RENAL AND URINARY DISORDERS	
Total number of patients with at least one condition	4 (16.0%)
Total number of conditions	7
HAEMATURIA	2 (8.0%)
PROTEINURIA	2 (8.0%)
DYSURIA	1 (4.0%)
GLOMERULONEPHRITIS RAPIDLY PROGRESSIVE	1 (4.0%)
RENAL FAILURE	1 (4.0%)

Investigator text for medical history conditions is coded using MedDRA version 20.1.
Percentages are based on N (number of patients in SE population).

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_mh.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_mh_SE.out
01AUG2018 19:02

Previous Medical History, Safety-Evaluable Patients
Protocol: WA25615

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one condition	9 (36.0%)
Total number of conditions	15
EPISTAXIS	3 (12.0%)
ASTHMA	2 (8.0%)
COUGH	2 (8.0%)
OROPHARYNGEAL PAIN	2 (8.0%)
DYSPNOEA	1 (4.0%)
NASAL CONGESTION	1 (4.0%)
NASAL INFLAMMATION	1 (4.0%)
NASAL POLYPS	1 (4.0%)
NASAL SEPTUM DEVIATION	1 (4.0%)
PLEURAL EFFUSION	1 (4.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Total number of patients with at least one condition	5 (20.0%)
Total number of conditions	6
ACNE	1 (4.0%)
MACULE	1 (4.0%)
PRURITUS	1 (4.0%)
PURPURA	1 (4.0%)
SKIN NECROSIS	1 (4.0%)
VASCULITIC RASH	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one condition	24 (96.0%)
Total number of conditions	28
GRANULOMATOSIS WITH POLYANGIITIS	19 (76.0%)
MICROSCOPIC POLYANGIITIS	5 (20.0%)
FLUSHING	1 (4.0%)
HYPERTENSION	1 (4.0%)

Investigator text for medical history conditions is coded using MedDRA version 20.1.
Percentages are based on N (number of patients in SE population).

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_mh.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_mh_SE.out
01AUG2018 19:02

Table 17 Immunization history, safety-evaluable patients

Immunization History, Safety-Evaluable Patients
Protocol: WA25615

	Rituximab (N=25)
Tetanus Immunoglobulin	
n	25
Yes	2 (8.0%)
No	23 (92.0%)
Hepatitis B Immunoglobulin	
n	25
Yes	2 (8.0%)
No	23 (92.0%)
Hepatitis A Immunoglobulin	
n	25
Yes	2 (8.0%)
No	23 (92.0%)
Rabies Antiserum	
n	25
Yes	0
No	25 (100.0%)
Varicella Zoster Immunoglobulin	
n	25
Yes	2 (8.0%)
No	23 (92.0%)
Other Immunization	
n	25
Yes	0
No	25 (100.0%)

From Immunization History Log in eCRF, all passive immunizations that the subject has received are recorded; If subject has received multiple doses of the same antibody only information on the most recent passive immunization recorded; Yes, if subject has previously received this immunization; No, if the subject has not previously received this immunization; The form will allow for additional OTHER Passive Immunizations to be added as needed.
Percentages are based on n.

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_immuhist.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_immuhist_SE.out
28AUG2018 21:56

Table 18 Vaccination history, safety-evaluable patients

Vaccination History, Safety-Evaluable Patients
Protocol: WA25615

	Rituximab (N=25)
Bacillus Calmette-Guerin	3 (12.0%)
Diphtheria	17 (68.0%)
Haemophilus Influenza B (Hib)	14 (56.0%)
Hepatitis A	7 (28.0%)
Hepatitis B	8 (32.0%)
Human Papilloma Virus	2 (8.0%)
Influenza	4 (16.0%)
Measles	17 (68.0%)
Meningococcal	15 (60.0%)
Mumps	17 (68.0%)
Pertussis	16 (64.0%)
Pneumococcus Polysaccharide	6 (24.0%)
Polio	16 (64.0%)
Rubella	17 (68.0%)
Tetanus	18 (72.0%)
Typhoid	2 (8.0%)
Varicella	7 (28.0%)

From Vaccination History Log in eCRF
Percentages are based on n.

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_vachist.sas
Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_vachist_SE.out
28AUG2018 22:31

Table 19 Previous medications for GPA/MPA, safety-evaluable patients

Protocol: WA25615

Class Other Treatment	Rituximab (N=25)
Total number of patients with at least one treatment	20 (80.0%)
Overall total number of treatments	123
ALKYLATING AGENTS	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	2
CYCLOPHOSPHAMIDE	2 (8.0%)
ANTIMETABOLITES	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	3
METHOTREXATE	2 (8.0%)
ANTIMICROBIAL/OTHER DRUG COMBINATIONS	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	1
DEXAMETHASONE/NEOMYCIN SULFATE/POLYMYXIN B SULFATE	1 (4.0%)
IMMUNOSUPPRESSANTS	
Total number of patients with at least one treatment	6 (24.0%)
Total number of treatments	18
MYCOPHENOLATE MOFETIL	4 (16.0%)
AZATHIOPRINE	2 (8.0%)
NON-STEROIDAL ANTI-INFLAMMATORIES	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	7
IBUPROFEN	1 (4.0%)
STEROIDS	
Total number of patients with at least one treatment	19 (76.0%)
Total number of treatments	92
METHYLPREDNISOLONE	10 (40.0%)
PREDNISOLONE	10 (40.0%)
PREDNISONE	5 (20.0%)
DEXAMETHASONE	1 (4.0%)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (4.0%)
STEROID NOS	1 (4.0%)
TRIAMCINOLONE HEXACETONIDE	1 (4.0%)

Multiple uses of a specific treatment for a patient were counted once in the frequency for the treatment. Likewise, multiple uses within a specific treatment class for a patient were counted once in the frequency for the treatment class.

Concomitant Treatments for GPA/MPA and Diseases Other than GPA/MPA

All patients (100%) received at least one concomitant treatment for diseases other than GPA/MPA during the study. The most frequently reported concomitant treatments included antihistamines (147 treatments in 25 patients [100%]), analgesics (166 treatments in 24 patients [96%]) and steroids (99 treatments in 21 patients [84%]). Five patients (20%) received treatment with immunosuppressants for diseases other than GPA/MPA (azathioprine [3 patients, 12%] and mycophenolate mofetil [2 patients, 8%]). Three patients received treatment with intravenous immunoglobulin (IVIG).

The CHMP noted that while concomitant immunosuppressive treatment was explicitly allowed in the Follow-up Phase, it seems that 5 patients received immunosuppressive treatment in the Remission-Induction Phase (azathioprine, mycophenolate mofetil, cyclophosphamide). The MAH explained how in the remission-induction period 3 (not 5) patients received additional immunosuppressive treatment, which was mycophenolate in all cases. In one of the patients, use was 18 days between months 2 and 3 and will not have impacted the assessment at month 6. Two of the patients used mycophenolate up to month 6, one of them reached PVAS remission while the other one did not. Consequently, it is considered that the overall efficacy results at month 6 are not meaningfully impacted by concomitant

therapy in these three patients. Combination therapy with different immunosuppressive agents and corticosteroids is common practice in the treatment of auto-immune-disorders, mainly to reduce the dose levels of potential toxic drugs.

Table 20 Concomitant medications for GPA/MPA, safety-evaluable patients

Protocol: WA25615

Class Other Treatment	Rituximab (N=25)
Total number of patients with at least one treatment	25 (100.0%)
Overall total number of treatments	560
ALKYLATING AGENTS	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	15
CYCLOPHOSPHAMIDE	2 (8.0%)
ANALGESICS	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	2
PARACETAMOL	2 (8.0%)
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	
Total number of patients with at least one treatment	3 (12.0%)
Total number of treatments	7
ENALAPRIL	1 (4.0%)
ENALAPRIL MALEATE	1 (4.0%)
LISINOPRIL	1 (4.0%)
ANTIHISTAMINES	
Total number of patients with at least one treatment	3 (12.0%)
Total number of treatments	4
CHLORPHENIRAMINE	3 (12.0%)
ANTIMALARIAL AGENTS	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	1
HYDROXYCHLOROQUINE SULFATE	1 (4.0%)
ANTIMETABOLITES	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	4
METHOTREXATE	1 (4.0%)
IMMUNOMODULATORS	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	5
ABATACEPT	1 (4.0%)
IMMUNOSUPPRESSANTS	
Total number of patients with at least one treatment	10 (40.0%)
Total number of treatments	24
MYCOPHENOLATE MOFETIL	6 (24.0%)
AZATHIOPRINE	4 (16.0%)
MUCOLYTICS	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	1
MESNA	1 (4.0%)
NON-STEROIDAL ANTI-INFLAMMATORIES	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	1
IBUPROFEN	1 (4.0%)
PROTON PUMP INHIBITORS	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	2
LANSOPRAZOLE	2 (8.0%)
SALICYLATES	
Total number of patients with at least one treatment	1 (4.0%)
Total number of treatments	1
ASPIRIN	1 (4.0%)
STEROIDS	
Total number of patients with at least one treatment	25 (100.0%)
Total number of treatments	491
PREDNISOLONE	16 (64.0%)
PREDNISONE	10 (40.0%)
METHYLPREDNISOLONE	9 (36.0%)
BECLOMETASONE	1 (4.0%)
DEXAMETHASONE	1 (4.0%)
FORMOTEROL FUMARATE/MOMETASONE FUROATE	1 (4.0%)
HYDROCORTISONE	1 (4.0%)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (4.0%)
STEROID NOS	1 (4.0%)
TRIAMCINOLONE ACETONIDE	1 (4.0%)
TRIAMCINOLONE HEXACETONIDE	1 (4.0%)
SULFONAMIDES	
Total number of patients with at least one treatment	2 (8.0%)
Total number of treatments	2
SULFAMETHOXAZOLE/TRIMETHOPRIM	2 (8.0%)

Included medications started anytime (after, on or before baseline) and is ongoing during study.
Concomitant medications that begin on the date of entry to the follow-up phase will not be included.

Rituximab treatment

In the Remission Induction Phase, all 25 patients (100%) completed the 4 scheduled rituximab infusions (four weekly IV infusions of 375 mg/m2 on Days 1, 8, 15, and 22). In accordance with the protocol, per investigator's discretion, patients could receive subsequent rituximab infusions on or after Month 6 to maintain remission and/or to control disease activity (including disease flares). Eight out of 25 patients received the induction regimen of 4 x 375 mg/m2 infusions only, and no further treatment with rituximab (Figure below). Seventeen patients (68%) received additional rituximab infusions on or after Month 6 until the Common Close-out date (Figure below), nine patients (36%) received a 5th infusion at Month 6.

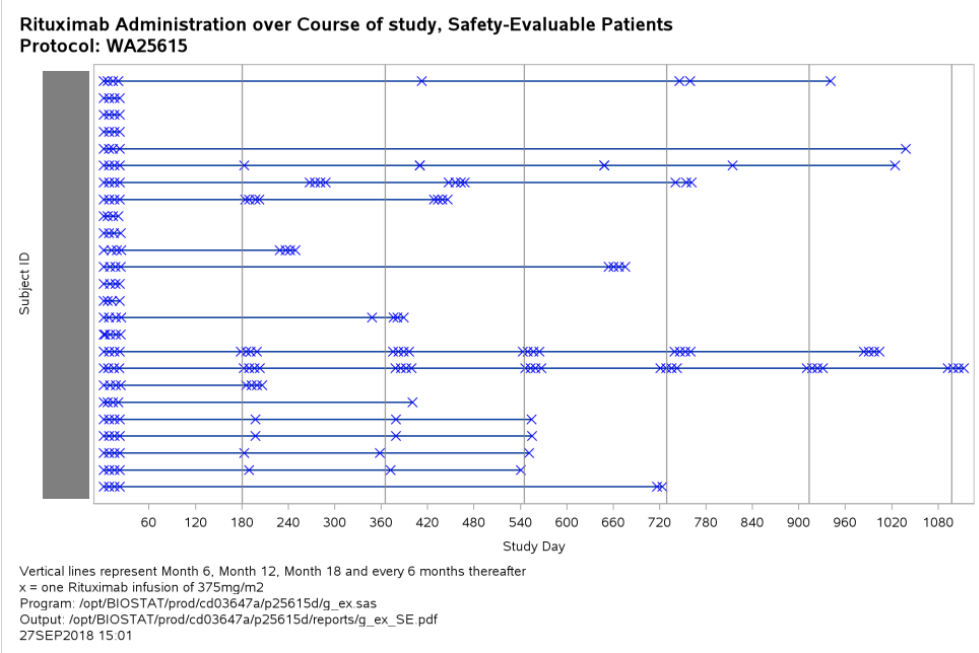


Figure 15 Rituximab administration over the course of the study

During the Overall Study Period (Remission Induction Phase + Follow-up Phase), patients received between 4 and 28 infusions of rituximab (up to 4.5 yrs [53.8 months]). In the Follow-up period, 5 patients received 375 mg/m2 once weekly x 4 rituximab infusions approximately every 6 months; 5 patients received one 375mg/m2 rituximab infusion every 6 months and a further 7 patients received other varied rituximab doses/regimens. The CHMP noted that in the figure above it can clearly be seen that the period from baseline to month 6 is the most informative part of the study. After month 6, several patterns arise, which appear to vary from repeating a course of 4 weekly infusions as reaction to a flare, to what may look like maintenance treatment of regular single infusions with a view to prevent a flare.

Numbers analysed

All of the 25 patients enrolled contributed to the safety, PK and efficacy analyses (see Table below).

Table 21 Analysis populations

Protocol: WA25615

Analysis Populations	Rituximab
Treated Patients (Assigned Treatment)	25
Safety Evaluable Population (Treatment Received)	25 (100.0%)
PK Population (Safety population with at least one evaluable PK sample)	25 (100.0%)

Outcomes and estimation

PVAS

Table 22 PVAS remission by key time-points (month 6, 12, 18), safety-evaluable patients

PVAS Remission by Key Time-Points (Month 6, 12 and 18), Safety-Evaluable Patients
Protocol: WA25615

		Rituximab (N=25)
PVAS Remission by MONTH 6	In Remission	14 (56.0%)
	95% CI	(34.9, 75.6)
PVAS Remission by MONTH 12	In Remission	23 (92.0%)
	95% CI	(74.0, 99.0)
PVAS Remission by MONTH 18	In Remission	25 (100.0%)
	95% CI	(86.3, 100.0)

PVAS remission by month 6, 12 and 18 is defined as: a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower), or a PVAS of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose
Percentages are based on N.

Table 23 PVAS remission, partial remission at **key time-points (month 6, 12, 18), safety-evaluable patients**

PVAS Remission, Partial Remission at Key Time-Points (Month 6, 12 and 18), Safety-Evaluable Patients
Protocol: WA25615

		Rituximab (N=25)
PVAS Remission at MONTH 6	In Remission	13 (52.0%)
	95% CI	(31.3, 72.2)
PVAS Partial Remission at MONTH 6	In Remission	0
	95% CI	(0.0, 13.7)
PVAS Remission at MONTH 12	In Remission	18 (72.0%)
	95% CI	(50.6, 87.9)
PVAS Partial Remission at MONTH 12	In Remission	0
	95% CI	(0.0, 13.7)
PVAS Remission at MONTH 18	In Remission	18 (72.0%)
	95% CI	(50.6, 87.9)
PVAS Partial Remission at MONTH 18	In Remission	1 (4.0%)
	95% CI	(0.1, 20.4)

Remission is defined as: PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) at the assessment time-point. Patients without any qualifying records post-baseline will be assumed to be not in remission.
Partial remission, defined as a 0 < PVAS <= 2 with no new or worse items and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) at the assessment time-point.
Percentages are based on N.

Table 24 PVAS duration of **remission, safety-evaluable patients**

PVAS Duration of remission, Safety-Evaluable Patients
Protocol: WA25615

Status	Rituximab (N=25)
Time on Remission (weeks)	
n	24
Mean (SD)	71.67 (50.95)
Median	56.14
Q1 - Q3 (IQR)	38.57 - 83.64 (45.07)
Min - Max	6.9 - 193.4

SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range
Duration of remission is defined as: PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) until the time to major or minor PVAS relapse/flare after remission, or until the end of the main study (common closeout date) or early study withdrawal, whichever comes first; This would apply only to the first occurrence of remission since it is measured from the first occurrence of PVAS 0 taper at goal to the earliest subsequent occurrence of PVAS flare.
n is the number of patients achieved at least one remission during the study.

Table 25 Comparison of BVAS/WG and PVAS Scores and Explanation of Differences in Remission Response Status at Month 6

Study Day	Study Visit	Discrepancy (difference in score)	Explanation of differences in scores	BVAS/WG score	BVAS/WG components	PVAS score	PVAS components
181	Month 6	1	Persistent disease item (arthralgia) present at baseline has persisted (but remained stable) for over 3 months is captured but not scored in the PVAS tool	1	Arthralgia/arthritis - persistent	0	Arthralgia/arthritis - persistent
176	Month 6	2	PVAS does not score minor items selected in the 'Other' category	2	Other minor item-new/worse	0	'other' PVAS minor item active
183	Month 6	2	Persistent minor item is not captured or scored in PVAS	2	Other minor item: persistent	0	No items marked as new, active or worsening disease
197	Month 6	1	Persistent hematuria not captured or scored in PVAS	1	Hematuria-persisten t	0	No items marked as new, active or worsening disease

Number of Major and Minor PVAS Relapses/ Flares

At month 6, 2 patients (8%) were reported to have one major PVAS flare, 1 patient (4%) had ≥5 minor PVAS flares, and 1 patient (4%) had one minor PVAS flare. At Month 12, 0 patients had major flares and 1 patient (4%) had one minor PVAS flare. At Month 18, 0 patients had PVAS flares. The number of major and minor PVAS relapses/flares at Months 6, 12, and 18 are provided.

PVAS Overall Score

Median baseline PVAS was 8 (IQR 5-15). At Month 6, 12 and 18, the median PVAS overall score was 0. The median change from baseline was -7.5 (IQR: -16.0 - -3.5) at Month 6, -7 (IQR: -15.0 - -5.0) at Month 12, and -8 (IQR: -19.0 - -5.0) at Month 18, indicating a clinically significant decrease in current vasculitis disease activity as shown by the overall decrease in PVAS scores from baseline.

PVAS Remission and ADA Status

A total of 4 out of 21 evaluable patients (19%) developed treatment-induced ADA during the Overall Study Period (see Section 6.1). One patient first tested positive for ADA at Month 4 and continued to have a positive titer at subsequent study visits (Months, 6, 9 and 18). Three additional patients first tested positive for ADA at Month 18. All of these 4 patients had achieved PVAS remission by Month 6 and by Month 12 and 18.

BVAS/WG

Table 16BVAS remission by month 6, safety-evaluable patients

BVAS Remission by Month 6, Safety-Evaluable Patients
Protocol: WA25615

		Rituximab (N=25)
BVAS Remission by MONTH 6	In Remission	12 (48.0%)
	95% CI	(27.8, 68.7)

BVAS remission by month 6 is defined as: a BVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower), or a BVAS of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose
Percentages are based on N.

Table 177 BVAS remission, partial remission at key time-points (month 6, 12, 18), safety-evaluable patient

Protocol: WA25615

		Rituximab (N=25)
BVAS Remission at MONTH 6	In Remission	9 (36.0%)
	95% CI	(18.0, 57.5)
BVAS Partial Remission at MONTH 6	In Remission	6 (24.0%)
	95% CI	(9.4, 45.1)
BVAS Remission at MONTH 12	In Remission	16 (64.0%)
	95% CI	(42.5, 82.0)
BVAS Partial Remission at MONTH 12	In Remission	4 (16.0%)
	95% CI	(4.5, 36.1)
BVAS Remission at MONTH 18	In Remission	17 (68.0%)
	95% CI	(46.5, 85.1)
BVAS Partial Remission at MONTH 18	In Remission	2 (8.0%)
	95% CI	(1.0, 26.0)

Remission is defined as: BVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) at the assessment time-point. Patients without any qualifying records post-baseline will be assumed to be not in remission.
Partial remission, defined as a 0 < BVAS <= 2 with no new or worse items and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) at the assessment time-point.
Percentages are based on N.

Table 28 BVAS duration of remission, safety-evaluable patients

Protocol: WA25615

Status	Rituximab (N=25)
Time on Remission (weeks)	
n	22
Mean (SD)	70.36 (54.19)
Median	54.64
Q1 - Q3 (IQR)	32.00 - 90.14 (58.14)
Min - Max	6.9 - 193.4

SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range.
Duration of remission is defined as: BVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower) until the time to major or minor BVAS relapse/flare after remission or until the end of the main study (common closeout date) or early study withdrawal, whichever comes first; This would apply only to the first occurrence of remission since it is measured from the first occurrence of BVAS 0 taper at goal to the earliest subsequent occurrence of BVAS flare.
n is the number of patients achieved at least one remission during the study.

Number of BVAS/PVAS Flares by Category by Visit, Safety-Evaluable Patients
Protocol: WA25615

	Assessment	Flares type	Number of Flares	Rituximab (N=25)
MONTH 1	BVAS	Major Flares	0	25 (100.0%)
			1	0
			2	0
			3	0
			4	0
			>=5	0
		Minor Flares	0	23 (92.0%)
			1	1 (4.0%)
			2	0
			3	1 (4.0%)
			4	0
			>=5	0
		Total Flares	0	23 (92.0%)
			1	1 (4.0%)
			2	0
			3	1 (4.0%)
			4	0
			>=5	0
	PVAS	Major Flares	0	25 (100.0%)
			1	0
			2	0
			3	0
			4	0
			>=5	0
		Minor Flares	0	24 (96.0%)
			1	0
			2	0
			3	1 (4.0%)

By BVAS/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 BVAS/PVAS items listed in protocol or disease that is severe enough to require treatment with CYC).
By BVAS/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 BVAS/PVAS items listed in protocol).
Percentages are based on N.

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_ef06.sas / Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_ef06_SE.out
01AUG2018 19:30 Page 1 of 27

BVAS Disease Progression prior to Remission by Month 6, Safety-Evaluable Patients
Protocol: WA25615

	Rituximab (N=25)
BVAS Progressive Disease Before Remission by Month 6	3/ 12 (25.0%)
95% CI	(5.5, 57.2)

BVAS remission by month 6 is defined as: a BVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower), or a BVAS of 0 on two consecutive readings at least 4 weeks apart, irrespective of glucocorticoid dose.
Patients without any qualifying records post-baseline will be assumed to be not in remission.
Progressive disease before remission by BVAS is defined as:
1. Persistence or worsening of a major BVAS item present at entry, and/or
2. A new major BVAS item that is not present at entry.
Major (and minor) BVAS items are defined in Protocol, Table 3.
Percentages are based on the number of patients in remission by month 6.

Program: /opt/BIOSTAT/prod/cd03647a/p25615d/t_ef02.sas / Output: /opt/BIOSTAT/prod/cd03647a/p25615d/reports/t_ef02_SE.out
28AUG2018 22:21 Page 1 of 1

Other efficacy endpoints

Cumulative Glucocorticoid Dose

A decrease in median overall oral glucocorticoid (prednisone or equivalent) use was observed over time, from Week 1 to Month 18 (figure below). A clinically meaningful decrease in median oral glucocorticoid use was observed from Week 1 (median=45 mg [IQR: 35 – 60]) prednisone equivalent dose to Month 6 (median = 7.5 mg [IQR: 4-10])) during the protocol-defined oral steroid taper, which was subsequently maintained at Month 12 (median = 5 mg [IQR: 2-10])) and Month 18 (median = 5 mg [IQR: 1-5]).).

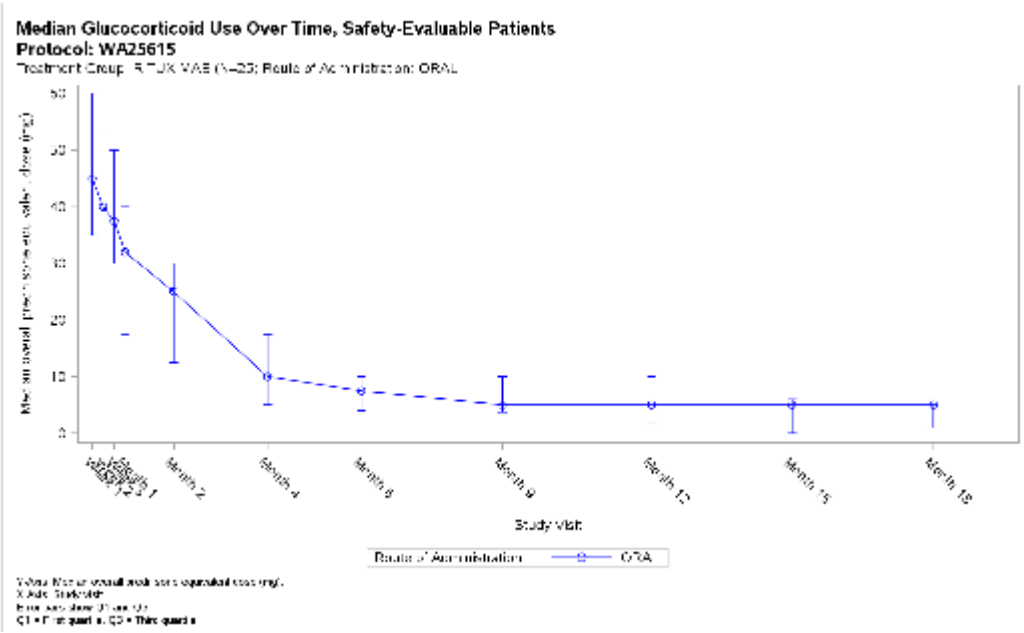


Figure 16 Median Glucocorticoid Use Over Time (Oral Administration)

Glomerular Filtration Rate

There was a slight decline in the median GFR between Months 6 and 18, possibly due to variations in disease activity in selected patients; however, by Month 18 it had returned to almost baseline levels.

Table 29 Glomerular filtration rate (GFR) results and change from baseline by visit, safety-evaluable patients

Protocol: WA25615

Laboratory Test: Urinalysis - Glomerular Filtration Rate (mL/min/1.73m2)

	Rituximab (N=25)	
Visit	Value at Visit	Change from Baseline
Baseline		
n	25	
Mean (SD)	140.26 (36.75)	
Median	137.78	
Q1 -Q3 (IQR)	120.31 - 156.81 (36.50)	
Min - Max	79.9 - 260.7	
Month 1		
n	24	24
Mean (SD)	122.40 (20.80)	-12.84 (27.07)
Median	122.78	-11.31
Q1 -Q3 (IQR)	106.73 - 132.98 (26.25)	-31.26 - 9.80 (41.06)
Min - Max	84.0 - 169.2	-68.3 - 30.4
Month 4		
n	25	25
Mean (SD)	123.95 (24.06)	-16.31 (28.18)
Median	118.64	-13.30
Q1 -Q3 (IQR)	110.14 - 133.73 (23.59)	-40.99 - 9.97 (50.96)
Min - Max	89.9 - 198.5	-62.8 - 28.6
Month 6		
n	24	24
Mean (SD)	123.42 (22.98)	-11.82 (24.84)
Median	123.05	-7.92
Q1 -Q3 (IQR)	107.40 - 140.81 (33.42)	-32.65 - 4.43 (37.08)
Min - Max	85.6 - 176.2	-57.5 - 32.1
Month 12		
n	22	22
Mean (SD)	132.25 (22.91)	-2.13 (27.58)
Median	126.80	-2.93
Q1 -Q3 (IQR)	117.07 - 148.04 (30.97)	-23.15 - 15.74 (38.89)
Min - Max	90.2 - 177.9	-50.3 - 65.9
Month 18		
n	20	20
Mean (SD)	135.44 (27.66)	-2.31 (25.49)
Median	136.38	-2.85
Q1 -Q3 (IQR)	116.29 - 152.11 (35.82)	-26.23 - 14.40 (40.62)
Min - Max	91.2 - 195.7	-34.0 - 51.6

SD = Standard Deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range
Baseline is the patient's last observation prior to initiation of study drug.
GFR is estimated using the Schwartz formula.

Assessment of Damage: Paediatric Vasculitis Damage Index

PVDI measures cumulative assessment of organ dysfunction, damage or scarring that has been present for at least 3 months and has occurred since the onset of vasculitis. As time progresses, the damage index score can only either remain stable or deteriorate. PVDI had a median value of 2 at Months 6, 12 and 18, with median change from baseline equal to 0, indicating that after an initial increase between baseline and Month 6, the median PDVI damage index score subsequently remained stable between Months 6 and 18 (Table below).

Table 30 Paediatric vasculitis damage index (PVDI) by visit, safety-evaluable patients

Protocol: WA25615

Visit		Rituximab (N=25) Value at Visit	Rituximab (N=25) Change from Baseline
Day 1 (Baseline)			
	n	25	
	Mean (SD)	2.64 (5.94)	
	Median	0.00	
	Q1 - Q3 (IQR)	0.00 - 3.00 (3.00)	
	Min - Max	0.0 - 29.0	
Month 6			
	n	24	24
	Mean (SD)	3.54 (6.03)	0.83 (1.74)
	Median	2.00	0.00
	Q1 - Q3 (IQR)	0.00 - 4.00 (4.00)	0.00 - 1.00 (1.00)
	Min - Max	0.0 - 29.0	-1.0 - 7.0
Month 12			
	n	25	25
	Mean (SD)	3.72 (5.74)	1.08 (2.12)
	Median	2.00	0.00
	Q1 - Q3 (IQR)	0.00 - 4.00 (4.00)	0.00 - 1.00 (1.00)
	Min - Max	0.0 - 28.0	-1.0 - 7.0
Month 18			
	n	22	22
	Mean (SD)	4.05 (6.19)	1.09 (2.81)
	Median	2.00	0.00
	Q1 - Q3 (IQR)	0.00 - 5.00 (5.00)	0.00 - 1.00 (1.00)
	Min - Max	0.0 - 28.0	-2.0 - 9.0

SD = Standard deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range
Baseline is the patient's last observation prior to initiation of study drug.

Evaluation of Anti-Drug Antibodies on Efficacy Outcomes

A total of 4 out of 21 evaluable patients (19%) developed treatment-induced ADA during the Overall Study Period (see CSR WA25615). One patient first tested positive for ADA at Month 4 during the Remission Induction Phase, after the first 4 rituximab infusions, and continued to have a positive titer at subsequent study visits (Months, 6, 9 and 18). Three other patients tested positive for ADA for the first time at Month 18. The PopPK analysis conducted in adult and paediatric patients showed that patients with detected ADA had 38.2% higher clearance, resulting in 27.6% lower AUC during the Remission Induction Phase; however, this had no impact on efficacy outcomes. All 4 patients with detected ADA had achieved PVAS remission by Months 6, 12 and 18.

Autoantibody Levels

A total of 22 out of 25 patients (88%) were ANCA positive as measured by cytoplasmic immunofluorescence staining at baseline. Of the 3 patients reported to be ANCA negative at baseline, 1 patient was a relapsed patient who was ANCA negative at baseline but was pANCA and MPO positive at the time of original diagnosis, 1 patient was a relapsed patient who was ANCA negative at baseline but MPO positive at the time of original diagnosis, and 1 patient was newly diagnosed who was ANCA negative at baseline but positive for pANCA 51 days prior to baseline (outside of the 30 day window for baseline laboratory values). Seropositivity for PR3-ANCA (56% of patients at baseline and 32% and 21% by Months 6 and 12, respectively) and MPO-ANCA autoantibodies (28% at baseline and 4% and 0% by Months 6 and 12, respectively) decreased over time from baseline. Likewise, seropositivity for P-ANCA (16.7% of patients at baseline and 0% at Month 12) and C-ANCA (50% of patients at baseline and 13.6% at Month 12) decreased from baseline.

CHQ-PF28

On average, CHQ-PF28 improved between baseline and month 6 in the subscales: Physical Functioning, Role/Social Limitations – Emotional/Behavioral, Role/Social Limitations – Physical, Bodily

Pain Discomfort, Mental Health, Change in Health, Parental Impact – Emotional, Parental Impact – Time, Family Activities. On average, CHQ-PF28 deteriorated between baseline and month 6 in Behavior, Global Behavior Item, General Health Perceptions, Family Cohesion.

Ancillary analyses

Subgroup analyses for the main efficacy outcome of interest, PVAS remission at month 6, was performed for ANCA status, disease state and Age class at baseline (Table below). There was one patient developing ADA before month 6, PVAS remission at 6 months is therefore not presented.

Table 31 PVAS remission at month 6, for ANCA status, disease state and Age class at baseline

		n=	PVAS remission month 6
ANCA	Positive	22	12 (54%)
	Negative	3	1 (33%)
AAV diagnosis	New	18	10 (55%)
	Relapse	7	3 (42%)
Age	≥6 to <12 years	6	5 (83%)
	≥12 years to ≤17	19	9 (47%)

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32 Summary of Efficacy for trial WA25615

Title: Paediatric Polyangiitis and Rituximab Study (PePRS)			
Study identifier	WA25615		
Design	A Phase IIa, international, multicenter, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4x375 mg/m2 intravenous rituximab in paediatric patients with new or established severe granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), concomitantly treated with glucocortocoids.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicable 12 months and beyond
Hypothesis	None, exploratory efficacy objectives		
Treatments groups	Rituximab (n=25)		4 intravenous (IV) rituximab infusions of 375 mg/m^2 body surface area (BSA) on Days 1, 8, 15 and 22 with oral prednisolone or prednisone 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6, preceded by 3 doses of methylprednisolone IV (30 mg/kg/day, max 1 g/day) prior to first rituximab infusion.
Endpoints and definitions	Exploratory Efficacy Objective	PVAS remission at month 6	PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower)

	Exploratory Efficacy Objective	BVAS/WG remission at month 6	BVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever was lower)
		Glucocorticoid use at month 6	Median dose (mg)
		PGADA	Physician's Global Assessment of Disease Activity (VAS)
		CHAQ	Children's Health Assessment Questionaire disability index (0-3)

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Exploratory before-after analysis, between baseline and month 6		
Descriptive statistics and estimate variability	Treatment group	**Rituximab**	**--**
	Number of subjects	N=25	--
	PVAS remission at month 6	56%	
	95%CI	(35%-76%)	
	BVAS remission at month 6	36%	
	95%CI	(18%-57.5%)	
	Median duration of PVAS remission up to CCO	56 weeks	
	(P25 – P75)	(39 – 84)	
	Median oral glucocorticoid dose at month 6	7.5 mg	
	(P25 – P75)	(4-10)	
	Mean PGADA change at month 6	-38 mm	
	(SD)	(32)	
	Mean CHAQ change at month 6	-0.16	
	(SD)	(0.73)	
Notes	The (exploratory) efficacy analyses were from a single cohort of patients exposed to Rituximab, in the Remission-Induction Phase from baseline to 6 months. Changes at month 6 were calculated from baseline. The usual table parts with statistical testing and the effect estimate per comparison have been deleted.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

As agreed with the PDCO the MAH has provided one pivotal single-arm trial, Study WA25615, in paediatric patients with severe GPA or MPA. Despite the uncontrolled nature of this study, the design is fully acceptable in this very rare disease setting. The MAH clearly defined the objectives of this study. The study's primary objectives are safety and PK, while exploratory endpoints were efficacy objectives.

The study design consisted of an initial 6-month remission induction phase, with a minimum 18-month follow-up, up to a maximum of 54 months (4.5 years) overall. Patients were to receive a minimum of 3 doses of IV methylprednisolone (30 mg/kg/day, not exceeding 1 g/day) prior to the first MabThera IV infusion. If clinically indicated, additional daily doses (up to three), of IV methylprednisolone could be given. The remission induction regimen consisted of four once weekly IV infusions of MabThera at a dose of 375 mg/m2 BSA, on study days 1, 8, 15 and 22 in combination with oral prednisolone or prednisone at 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6. After the remission induction phase, patients could, at the discretion of the investigator, receive subsequent MabThera infusions on or after Month 6 to maintain PVAS remission and control disease activity (including progressive disease or flare) or to achieve first remission.

Patients were diagnosed using EULAR/PRINTO/PRES criteria for GPA or Chapel Hill Consensus Conference criteria for MPA. This is fully acceptable from a clinical point of view. Both newly diagnosed and relapsing patients were included in the study: Eighteen patients (72%) had newly diagnosed disease upon study entry (13 patients with GPA and 5 patients with MPA) and 7 relapsing disease (6 patients with GPA and 1 patient with MPA). The exclusion criteria clearly exclude any patient with limited or very severe and extensive disease, concomitant disease, etc.

Patients were treated with four weekly infusions of 375 mg/m2 rituximab. This body-surface-area dose regimen was based on the assumption that mechanism of clearance and linear PK properties, and that PK of rituximab in children are expected to be similar to those in adults. The dose regimen is considered acceptable (see clinical pharmacology).

Patients received IV methylprednisolone and oral prednisolone/prednisone in order to avoid severe infusion related reactions (IRRs). The doses used are fully acceptable from a clinical point of view. Adequate recommendations on premedication and prophylactic medications have been included in Section 4.2 of the SmPC.

The MAH has defined multiple clinically relevant endpoints. Since these are all exploratory endpoints, there is no adjustment for multiplicity.

There were 4 protocol amendments during the conduct of the study, but none of the amendments are considered critical with regards to study design and conduct of the study. After amendment (protocol version 5) it was allowed to include patients who had previously been treated with rituximab or other biologic B cell−targeted therapy (e.g., anti-CD19, anti-CD20, anti-CD22, or anti-B-lymphocyte stimulator [BLys]/BAFF), except if within 6 months prior to baseline visit. This was done to facilitate recruitment but may lead to a positive selection of included patients. However, as it appeared no patients with previous B-cell depleting therapy were included.

Four patients had a total of 4 major protocol deviations. Three of the deviations were related to concomitant medication. One patient was included in the study despite fulfilling an exclusion criterion. These deviations did not have any significant impact on safety and efficacy results.

All 25 patients completed all four once weekly IV infusions for the 6-month remission induction phase. A total of 24 out of 25 patients completed at least 18 months of follow-up.

Most of the patients were female, white and aged 12-17 years. There were 6 patient aged 2-11; however, min and max were 6 and 17 years. Children below the age of 6 did not happen to be included in the study, the use of rituximab in patients of the age between 2 and 6 will rely on extrapolation from PK/PD data. Based on similarity of the pathogenesis over age and the absence of an age effect in reaching PVAS remission this is acceptable to the CHMP.

Patients below the age of 2 were not eligible for the study and will not be eligible for treatment with rituximab according to the SmPC. The reason is that rituximab is potentially unsafe for children in whom the immune system is not fully developed.

Three patients were ANCA negative at baseline, however, one patient was a relapsed patient that was pANCA/MPO positive at diagnosis, the second patient was MPO positive at diagnoses, and the third patient was newly diagnosed and negative at baseline but became pANCA positive during treatment.

The majority of the patients had severe disease; however, the MAH applied for an indication in *"active" GPA (Wegener's) and MPA.* Since the disease can present itself in different degree of severity, no solid arguments have been provided by the MAH to treat paediatric patient with slow and few symptoms. B-cell depletion is a serious matter and it would be inappropriate to start with rituximab in patients with few and mild symptoms. The inclusion criteria of study WA25615 appropriately describe children with 'active severe' GPA/MPA. Mabthera is indicated in severe, active GPA / MPA in the adult population. Therefore, at the CHMP's request, the MAH has revised the indication accordingly.

The majority of the patients are diagnosed with GPA, while only 6 patients had MPA. Furthermore, most patients were newly diagnosed. However, the CHMP acknowledged that MPA and GPA overlap as disease entities and that the numbers are low as it is a very rare disease.

Efficacy data and additional analyses

Twenty-four out of 25 patients (96%) in Study WA25615 achieved oral glucocorticoid taper to 0.2 mg/kg/day (or less than or equal to 10 mg/day, whichever was lower) at or by Month 6 during the protocol-defined oral steroid taper.

A decrease in median overall oral glucocorticoid use was observed from Week 1 (median = 45 mg prednisone equivalent dose [IQR: 35 – 60]) to Month 6 (median = 7.5 mg [IQR: 4-10]), which was subsequently maintained at Month 12 (median = 5 mg [IQR: 2-10]) and Month 18 (median =5 mg [IQR: 1-5]).

Clinically encouraging results were observed in terms of PVAS and BVAS. The proportion of patients with PVAS remission was 52% at month 6, 72% at month 12 and 72% at month 18. The mean duration of response 71.67 weeks, where the min and max are 6.9 and 193.4 weeks respectively. The number of major and minor PVAS relapses/flares at different time-points decreased over time, as expected. By month 12 no patients had PVAS flares. Similar results were observed in terms of BVAS. The CHMP noted that the effect in MPA and GPA patients cannot be disentangled.

Looking at other exploratory efficacy endpoints, the median oral glucocorticoid use declined rapidly over the first weeks of treatment, and by month 6 it reaches a very low plateau, median 7.5 mg. Patients were subsequently maintained on 5 mg as per protocol.

With regards to GFR, slight decrease was observed at month 6, but by month 18 the GFR rate was almost at the same level as at baseline. The paediatric vasculitis damage index (PVDI), which is a measure for cumulative organ damage, dysfunction or scarring, showed that from baseline to month 6, there is an increase in median value to 2; however, subsequently the PVDI value remained stable after month 6. Thus, indicating that after an initial increase in organ damage/dysfunction/scarring treatment

with rituximab stabilises the disease and thereby organ damage. Changes in CHQ-PF28 are difficult to interpret in meaning, and the clinical relevance unclear.

The CHMP noted that only few patients were ANCA negative at baseline, results are difficult to interpret for this subgroup. It is reassuring that efficacy appears to be similar for patients with new disease or with a relapse of established disease (see table 28). There is no clear indication for an age effect, due to small numbers. Given the lack of patients between 2 and 6, the higher response proportion in the lower age group (see table 28) is reassuring.

The study was not designed to evaluate rituximab in the maintenance setting, but only the induction of remission. Although, in the absence of comparative clinical data on maintenance strategies in children, the CHMP agreed that the efficacy in the maintenance regimen may be supported by the PK and clinical data of the RAVE and WA25615 studies. However, the lack of data on long-term safety in the maintenance setting was of major concern to the CHMP. The MAH was asked repeatedly to make a proposal, present the outline and commit to conducting a PASS study post-approval in order to address the concerns related to long-term safety in the maintenance setting. Regrettably, the MAH could not commit to conducting a PASS study in the maintenance setting. Section 4.1. has been limited to the induction setting.

2.4.4. Conclusions on the clinical efficacy

The totality of evidence, including Mechanism of Action, disease pathophysiology, approved use in adults and the observed efficacy results in Study WA25615 can be considered clinically meaningful. Although the efficacy outcomes for this study were exploratory, they were as expected and in line with the results observed in the adult population.

The majority of the patients had severe disease; however, the MAH applied for an indication in "active" GPA (Wegener's) and MPA. Since the disease can present itself in different degree of severity, no solid arguments have been provided by the MAH to treat paediatric patient with slow and few symptoms. B-cell depletion is a serious matter and it would be inappropriate to start with rituximab in patients with few and mild symptoms. The inclusion criteria of study WA25615 appropriately describe children with 'active severe' GPA/MPA. Mabthera is indicated in severe, active GPA / MPA in the adult population. Therefore, at the CHMP's request, the MAH has revised the indication accordingly.

2.5. Clinical safety

Introduction

Study WA25615 represents the first global clinical trial investigating safety, pharmacokinetic (PK) and/or pharmacodynamics (PD), and effectiveness of rituximab in paediatric patients with GPA or MPA. The number of patients planned and recruited into the study is reflective of GPA and MPA being rare diseases. The safety and tolerability of rituximab is described for the initial 6-month Remission Induction Phase and the Overall Study Period (period of Remission Induction Phase together with the 12-months Follow-up Phase with data reported until the common closeout date [CCO]). The CCO occurred on 10 May 2018, 18 months after enrolment of the last patient.

Additionally, post-marketing safety data reported in the company global safety database and in the published literature from paediatric patients treated with rituximab for GPA or MPA are summarized to further support the evaluation of safety data in pediatric patients.

Patient exposure

All patients (100%) completed the 4 scheduled rituximab infusions (four weekly intravenous [IV] infusions of 375 mg/m2 on Days 1, 8, 15, and 22) in the Remission Induction Phase. Five patients (20%) had rituximab infusions, which were interrupted or modified (rate slowed or adjusted primarily due to IRRs) upon first exposure. The mean total cumulative dose during the Remission Induction Phase was 2301.5 mg (range: 1290 – 3413 mg). In accordance with the protocol, per investigator's discretion, patients could receive subsequent rituximab infusions on or after Month 6 to maintain remission and/or to control disease activity (including disease flares).

During the Overall Study Period, patients received between 4 and 28 infusions of rituximab (up to 4.5 years [53.8 months]). Seventeen out of 25 patients (68%) received additional rituximab infusions on or after Month 6 until the CCO. Five patients received 375 mg/m2 once weekly x 4 rituximab infusions approximately every 6 months; 5 patients received one 375 mg/m2 rituximab infusion approximately every 6 months and a further 7 patients received other varied rituximab doses/regimens (e.g. one infusion or cycle of 4 infusions, or other dose combination at Month 9, Month15, or other time-point) according to their treating physician. Dosing of rituximab was weight-based (375 mg/m2) and actual dose received in 'mg' was calculated according to the patient's body surface area (BSA) at screening as this is the only time it was captured in the database. Therefore, there may be a slight under representation of actual dose administered, as it is expected that height and weight were measured locally before dosing and they likely increased with age over the study duration.

The majority of patients (68%) were followed in the study for between 18 months and 3 years. Six patients (24%) were followed for over 3 years, up to a maximum of 4.5 years. The total duration of observation for all patients was 61.1 patient years.

Table 1833 Rituximab Treatment Exposure by Visit during Remission Induction Phase, Safety-Evaluable Patients

Protocol: WA25615

	RITUXIMAB (N=25)
Infusions started	
n	25
BASELINE	25 (100.0%)
WEEK 1	25 (100.0%)
WEEK 2	25 (100.0%)
WEEK 3	25 (100.0%)
MONTH 6	8 (32.0%)
UNSCHEDULED	1 (4.0%)
Infusion Interrupted/Modified	
BASELINE	5/25 (20.0%)
WEEK 1	2/25 (8.0%)
WEEK 2	2/25 (8.0%)
WEEK 3	0/25
MONTH 6	1/ 8 (12.5%)
UNSCHEDULED	1/ 1 (100.0%)
Total number of infusions completed	
n	25
1	0
2	0
3	0
4	16 (64.0%)
5	9 (36.0%)
Total cumulative dose (mg)	
n	25
Mean (SD)	2301.5 (441.1)
Median	2262.0
Q1 - Q3 (IQR)	2000.0 - 2585.5 (585.5)
Min - Max	1290 - 3413

SD = Standard Deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile
SD = Standard Deviation.
Percentages are based on n.
Duration of observation = day of first exposure to Rituximab to date of last contact. 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.
For "Infusion started" section, percentages are based on n.

For "Infusion Interrupted/Modified" section, percentages are based on the number of infusions in corresponding visit.

Table 34 Summary of Rituximab Exposure Overall, Safety-Evaluable Patients

Protocol: WA25615

	RITUXIMAB (N=25)
Total number of infusions administered	
n	25
Mean (SD)	8.4 (6.1)
Median	7.0
Q1 - Q3 (IQR)	4.0 - 8.0 (4.0)
Min - Max	4 - 28
Total cumulative dose (mg)	
n	25
Mean (SD)	4520.8 (3932.2)
Median	3211.0
Q1 - Q3 (IQR)	2608.0 - 4389.9 (1781.9)
Min - Max	1894 - 16850
Duration of Observation (Months)	
n	25
Mean (SD)	29.51 (11.37)
Median	24.23
Q1 - Q3 (IQR)	20.83 - 35.93 (15.11)
Min - Max	15.7 - 53.8
Duration of Observation (Months)	
n	25
Duration <= 6	0
6 < Duration <= 12	0
12 < Duration <= 18	2 (8.0%)
18 < Duration <= 24	9 (36.0%)
24 < Duration <= 36	8 (32.0%)
36 < Duration <= 48	3 (12.0%)
48 < Duration <= 60	3 (12.0%)
Duration > 60	0
Total patient years of observation	61.1

SD = Standard Deviation, Q1 = First quartile, Q3 = Third quartile, IQR = interquartile range
Include infusions administrated during Day 1 to common closeout date.
Common closeout date is 18 months after enrollment of last patient.
Percentages are based on n.

Adverse events

Table 35 Overview of Adverse Events during Remission Induction Phase and Overall, Safety-Evaluable Patients

Protocol: WA25615
Phase: REMISSION INDUCTION

	Rituximab (N=25)
Total number of adverse events	158
Total number of serious adverse events	10
Total number of deaths	0
Total number of patients with at least one	
Adverse event	25 (100.0%)
Severe adverse event (at greatest intensity)	7 (28.0%)
Adverse event assessed as related to study drug by investigator	13 (52.0%)
Serious adverse event	7 (28.0%)
Serious adverse event assessed as related to study drug by investigator	1 (4.0%)
Adverse event leading to discontinuation from study treatment	0
Specific AEs	
Infection	17 (68.0%)
Serious infection	3 (12.0%)
Opportunistic infection	0
Infusion related reaction	15 (60.0%)
Cardiac event	0
Malignancies	0
Phase: OVERALL	
Total number of adverse events	404
Total number of serious adverse events	27
Total number of deaths	0
Total number of patients with at least one	
Adverse event	25 (100.0%)
Severe adverse event (at greatest intensity)	15 (60.0%)

Adverse event assessed as related to study drug by investigator	15 (60.0%)
Serious adverse event	12 (48.0%)
Serious adverse event assessed as related to study drug by investigator	1 (4.0%)
Adverse event leading to discontinuation from study treatment	0
Specific AEs	
Infection	23 (92.0%)
Serious infection	7 (28.0%)
Opportunistic infection	0
Infusion related reaction	17 (68.0%)
Cardiac event	1 (4.0%)
Malignancies*	1 (4.0%)

Percentages are based on N.
Severe adverse event = Adverse events with NCI-CTCAE grade >= 3
Specific Adverse Events:
Infections Include AEs with System Organ Class equals 'INFECTIONS AND INFESTATIONS'.
Serious Infections Include serious AEs with System Organ Class equals 'INFECTIONS AND INFESTATIONS'.
Opportunistic Infection Include AEs with Prefer Term defined in AEGT basket;'Roche Standard AEGT oportunistic Infections'.
AEGT = Adverse event grouped terms
IRR is defined as events that occur during or within 24 hours of an infusion and fall within Roche standard AEGT basket for Infusion Related Reactions + Hypersensitivity.
Cardiac events Include AEs with System Organ Class equals 'CARDIAC DISORDERS'.
Malignancies Include AEs with Prefer Term defined in the Malignant or Unspecified Tumors SMQ (Wide).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Investigator text for AEs is coded using MedDRA version 20.1.

- *Note, the AE displayed as malignancy in the above table from the SOC Neoplasm benign, malignant and unspecified [incl cysts and polyps] was a Grade 1 benign tracheal neoplasm.

Table 36 Common Adverse Events Reported in ≥10% of Patients during Remission Induction Phase and Overall, Safety-Evaluable Patients

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Phase: Remission Induction	
Overall total number of patients with at least one AE	20 (80.0%)
GASTROINTESTINAL DISORDERS	
NAUSEA	4 (16.0%)
ABDOMINAL PAIN UPPER	3 (12.0%)
CONSTIPATION	3 (12.0%)
INFECTIONS AND INFESTATIONS	
UPPER RESPIRATORY TRACT INFECTION	4 (16.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
INFUSION RELATED REACTION	15 (60.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
ARTHRALGIA	3 (12.0%)
BACK PAIN	3 (12.0%)
NERVOUS SYSTEM DISORDERS	
HEADACHE	4 (16.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
COUGH	3 (12.0%)
EPISTAXIS	3 (12.0%)
GASTROINTESTINAL DISORDERS	
DIARRHOEA	7 (28.0%)
NAUSEA	5 (20.0%)
ABDOMINAL PAIN UPPER	4 (16.0%)
VOMITING	4 (16.0%)
ABDOMINAL PAIN	3 (12.0%)
CONSTIPATION	3 (12.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
CHEST PAIN	3 (12.0%)
IMMUNE SYSTEM DISORDERS	
HYPOGAMMAGLOBULINAEMIA	3 (12.0%)
INFECTIONS AND INFESTATIONS	
UPPER RESPIRATORY TRACT INFECTION	12 (48.0%)
INFLUENZA	6 (24.0%)
CONJUNCTIVITIS	5 (20.0%)
NASOPHARYNGITIS	5 (20.0%)
LOWER RESPIRATORY TRACT INFECTION	4 (16.0%)
SINUSITIS	4 (16.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	4 (16.0%)
EAR INFECTION	3 (12.0%)
GASTROENTERITIS	3 (12.0%)
PHARYNGITIS	3 (12.0%)
URINARY TRACT INFECTION	3 (12.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
INFUSION RELATED REACTION	17 (68.0%)
MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Phase: Overall	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
ARTHRALGIA	5 (20.0%)
BACK PAIN	5 (20.0%)
PAIN IN EXTREMITY	4 (16.0%)

NERVOUS SYSTEM DISORDERS	
HEADACHE	9 (36.0%)
MIGRAINE	3 (12.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
EPISTAXIS	7 (28.0%)
COUGH	6 (24.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
ERYTHEMA	3 (12.0%)
VASCULAR DISORDERS	
GRANULOMATOSIS WITH POLYANGIITIS	6 (24.0%)
HYPERTENSION	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.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.

The CHMP noted that the pattern of common AEs and of grade 3-4 AEs in the Remission-Induction Period is in line with the safety experience in adults.

The common AEs can also be found in section 4.8 of the SmPC for adults, except for epistaxis. However, epistaxis and cough may well occur as manifestations of GPA/MPA. The MAH used a cut-point of ≥10% to denote "common AEs" for this study. This was agreed by the CHMP, as for this study it means that AEs occurred in more than 2 patients (of 25).

There were 11 AEs of grade 3-4 in 7 patients, most of them (3) infections. There were 3 AEs that are identical to (granulomatosis with polyangiitis, vasculitis) or may be associated with (rhinalgia) the indication. One of the grade 3-4 AEs was an infusion-related reaction. When analysed per infusion the occurrence of Infusion-Related Reactions (IRRs) decreases from 32% to 8%, but in total 60% of the patients had an IRR. In the adult remission-induction RAVE study, the incidence of IRRs was the highest during the first infusion and decreased with subsequent infusions. It is known for rituximab that generally the occurrence of IRRs decreases with the number of infusions.

In the RTX group, the proportion of patients experiencing an IRR was 12.1%, 5.1%, 4.1%, and 1.1% following the first, second, third, and fourth infusions, respectively. The same kind of decrease is noticed following the 4 infusions in the remission-induction phase in study WA25615. Use of pre-medication to prevent infusion related reactions was applied in adults (RAVE) and in children (WA25615) as is described in the SmPC. The Applicant explains that a difference in definitions of IRR (investigator-attributed in RAVE or predefined definitions 'Roche standard AEGT basket for IRRs+hypersensitivity') may have contributed to a difference in occurrence of IRR. RAVE definitions for IRR were applied post-hoc to study WA25615, leading to a lower occurrence of IRR with n=6 (24%) children experiencing ≥1 IRR. Hence, it is likely that the occurrence of IRR in children is not higher than for adults with GPA/MPA.

In the overall treatment period, the most common AEs were also GI related (as above), IRR and infections (primarily upper respiratory tract infections). These AEs are in line with the known safety profile of rituximab. Furthermore, the majority of these AEs are clinically manageable, e.g. pre-treatment with corticosteroids before IV infusion of rituximab in order to avoid IRR.

Table 37 Adverse events related to study treatment during remission induction phase and overall, safety-evaluable patients

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	13 (52.0%)
Overall total number of AEs	30
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	6 (24.0%)
Total number of AEs	11
INFUSION RELATED REACTION	6 (24.0%)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	6 (24.0%)
Total number of AEs	11
UPPER RESPIRATORY TRACT INFECTION	1 (4.0%)
CONJUNCTIVITIS	1 (4.0%)
EAR INFECTION	1 (4.0%)
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
NASOPHARYNGITIS	1 (4.0%)
ORAL HERPES	1 (4.0%)
SEPSIS	1 (4.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (4.0%)
VULVOVAGINAL MYCOTIC INFECTION	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
NAUSEA	2 (8.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
HYPOGAMMAGLOBULINAEMIA	1 (4.0%)
INVESTIGATIONS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
BLOOD IMMUNOGLOBULIN G DECREASED	2 (8.0%)
BLOOD IMMUNOGLOBULIN M DECREASED	1 (4.0%)
EYE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PHOTOPSIA	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PARAESTHESIA	1 (4.0%)

Overall total number of patients with at least one AE	15 (60.0%)
Overall total number of AEs	42
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	7 (28.0%)
Total number of AEs	16
INFUSION RELATED REACTION	7 (28.0%)
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	6 (24.0%)
Total number of AEs	14
UPPER RESPIRATORY TRACT INFECTION	2 (8.0%)
CONJUNCTIVITIS	1 (4.0%)
EAR INFECTION	1 (4.0%)
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
NASOPHARYNGITIS	1 (4.0%)
ORAL HERPES	1 (4.0%)
SEPSIS	1 (4.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	1 (4.0%)
VULVOVAGINAL MYCOTIC INFECTION	1 (4.0%)
FUNGAL SKIN INFECTION	1 (4.0%)
PHARYNGITIS	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
NAUSEA	2 (8.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	3
HYPOGAMMAGLOBULINAEMIA	2 (8.0%)
SERUM SICKNESS	1 (4.0%)
INVESTIGATIONS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
BLOOD IMMUNOGLOBULIN G DECREASED	2 (8.0%)
BLOOD IMMUNOGLOBULIN M DECREASED	1 (4.0%)
EYE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PHOTOPSIA	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PARAESTHESIA	1 (4.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
RASH	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Relationship to treatment is based on Investigator causality.

The CHMP noted that looking at AEs deemed to be related to study treatment by the investigators, a similar pattern as described above is seen. Half of the patients experienced at least one AE and the most common AEs were IRR, GI related and infections.

Table 38 NCI CTCAE Grade 3 and 4 Adverse Events by Preferred Term during Remission Induction Phase and Overall, Safety-Evaluable Patients

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	7 (28.0%)
Overall total number of AEs	11
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	3
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
GRANULOMATOSIS WITH POLYANGIITIS	1 (4.0%)

VASCULITIS	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
BRONCHOSTENOSIS	1 (4.0%)
RHINALGIA	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	2
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)
Phase: OVERALL	
Overall total number of patients with at least one AE	15 (60.0%)
Overall total number of AEs	34
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	8 (32.0%)
Total number of AEs	10
INFLUENZA	2 (8.0%)
LOWER RESPIRATORY TRACT INFECTION	2 (8.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
SINUSITIS	2 (8.0%)
DEVICE RELATED SEPSIS	1 (4.0%)
EYE INFECTION BACTERIAL	1 (4.0%)
GASTROENTERITIS NOROVIRUS	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	5 (20.0%)
Total number of AEs	8
GRANULOMATOSIS WITH POLYANGIITIS	4 (16.0%)
VASCULITIS	1 (4.0%)
HYPERTENSION	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	4 (16.0%)
Total number of AEs	4
BRONCHOSTENOSIS	1 (4.0%)
RHINALGIA	1 (4.0%)
HYPOXIA	1 (4.0%)
LARYNGEAL OBSTRUCTION	1 (4.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	4
NEUTROPENIA	1 (4.0%)
NEUTROPENIA*	1 (4.0%)
SICKLE CELL ANAEMIA WITH CRISIS	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	2
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PANCREATITIS	1 (4.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVE VASCULITIS*	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MIGRAINE	1 (4.0%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SUICIDAL IDEATION	1 (4.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MENSTRUATION IRREGULAR	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows,multiple occurrences of the same AE in an individual are counted separately.
The grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.
Most Extreme Intensity NCI CTCAE Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.
"*"= NCI CTCAE Grade 4 Adverse Event.
NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Table 39 Grade 4 Adverse Events Reported during Remission Induction Phase, Overall Study Period, and Post Month 6 to Common Closeout Date, Safety-Evaluable Patients

Protocol: WA25615

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	0

Phase: FOLLOW-UP

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	2 (8.0%)
Overall total number of AEs	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
NEUTROPENIA	1 (4.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVE VASCULITIS	1 (4.0%)

Phase: OVERALL

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	2 (8.0%)
Overall total number of AEs	2
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
NEUTROPENIA	1 (4.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVE VASCULITIS	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 22.0.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
The grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.
Most Extreme Intensity NCI CTCAE Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.
NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

The CHMP noted that with regards to Grade 3-4 AEs, 15 patients (60%) experienced at least one Grade3-4 AE. The most common AEs were infections, respiratory (bronchostenosis, hypoxia, rhinalgia and laryngeal obstruction) and vascular disorders (GPA). The MAH clarifies that during the remission induction phase no Grade 4 AEs were reported, while 11 Grade 3 AE occurred in 7 patients. Of these 11 AEs, 10 resolved without sequelae and only one AE resolved with sequelae. There were 2 Grade 4 AEs during the follow-up period and both resolved without sequelae.

Adverse events of special interest

Infusion-Related Reactions (IRRs)

IRRs were predominantly seen with the first rituximab infusion (8 patients [32%]). The incidence of IRRs subsequently decreased thereafter with the number of rituximab infusions (20% with the second infusion, 12% with the third infusion and 8% with the fourth infusion). Overall, a total of 15 patients (60%) experienced at least one IRR at any time during the Remission Induction Phase, irrespective of the infusion number.

The most frequently reported symptoms of IRRs during the four rituximab infusions in the Remission Induction Phase were rash (3 events in 2 patients [8%]), headache (2 events in 2 patients [8%]), rhinorrhoea (2 events in 2 patients [8%]) and pyrexia (2 events in 2 patients [8%]). For the majority of IRRs in the Remission Induction Phase, the rituximab dose remained unchanged (16 out of 29 events) or was interrupted (12 out of 29 events).

During the Overall Study Period, the incidence of IRRs decreased over time with the number of rituximab infusions (figure below). The most frequent symptoms of IRRs reported in the Overall Study Period were rash (5 events in 2 patients [8%]), urticaria (4 events in 1 patient [4%]), and vomiting (3 events in 2 patients [8%]). The majority of IRRs during both the Remission Induction Phase and the Overall Study Period were Grade 1 and Grade 2 in severity. One serious Grade 2 IRR symptom (PT: Generalized oedema) was reported which resolved with treatment and is discussed in the CSR.

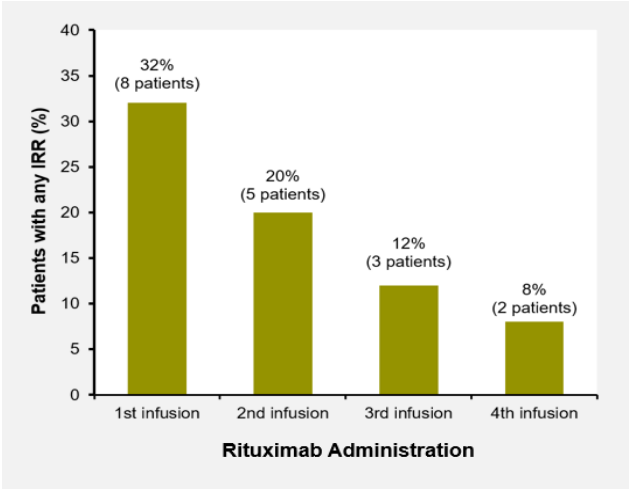


Figure 17 Infusion Related Reactions by Infusion during the Remission Induction Phase

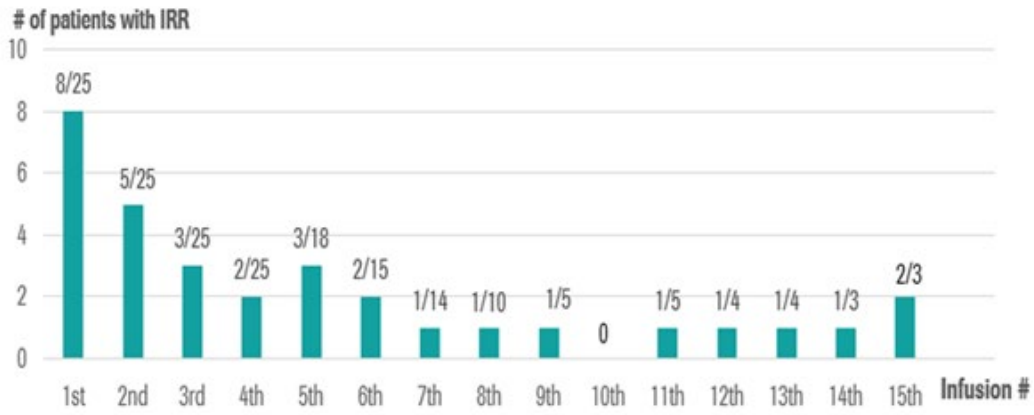


Figure 18 Infusion Related Reactions by Infusion during the Overall Study Period

Infections

Infections during the Remission Induction Phase and Overall Study Period are summarized in the table below. A total of 31 infection AEs (serious + non-serious) in 17 patients (68%) were reported in the Remission Induction Phase. The most frequently reported infections were upper respiratory tract infections (4 patients [16%]). A majority of the infections (28 out of 31 infections [90%]) were Grade 1 or Grade 2, non-serious, and resolved with or without treatment. Three infections during the Remission Induction Phase were serious and of Grade 3 severity and resolved.

During the Overall Study Period, 105 infection AEs (serious +non-serious) were reported in 23 patients (92%) of which the majority (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the Overall Study Period were upper respiratory tract infections (12 patients [48%]) all of which were non-serious.

There were no cases of PML or other opportunistic infections reported during the study.

Table 40 Infection during remission induction phase and overall, safety-evaluable patients

Protocol: WA25615

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	17 (68.0%)
Overall total number of AEs	31
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	17 (68.0%)
Total number of AEs	31
UPPER RESPIRATORY TRACT INFECTION	4 (16.0%)
INFLUENZA	2 (8.0%)
CONJUNCTIVITIS	2 (8.0%)
NASOPHARYNGITIS	2 (8.0%)
LOWER RESPIRATORY TRACT INFECTION	2 (8.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	2 (8.0%)
GASTROENTERITIS	2 (8.0%)
EAR INFECTION	1 (4.0%)
GASTROENTERITIS VIRAL	2 (8.0%)
ORAL HERPES	2 (8.0%)
GASTROENTERITIS NOROVIRUS	1 (4.0%)
TOOTH INFECTION	1 (4.0%)
CANDIDA INFECTION	1 (4.0%)
CELLULITIS	1 (4.0%)
PARONYCHIA	1 (4.0%)
PHARYNGITIS STREPTOCOCCAL	1 (4.0%)
SEPSIS	1 (4.0%)
TONSILLITIS	1 (4.0%)
VULVOVAGINAL MYCOTIC INFECTION	1 (4.0%)

INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	23 (92.0%)
Total number of AEs	105
UPPER RESPIRATORY TRACT INFECTION	12 (48.0%)
INFLUENZA	6 (24.0%)
CONJUNCTIVITIS	5 (20.0%)
NASOPHARYNGITIS	5 (20.0%)
LOWER RESPIRATORY TRACT INFECTION	4 (16.0%)
VIRAL UPPER RESPIRATORY TRACT INFECTION	4 (16.0%)
GASTROENTERITIS	3 (12.0%)
EAR INFECTION	3 (12.0%)
GASTROENTERITIS VIRAL	2 (8.0%)
ORAL HERPES	2 (8.0%)
SINUSITIS	4 (16.0%)
GASTROENTERITIS NOROVIRUS	2 (8.0%)
PHARYNGITIS	3 (12.0%)
TOOTH INFECTION	2 (8.0%)
URINARY TRACT INFECTION	3 (12.0%)
CANDIDA INFECTION	1 (4.0%)
CELLULITIS	1 (4.0%)
FUNGAL SKIN INFECTION	2 (8.0%)
HERPES ZOSTER	2 (8.0%)
PARONYCHIA	1 (4.0%)
PHARYNGITIS STREPTOCOCCAL	1 (4.0%)
PNEUMONIA	2 (8.0%)
SEPSIS	1 (4.0%)
TONSILLITIS	1 (4.0%)
VULVOVAGINAL MYCOTIC INFECTION	1 (4.0%)
BRONCHITIS	1 (4.0%)
DEVICE RELATED SEPSIS	1 (4.0%)
EYE INFECTION BACTERIAL	1 (4.0%)
HELICOBACTER GASTRITIS	1 (4.0%)
HERPES VIRUS INFECTION	1 (4.0%)
OTITIS MEDIA	1 (4.0%)
PYURIA	1 (4.0%)
RHINITIS	1 (4.0%)
SKIN INFECTION	1 (4.0%)
VULVOVAGINAL CANDIDIASIS	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Include AEs with System Organ Class equals 'INFECTIONS AND INFESTATIONS'.
Percentages are based on N.

Table 41 Grade 3 Adverse Events Reported During Remission Induction Phase, Overall, and Post Month 6 to Common Closeout Date, Safety-Evaluable Patients

Protocol: WA25615

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	7 (28.0%)
Overall total number of AEs	11
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	3
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
GRANULOMATOSIS WITH POLYANGIITIS	1 (4.0%)
VASCULITIS	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
BRONCHOSTENOSIS	1 (4.0%)
RHINALGIA	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	2
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)

Phase: FOLLOW-UP

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)

Overall total number of patients with at least one AE	11 (44.0%)
Overall total number of AEs	21
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	6 (24.0%)
Total number of AEs	7
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
SINUSITIS	2 (8.0%)
DEVICE RELATED SEPSIS	1 (4.0%)
EYE INFECTION BACTERIAL	1 (4.0%)
GASTROENTERITIS NOROVIRUS	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	4 (16.0%)
Total number of AEs	5
GRANULOMATOSIS WITH POLYANGIITIS	4 (16.0%)
HYPERTENSION	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
HYPOXIA	1 (4.0%)
LARYNGEAL OBSTRUCTION	1 (4.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
NEUTROPENIA	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PANCREATITIS	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MIGRAINE	1 (4.0%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SUICIDAL IDEATION	1 (4.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MENSTRUATION IRREGULAR	1 (4.0%)

Phase: OVERALL

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	14 (56.0%)
Overall total number of AEs	32
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	8 (32.0%)
Total number of AEs	10
INFLUENZA	2 (8.0%)
LOWER RESPIRATORY TRACT INFECTION	2 (8.0%)
SINUSITIS	2 (8.0%)
DEVICE RELATED SEPSIS	1 (4.0%)
EYE INFECTION BACTERIAL	1 (4.0%)
GASTROENTERITIS NOROVIRUS	1 (4.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	5 (20.0%)
Total number of AEs	8
GRANULOMATOSIS WITH POLYANGIITIS	4 (16.0%)
HYPERTENSION	1 (4.0%)
VASCULITIS	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	4 (16.0%)
Total number of AEs	4
BRONCHOSTENOSIS	1 (4.0%)
HYPOXIA	1 (4.0%)
LARYNGEAL OBSTRUCTION	1 (4.0%)
RHINALGIA	1 (4.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	3
NEUTROPENIA	1 (4.0%)
SICKLE CELL ANAEMIA WITH CRISIS	1 (4.0%)

GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PANCREATITIS	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	2
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MIGRAINE	1 (4.0%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SUICIDAL IDEATION	1 (4.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MENSTRUATION IRREGULAR	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 22.0.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
The grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.
Most Extreme Intensity NCI CTCAE Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life-Threatening, 5=Death.
NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Serious Infections

Serious infections during the Remission Induction Phase and Overall Study Period are summarized in the Table below. A total of 3 serious infections in 3 patients (12%) were reported in the Remission Induction Phase and included influenza (1 patient [4%]), lower respiratory tract infection (1 patient [4%]), and gastroenteritis (1 patient [4%]). One event of serious infection (influenza) was assessed by the investigator as related to study treatment.

During the Overall Study Period, 9 serious infections were reported in 7 patients (28%) and included influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

Overall, the majority of serious infections resolved (8 out of 9 events) and one event resolved with sequelae (a serious bacterial eye infection due to Ureaplasma urealyticum).

Table 42 Serious infections during remission induction phase and overall, safety-evaluable patients

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	3 (12.0%)
Overall total number of AEs	3
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	3
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
GASTROENTERITIS VIRAL	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Include serious AEs with System Organ Class equals 'INFECTIONS AND INFESTATIONS'.
Percentages are based on N.

Serious Infections with Laboratory Abnormalities of Prolonged Low Ig Levels in the Overall Study Period

During the Overall Study Period, 18 patients (72%) had prolonged low IgG levels. Of these 18 patients, 6 patients (33%) had serious infections during or after prolonged low IgG. A total of 7 serious infections (PTs: lower respiratory tract infection [2 cases], eye infection bacterial, gastroenteritis norovirus, influenza [2 cases], and sinusitis) were reported in these 6 patients during or after prolonged IgG. During the Overall Study Period, 19 patients (76%) had prolonged low IgM. Of these 19 patients, 6 patients (32%) had serious infections during or after prolonged IgM. A total of 8 serious infections (PT: lower respiratory tract infection [2 cases], device related sepsis, gastroenteritis viral, influenza [2 cases], sinusitis, gastroenteritis norovirus) were reported in these 6 patients during or after prolonged IgM. Most of the infections were reported as unrelated to study treatment. In summary, there was no evidence of association between prolonged low IgG or IgM and increase of serious infections.

Cardiac Events

One cardiac event (Grade 1 aortic valve incompetence) was reported in one patient during the Overall Study Period. This event was reported as non-serious and unrelated to study treatment.

Table 43 Cardiac events during remission induction phase and overall, safety-evaluable patients

Protocol: WA25615

Phase: OVERALL

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	1 (4.0%)
Overall total number of AEs	1
CARDIAC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
AORTIC VALVE INCOMPETENCE	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Include AEs with System Organ Class equals 'CARDIAC DISORDERS'.
Percentages are based on N.

Malignancies

No malignancies were reported in the study. One patient experienced an AE of Grade 1 benign tracheal neoplasm (from the SOC Neoplasm benign, malignant and unspecified [including cysts and polyps]), which was reported on 3 different study days as non-serious, and was assessed by the investigator as unrelated to study treatment, with GPA being the possible etiological factor.

Table 44 Malignancies during remission induction phase and overall, safety-evaluable patients

Protocol: WA25615

Phase: OVERALL

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	1 (4.0%)
Overall total number of AEs	3
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	3
BENIGN TRACHEAL NEOPLASM	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Include AEs with Prefer Term defined in the Malignant or Unspecified Tumors SMQ (Wide).
Percentages are based on N.

Hypogammaglobulinaemia

Three patients experienced AEs of hypogammaglobulinaemia, and all of them received treatment with IV immunoglobulin. All 3 patients had both prolonged low IgG and IgM levels during the study as indicated by IgG and/or IgM laboratory values below LLN for 4 months or longer and further details are provided in the CSR.

Pregnancies

No pregnancies were reported during the study.

Adverse Events by Anti-Drug Antibody (ADA) Status

No patients were tested positive for ADA to rituximab at baseline. A total of 4 out of 21 evaluable patients (19%) developed treatment-induced ADA during the Overall Study Period, of whom 1 patient (4%) developed ADA during the Remission Induction Phase. This patient tested positive for ADA at Month 4 (Day 125), whilst 3 patients tested positive for ADA for the first time at Month 18. All of the 4 ADA positive patients (100%) experienced an IRR before testing positive for ADA. One out of these 4 patients also experienced IRRs after testing positive for ADA. Based on available data, the occurrence of ADA does not appear to have a negative effect on safety. No serious IRRs and no increase in the occurrence of IRRs were observed after the development of ADA.

Serious adverse event/deaths/other significant events

Deaths

No patients died during the study up to the CCO date.

SAE

Table 45 Serious Adverse Events during Remission Induction Phase and Overall, Safety-Evaluable Patients

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	7 (28.0%)
Overall total number of AEs	10
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	3
INFLUENZA	1 (4.0%)
LOWER RESPIRATORY TRACT INFECTION	1 (4.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	3 (12.0%)
Total number of AEs	4
GRANULOMATOSIS WITH POLYANGIITIS	2 (8.0%)
VASCULITIS	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
BRONCHOSTENOSIS	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)
Phase: OVERALL	

Overall total number of patients with at least one AE	12 (48.0%)
Overall total number of AEs	27
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	7 (28.0%)
Total number of AEs	9
INFLUENZA	2 (8.0%)
LOWER RESPIRATORY TRACT INFECTION	2 (8.0%)
GASTROENTERITIS VIRAL	1 (4.0%)
DEVICE RELATED SEPSIS	1 (4.0%)
EYE INFECTION BACTERIAL	1 (4.0%)
GASTROENTERITIS NOROVIRUS	1 (4.0%)
SINUSITIS	1 (4.0%)
VASCULAR DISORDERS	
Total number of patients with at least one AE	5 (20.0%)
Total number of AEs	7
GRANULOMATOSIS WITH POLYANGIITIS	4 (16.0%)
VASCULITIS	1 (4.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
BRONCHOSTENOSIS	1 (4.0%)
LARYNGEAL OBSTRUCTION	1 (4.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
INFUSION RELATED REACTION	1 (4.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
MYOPATHY	1 (4.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	2
SICKLE CELL ANAEMIA WITH CRISIS	1 (4.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SICKLE CELL ANAEMIA	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
PANCREATITIS	1 (4.0%)
IMMUNE SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY POSITIVE VASCULITIS	1 (4.0%)
NERVOUS SYSTEM DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SEIZURE	1 (4.0%)
PSYCHIATRIC DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
SUICIDAL IDEATION	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

Table 46 Serious Adverse Events Related to study treatment during remission induction phase and overall, safety-evaluable patients

Phase: REMISSION INDUCTION MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	1 (4.0%)
Overall total number of AEs	1
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
INFLUENZA	1 (4.0%)
Phase: OVERALL	
Overall total number of patients with at least one AE	1 (4.0%)
Overall total number of AEs	1
INFECTIONS AND INFESTATIONS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
INFLUENZA	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
Relationship to treatment is based on Investigator causality.

Table 47 SAEs in the Remission Induction Phase

Preferred Term	Study Day of Onset	Outcome	AE duration in Days
Bronchostenosis	164	Resolved without sequelae	505
Infusion related reaction	23	Resolved without sequelae	5
Vasculitis	8	Resolved without sequelae	8
Granulomatosis with polyangiitis	15	Resolved without sequelae	47
Granulomatosis with polyangiitis	175	Resolved with sequelae	66
Granulomatosis with polyangiitis	53	Resolved without sequelae	206
Lower respiratory tract infection	75	Resolved without sequelae	22
Myopathy	48	Resolved without sequelae	863
Gastroenteritis viral	129	Resolved without sequelae	2
Influenza	161	Resolved without sequelae	23

Table 48 SAEs in the Follow-up Phase

Preferred Term	Study Day of Onset	Outcome	AE duration in Days
Seizure	300	Resolved without sequelae	2
Suicidal ideation	866	Resolved without sequelae	4
Lower respiratory tract infection	215	Resolved without sequelae	26
Granulomatosis with polyangiitis	386	Resolved without sequelae	160
Anti-neutrophil cytoplasmic antibody positive vasculitis	218	Resolved without sequelae	16
Pancreatitis	277	Resolved without sequelae	6
Laryngeal obstruction	459	Resolved with sequelae	1
Granulomatosis with polyangiitis	Not available	Resolved without sequelae	Not available
Sickle cell anaemia	358	Resolved without sequelae	12
Device related sepsis	456	Resolved without sequelae	6
Sickle cell anaemia with crisis	456	Resolved without sequelae	6
Sickle cell anaemia	672	Resolved without sequelae	6

Eye infection bacterial	811	Resolved with sequelae	30
Influenza	1396	Resolved without sequelae	8
Sinusitis	1404	Resolved without sequelae	8
Gastroenteritis norovirus	205	Resolved without sequelae	4
Granulomatosis with polyangiitis	694	Resolved without sequelae	124

The CHMP noted that 7 patients (28%) experienced a SAE during the remission induction phase, and the most common SAEs were infections. In the overall study period 12 patients (48%) experienced a SAE, and the most common AE was also infections. Interestingly one patients experienced suicidal ideation. This patient was treated with a cycle of rituximab and experienced suicidal ideation on study day 866. The patient was previously treated with steroids, which are known to cause psychiatric disorders. No firm conclusions can be drawn. Apparently, only one SAE (influenza) was deemed treatment related by the investigators. As discussed previously, there were a total of 27 SAEs. It is seen that SAEs occur from study day 8 to 1404. All SAEs resolved. Most of the events resolved without sequelae, while only a few resolved with sequelae; GPA, laryngeal obstruction and bacterial eye infection. The two first SAEs are related to the underlying disease.

Anti-drug Antibodies

No patients tested positive for ADA to rituximab at baseline. A total of 4 out of 21 evaluable patients (19%) developed treatment-induced ADA during the Overall Study Period, of whom 1 patient (4%) developed ADA during the Remission Induction Phase, at Month 4 (Day 125). The 3 other patients tested positive for ADA for the first time at Month 18. All of the 4 ADA positive patients (100%) experienced an IRR before testing positive for ADA. One out of these 4 patients also experienced IRRs after testing positive for ADA. No serious IRRs and no increase in the occurrence of IRRs were observed after the development of ADA.

The CHMP noted that 4 patients tested ADA positive in the course of treatment. Due to the low patient numbers, further analysis of the relation between ADA positivity and safety (notably IRR) is not pursued by the CHMP. There are no signals from the post-marketing data regarding ADA.

Laboratory findings

Study WA25615-Hematology

As summarized in the table below, few patients had shifts from baseline NCI CTC AE Grade 0,1, 2 to the most severe grade of 3,4 in any hematology parameter. Erythrocyte sedimentation rate (ESR) changes are summarized in the CSR.

Table 49 Summary of Hematology shifts from Baseline Levels of Grade 0,1,2 to the Most Severe Grade of 3,4

Parameter	Number of pts with a shift from 0,1,2 at baseline to the most severe grade of 3, 4 (NCI CTCAE) during treatment N=25
Hemoglobin (high)	0
Hemoglobin (low)	2
Lymphocytes (high)	0
Lymphocytes (low)	6
Neutrophils (low)	0
Platelets (low)	1
White Blood Cell Count (high)	0
White Blood Cell Count (low)	1

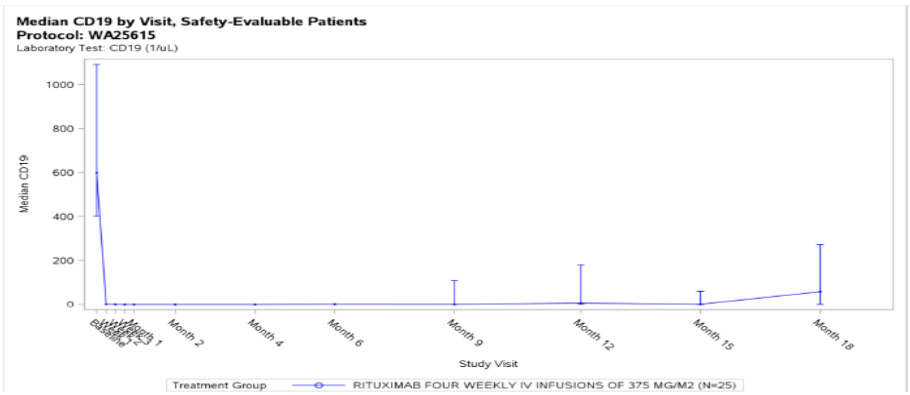


Figure 19 Median CD19 B cell levels by visit,safety-evaluable patients

Study WA25615-Chemistry

As summarized the Table below, few patients had shift from baseline values in chemistry parameters of 0,1, 2 to a worse Grade of 3,4 during the course of the study.

Table 50 Summary of Chemistry Parameter shifts from Baseline Levels of Grade 0,1,2 to the Most Severe Grade of 3,4

Parameter	Number of pts with a shift from 0,1,2 at baseline to the most severe grade of 3, 4 (NCI CTCAE) during treatment N=25
Alkaline Phosphatase (high)	1
Bilirubin (high)	1*
Calcium (high)	0
Calcium (low)	0
Creatinine (high)	1
Phosphorus (low)	0
Potassium (high)	0
Potassium (low)	0
SGOT/AST (high)	1*
SGPT/ALT (high)	1*
Sodium (high)	0
Sodium (low)	0
Uric Acid (high)	2

*Note, due to pre-existing illness (sickle cell anemia) in one patient, the investigator did not report these findings of elevated ALT and AST levels in combination with elevated bilirubin level as an AESI.

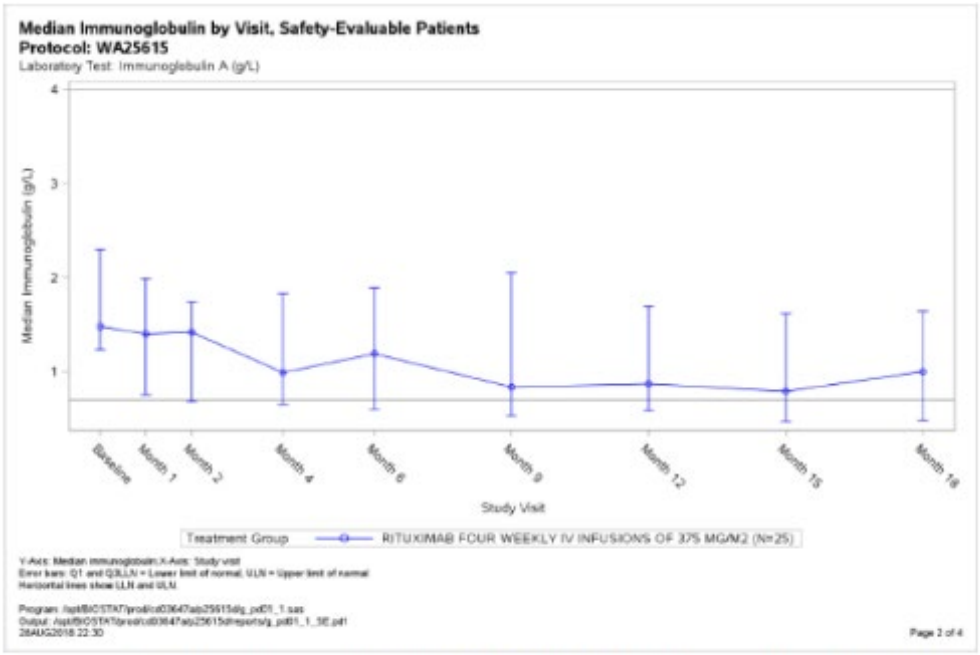
Study WA25615-B-Cells

Consistent with its mode of action, treatment with rituximab resulted in complete and sustained CD19+ peripheral B-cell depletion which persisted until at least Month 6, and in the majority of cases throughout the duration of follow-up, with administration of repeat rituximab infusions. The median CD19 absolute B-cell count at Day 1 baseline was 599.00 cells/μL (range: 197-2173), and mean CD19 absolute B-cell count at Day 1 baseline was 827.55 cells/μL (SD 559.48), this deceased rapidly after the first infusion by Week 1 (mean 2.59 cells/μl; median 1 cell/μl). B cells depletion was sustained through Month 6 (mean 41.77 cells/μl; median 1 cell/μl), after which, there was some evidence of slow return of circulating B cells (Month 12; mean 92.82/μL; median 6 cells/μL). By Month 18, CD19 levels had increased but still remained below baseline levels (mean: 160.10/μL, median: 58/μL).

Study WA25615-Immunoglobulins

A decrease in IgA, IgG, IgM and total immunoglobulin concentrations from baseline during the Overall Study Period was observed. Levels of IgG decreased to below the lower limit of normal (LLN) within

the first month of treatment but then returned to normal levels. Prolonged low IgG (defined as IgG levels <LLN for at least a 4 month period) was observed in 18 patients (72%) during the Overall Study Period. Median IgM levels decreased to below the LLN by Month 2 and remained under the LLN until Month 18. Median IgA levels remained within the normal laboratory reference ranges throughout the study.



The normal reference ranges are included in listing . The horizontal lines on the graph show the lowest ULN (4.0 g/L) and the highest LLN (0.7 g/L), respectively.

Figure 20 Plot of Median IgA by visit (safety-evaluable patients)

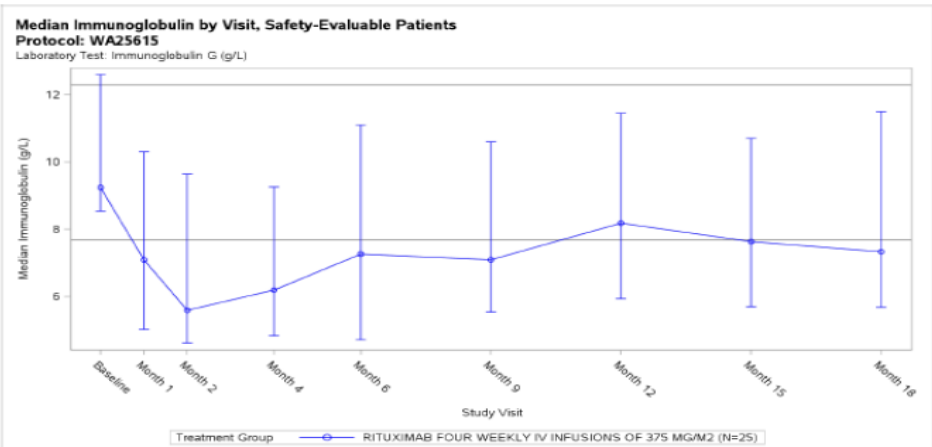
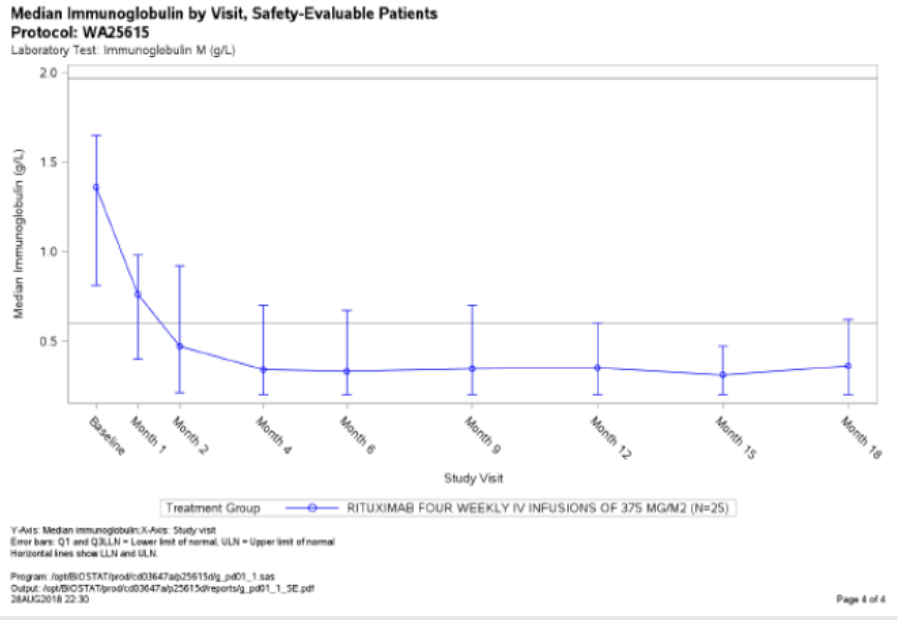


Figure 21 Plot of Median IgG by visit (safety-evaluable patients)



The normal reference ranges are included in listing . The horizontal lines on the graph show the lowest ULN (1.97g/L) and the highest LLN (0.6 g/L), respectively.

Figure 22 Plot of Median IgM by visit (safety-evaluable patients)

Chemistry

Table 51 Summary of chemistry parameter shifts from baseline levels of grade 0, 1, 2 to the most severe grade of 3, 4

Parameter	Number of pts with a shift from 0,1,2 at baseline to the most severe grade of 3, 4 (NCI CTCAE) during treatment N=25
Alkaline Phosphatase (high)	1
Bilirubin (high)	1*
Calcium (high)	0
Calcium (low)	0
Creatinine (high)	1
Phosphorus (low)	0
Potassium (high)	0
Potassium (low)	0
SGOT/AST (high)	1*
SGPT/ALT (high)	1*
Sodium (high)	0
Sodium (low)	0
Uric Acid (high)	2

The mean CRP level at baseline was 10.12 mg/L (SD: 12.17); Q1-Q3 was 1.8 – 14.90 (IQR = 13.10). The mean CRP varied throughout the first 6 months and there was interpatient variability. By month 6, the mean CRP had increased to 22.41 mg/L (SD 73.88); Q1-Q3 1.4-6.5 (IQR=5.10). By month 12 and month 18, the mean CRP had decreased to 7.25 mg/L (SD18.48); Q1-Q3 1.1 -5.00 (IQR 3.90) and 4.12 (SD 2.96); Q1-Q3 1.10 -5.00 (IQR=3.90), respectively, and there was less interpatient variability. At baseline, the median CRP level was 5.00 mg/L (range 0.3 – 46.0). By month 6, the median CRP level was 1 mg/L lower than baseline (median range in change from baseline varied from -33.3 to 336 mg/L). By month 18, the median change from baseline remained at 1 mg/L lower than baseline (median range in change from baseline varied from -40.0 to 11.1 mg/L.

One patient had elevated ALT and AST levels in combination with elevated bilirubin levels, which were not reported as an AESI by the investigator because of the patient's medical history of hepatitis and sickle cell disease as causes of these significant laboratory abnormalities.

Urinalysis

There were no clinically significant changes from baseline in urine analyses.

VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

There were no clinically relevant effects on vital signs (diastolic blood pressure, systolic blood pressure, or heart rate) over the course of the study. No abnormal changes in the BSA, height, or weight were observed.

ECGs

All screening ECGs were normal and no AEs resulting from any ECG abnormalities were reported over the course of the study

Chest X-rays

Twenty patients had chest X-rays performed at screening (note, in accordance with the study protocol, chest X-rays were not required for all patients at screening). Nine out of 20 patients had abnormal X-rays at screening, corresponding with the observation that 44% of patients had pulmonary involvement related to their vasculitis disease at baseline.

Discontinuation due to adverse events

No AE led to withdrawal of the study treatment.

Table 52 Adverse events leading to infusion dose modification or interruption during remission induction phase and overall, safety-evaluable patients

Phase: REMISSION INDUCTION

MedDRA System Organ Class MedDRA Preferred Term	Rituximab (N=25)
Overall total number of patients with at least one AE	7 (28.0%)
Overall total number of AEs	12
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	7 (28.0%)
Total number of AEs	12
INFUSION RELATED REACTION	7 (28.0%)
Phase: OVERALL	
Overall total number of patients with at least one AE	12 (48.0%)
Overall total number of AEs	25
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Total number of patients with at least one AE	10 (40.0%)
Total number of AEs	21
INFUSION RELATED REACTION	10 (40.0%)
INVESTIGATIONS	
Total number of patients with at least one AE	2 (8.0%)
Total number of AEs	2
NEUTROPHIL COUNT DECREASED	1 (4.0%)
OXYGEN SATURATION DECREASED	1 (4.0%)
GASTROINTESTINAL DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
NAUSEA	1 (4.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Total number of patients with at least one AE	1 (4.0%)
Total number of AEs	1
RASH	1 (4.0%)

Investigator text for AEs is coded using MedDRA version 20.1.
Percentages are based on N.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

The CHMP noted that there were no discontinuations due to AEs. This seems to reflect the fact that the AEs related to rituximab are clinically manageable with dose modifications or interruptions in this patient population. There was a total of 12 patients with at least one AE (25 AEs in total) leading to a dose modification or interruption during the overall study period. The majority of the AEs were IRR.

Post marketing experience

Since the rituximab International Birth Date (IBD) (26 November 1997) until 30 September 2018 (data lock point of the most recent Rituximab Periodic Benefit-Risk Evaluation Report Number 1090384), approximately 6,371,208 patient-market exposures worldwide have been estimated for rituximab and exposure by indications is summarized in table below.

Table 53 Cumulative Rituximab Exposure from Marketing Experience

Hematological malignancies	~5,214,984
Autoimmune Indications	~ 1,156,225 (Unique patients = ~ 646,020)
RA	~ 853,968 (Unique patients = ~ 448,611)
Other Autoimmune indications (excluding RA)	~ 302,257 (Unique patients = ~ 197,409)
GPA and MPA	77,815 patients

Evidence from Company global Safety Database

A total of 1680 cases from the company global safety database, reporting 4315 AEs in paediatric patients with non-oncology indications, were analysed. A total of 41/1680 (2.4%) cases reporting 173 AEs (4.0%) were from patients with GPA or MPA. Of these 41 cases, 31 cases (75.6%) reported events already described as ADRs for rituximab in the adult population, such as IRRs and related signs/symptoms, infections, and hypogammaglobulinemia (immunoglobulins below the LLN). Of the remaining 10 cases with AEs not known as ADRs in adult patients, in seven cases (17.1%), any causal relationship to rituximab was highly unlikely as there were alternative explanations and risk factors (events were either manifestations of the underlying condition GPA or MPA or were associated with past/concomitant immunosuppressants) present. In the remaining three (7.3%) cases, there was insufficient information for an adequate assessment. Overall, in 16/41 (39.0%) cases, the majority of the events appeared to be manifestations of the underlying condition GPA or MPA.

From the total of 4315 AEs analysed, 97 (2.2%) fatal AEs were reported in non-oncology indications, of which, five were in GPA or MPA. Approximately 37% of the overall fatal events reported were related to infections. Out of the 4315 total AEs analysed, there were 895 infection events (20.7%) (27 out of 173 events [15.6%] were in GPA or MPA), 927 events (21.5%) reported as IRRs or IRR related signs/symptoms (21 out of 173 events [12.1%] were in GPA or MPA), 125 (2.9%) hypogammaglobulinemia events (five out of 173 events [2.9%] in GPA or MPA),of which, 49 (1.1%) hypogammaglobulinemia events were reported with infections (three out of 173 events [1.7%] in GPA or MPA). In eight cases overall, the infection events occurred during/post hypogammaglobulinemia. A total of 13 (0.3%) malignant events were reported and none were in GPA or MPA. One hundred and sixty-four (3.8%) cardiac events were reported including nine events (5.2%) in GPA or MPA.

The AEs were mainly reported in the age groups ≥2 years to <12 years (48.5%), and ≥12 years to <18 years (47.1%). The safety profile of rituximab was mostly comparable between these two age groups except for SOC Infections and infestations with higher proportion of AEs in patients aged ≥2 years to < 12 years as compared to ≥12 years to <18 years paediatric patients (25.4% vs 15.8%). This difference could be explained by an increased susceptibility to infections in younger paediatric patients. Some SOCs showed a different reporting ratio (RR), which could mostly be attributed to the low number of AEs and/or to the differences between the number of AEs reported across the age-groups. Overall, 4.4% AEs were reported in infants and neonates (<2 years) and were in other non-oncology indications. No AEs were reported in infants and neonates in GPA and MPA.

The evaluation also included post-marketing data from ≥2 to <6 year old patients (from a total of 257 cases, majority of these cases [~99%] were from other non-oncology conditions). The safety profile of rituximab observed in the paediatric population from post-marketing sources was overall consistent

with the well-known safety profile in the adult populations for the approved autoimmune indications. The AEs that were not known ADRs of rituximab either had alternative explanations and risk factors or had insufficient information for an adequate assessment.

Evidence from Literature

Of the 982 articles retrieved from the literature search, 90 were found relevant (i.e. articles that provided safety findings in paediatric patients exposed to rituximab) and the reviewed literature did not provide any new safety findings. The majority of the reported AEs (e.g. infections, hypogammaglobulinemia, IRRs) were consistent with the safety findings from the post-marketing data retrieved from the company global safety database, and with the known safety profile of rituximab in adults for the approved autoimmune indications.

Overall there was no evidence of an increased risk of serious infections associated with hypogammaglobulinemia. No specific conclusions could be made for the 2-6 years old GPA and MPA patients, as the reviewed publications with GPA and MPA patients included mostly patient aggregate data and very limited data on individual patients' age.

2.5.1. Discussion on clinical safety

Study WA25615 was an open-label, single arm study was conducted in 25 paediatric patients with severe, active GPA or MPA. The overall study period consisted of a 6-month remission induction phase and with a minimum 18-month follow-up phase, up to 4.5 years overall. During the follow-up phase, MabThera was given at the discretion of the investigator (17 out of 25 patients received additional MabThera treatment). Concomitant treatment with other immunosuppressive therapy was permitted.

All patients received the planned rituximab infusion (4 in total). At the discretion of the investigators, patients could continue rituximab treatment in order to keep patients in remission or control disease activity. The majority of patients were followed for 18 to 36 months, and 6 patients were followed for more than 36 months. Overall, all patients have been exposed to rituximab and followed for a sufficient period of time in order to allow an assessment of safety in the proposed patient population. Safety data are very sparse in the extended follow-up period. There were no SAE, no malignancies, no deaths or discontinuations due to AEs. No new safety findings.

The most common infections in the overall phase were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

Every patient experienced at least one AE during the course of the study. During the induction of remission phase the most common AEs were related to GI (nausea, abdominal pain and constipation), infections (upper respiratory tract infections) and infusion related reactions (IRR). In the overall treatment period, the most common AEs were also GI related (as above), IRR and infections (primarily upper respiratory tract infections). These AEs are in line with the known safety profile of rituximab.

With regards to Grade 3-4 AEs, 15 patients (60%) experienced at least one Grade3-4 AE. The most common AEs were infections, respiratory (bronchostenosis, hypoxia, rhinalgia and laryngeal obstruction) and vascular disorders (GPA).

Concerning AESI (IRR, infections, serious infections, cardiac, malignancies and hypogammaglobulinaemia) there were no unexpected findings.

The reported IRRs were predominantly seen with the first infusion (8 patients [32%]), and then decreased over time with the number of MabThera infusions (20% with the second infusion, 12% with the third infusion and 8% with the fourth infusion). The most common IRR symptoms reported during the remission of induction phase were: headache, rash, rhinorrhea and pyrexia (8%, for each symptom). The observed symptoms of IRRs were similar to those known in adult GPA or MPA patients treated with MabThera. The majority of IRRs were Grade 1 and Grade 2, there were two non-serious Grade 3 IRRs, and no Grade 4 or 5 IRRs reported. One serious Grade 2 IRR (generalized oedema which resolved with treatment) was reported in one patient.

Ninety one percent (91%) of reported infections were non-serious and 90% were mild to moderate.

No malignancies were reported with a follow-up period of up to 54 months.

The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

During the overall study period, 3/25 (12%) patients reported an event of hypogammaglobulinaemia, 18 patients (72%) had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (of whom 15 patients also had prolonged low IgM). Three patients received treatment with intravenous immunoglobulin (IV-IG). Based on limited data no firm conclusions can be drawn regarding whether prolonged low IgG and IgM led to an increased risk of serious infection in these patients. The consequences of long-term B cell depletion in paediatric patients are unknown.

There is an existing warning in Section 4.4 of the SmPC which states that rituximab should not be used if patients have an active severe infection or are severely immunocompromised. Treatment should be used with caution if patients have a history of recurrent infections, or with underlying predisposing conditions e.g. hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera. Regarding treatment of hypogammaglobulinaemia, the treatment with IV IG should always be at the discretion of the treating physician per common clinical practice and local country guidelines, as required.

Immunoglobins (IgA, IgG, IgM, total) decreased during the course of the study, and as discussed above, three patients received IV immunoglobulins due to hypogammaglobulinaemia. Chemistry: One patient had elevated ALT, AST and bilirubin levels. The patient had a medical history of hepatitis and sickle cell disease. The MAH has provided brief case narrative for this patient. No firm conclusions can be drawn. Therefore, this issue was not be pursued any further by the CHMP.

It is noted that two patients had a shift in uric acid from Grade 1-2 to Grade 3. Data are too limited to draw any firm conclusions. Therefore, this issue was not be pursued any further by the CHMP.

No patients died during the study up to the CCO date, but 7 patients (28%) experienced a SAE during the remission induction phase, and the most common SAEs were infections. In the overall study period 12 patients (48%) experienced a SAE, and the most common AE was also infections. There were a total of 27 SAEs.

There were no discontinuations due to AEs. This seems to reflect the fact that the AEs related to rituximab are clinically manageable with dose modifications or interruptions in this patient population. There was a total of 12 patients with at least one AE (25 AEs in total) leading to a dose modification or interruption during the overall study period. The majority of the AEs were IRR.

Section 4.4 of the SmPC was updated with a recommendation to bring up-to-date all immunisations in agreement with current immunisation guidelines prior to initiating MabThera therapy.

As discussed in the efficacy section, the lack of data on long-term safety in the maintenance setting was of major concern to the CHMP. The MAH was asked repeatedly to make a proposal, present the

outline and commit to conducting a PASS study post-approval in order to address the concerns related to long-term safety in the maintenance setting. Regrettably, the MAH could not commit to conducting a PASS study in the maintenance setting. Section 4.1. has been limited to the induction setting.

2.5.2. Conclusions on clinical safety

Overall, all patients have been exposed to rituximab and followed for a sufficient period of time in order to allow an assessment of safety in the induction of remission setting. There were no malignancies, no deaths or discontinuations due to AEs. No new safety findings.

The safety profile of MabThera in paediatric GPA or MPA patients in the induction of remission setting was consistent in type, nature and severity with the known safety profile in adult patients in the approved autoimmune indications with approved autoimmune diseases, including adult GPA or MPA.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 20.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 21.1 with the following content:

Safety concerns

Table 54 Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Infections, including serious infections (All Indications) 2. Progressive multifocal leukoencephalopathy (All Indications) 3. Hepatitis B reactivation (All Indications) 4. Hypogammaglobulinemia (non-oncology indications)
Important potential risks	5. Malignant events (non-oncology indications) 6. Impact on cardiovascular disease (non-oncology indications) 7. Relapses (GPA/MPA only) 8. Off-label use of the subcutaneous formulation (NHL/CLL, SC formulations) 9. Administration route error (NHL/CLL, SC formulations)
Missing information	1. Use in pregnancy and lactation (All Indications) 2. Long term use in GPA/MPA patients (GPA/MPA only)

Pharmacovigilance plan

Table 55 On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no planned or ongoing category 1 studies				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no planned or ongoing category 2 studies.				
Category 3 - Required additional pharmacovigilance activities				
MA28150 (RITAZAREM): An international, open label, randomized controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM)-Phase III, interventional, randomized, open-label, comparative trial Ongoing	Time to relapse / the primary endpoint is the time to disease relapse (either minor or major relapse) from randomization. Proportion of patients who maintain remission at 24 and 48 months	Relapses	Estimated study completion date	Estimated CSR availability September 2020
BE29950 (RIVAS): Prospective, single center, secondary data use, long-term surveillance, non-interventional PASS. Ongoing	Registry to collect serious adverse event data over 5 years to determine the long-term safety of rituximab for the treatment of GPA/MPA.	Long term use in GPA/MPA patients	Study start: Interim analyses: Final CSR is due	Q4 2016 Annual reporting of cumulative data in PBRER 31 Dec 2021

ANCA= Anti-Neutrophil Cytoplasmic Antibody, BVAS= Birmingham Vasculitis Activity Score, CLL= Chronic Lymphocytic Leukemia, CSR=Clinical study report, GPA= Granulomatosis with polyangiitis, SC =Subcutaneous

Risk minimisation measures

Table 56 Summary table of risk minimization activities by safety concern

Safety concern	Risk minimization measures
Infections, including serious infections **All Indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications)
Progressive Multifocal Leukoencephalopathy	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, including Magnetic Resonance Imaging scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of MabThera must be permanently discontinued. **Other risk minimization measures beyond the Product Information:**

	Medicine's legal status: Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (non oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications)
Hepatitis B Reactivation All Indications	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Hypogammaglobulinemia non-oncology indications	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **RA** EU SmPC Section 4.8: Undesirable effects **GPA/MPA** EU SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Immunoglobulin levels are recommended to be determined prior to initiating treatment with MabThera **Other risk minimization measures beyond the Product Information:**

	Medicine's legal status: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Malignant Events **(Non-oncology indications)**	**Routine risk communication:** EU SmPC Section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Impact on Cardiovascular Disease **(Non-oncology indications)**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Relapses **(GPA/MPA only)**	**Routine risk communication:** EU SmPC Section 5.1: Pharmacodynamic properties **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:*

	Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** None
Off-label Use of the Subcutaneous Formulation (NHL/CLL, SC formulations)	**Routine risk communication:** EU SmPC section 4.1 Therapeutic indications Separate EU SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). EU SmPC (for SC formulation) section 4.4: Special warnings and precautions for use EU SmPC (IV and SC) section 4.2: Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** Separate SmPCs are available for the IV (100 mg and 500 mg) and SC formulations (1400 mg for NHL and 1600 mg for CLL). **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals
Administration route error (NHL/CLL, SC formulations)	**Routine risk communication:** The IV and SC formulations are covered by separate EU SmPCs to reinforce the difference between the IV and SC formulations. EU SmPC (IV and SC) section 1: Name of the Medicinal Product EU SmPC (IV and SC) section 4.2: Posology and method of administration **Routine risk minimization activities recommending specific clinical measures to address the risk:** The IV and SC formulations are covered by separate SmPCs to reinforce the difference between the IV and SC formulations. **Other risk minimization measures beyond the Product Information:** **Packaging: Clear package differentiation** • Color differentiation (distinct colored bands) • Unique cap colors for the vials matching the colored bands

	• Clear statements on both the primary and secondary packaging i.e., words "*subcutaneous*", "*solution for subcutaneous injection*" and "Only *for subcutaneous use*" in red font. Peel-off sticker is included on the individual vials of the subcutaneous formulations specifying the strength, the route of administration and the indication. SC and IV formulations are covered by separate SmPCs, which include specific warning against incorrect route of administration. *Medicine's legal status*: Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Educational Material for Healthcare Professionals
Use in Pregnancy and Lactation **All Indications**	**Routine risk communication:** EU SmPC section 4.6 Fertility, pregnancy and lactation **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information**: *Medicine's legal status:* Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** None
Long term use in GPA/MPA patients (GPA/MPA only)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information**: *Medicine's legal status:* MabThera is a prescription only medicine. **Additional risk minimization measures:** None

2.7. Update of the Product information

As a consequence of this new indication, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.5, 8 of the SmPC have been updated for MabThera 100 mg and 500mg concentrate for solution for infusion. The PL was updated accordingly. In addition, the product information for the MabThera 100 mg and 500mg concentrate for solution for infusion have been combined.

The request for combined PL was reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Childhood onset GPA and MPA are rare, potentially life and organ-threatening systemic autoimmune diseases affecting small and medium-sized blood vessels. 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 systemic or renal complications of small-vessel vasculitis.

Paediatric patients with GPA and MPA often present with clinical features of the disease similar to that of adult patients and share many signs and symptoms of the disease with adults (Calatroni et al. 2017).

3.1.2. Available therapies and unmet medical need

Currently, there are no specific guidelines or recommendations for the treatment of paediatric GPA and MPA and treatment is adapted from available adult data with no clear guidance on dosage or duration of therapy in paediatric patients. Treatment decisions are based on clinical features of disease activity (as indicated by signs and symptoms of vasculitis) or remission, and corresponding laboratory tests including urinalysis for assessment of proteinuria, haematuria and worsening renal function.

There is a significant need to improve treatment options, as well as safety and efficacy outcomes, in paediatric GPA and MPA patients. As there are no guidelines for the treatment of paediatric patients with GPA or MPA, treatment of paediatric GPA or MPA relies on the studies performed in adults. The patients are often exposed to cytotoxic therapies for long periods along with high percentage of treatment failures and disease relapses.

3.1.3. Main clinical studies

Study WA25615 (PePRS) was a multicenter, open-label, single-arm, uncontrolled study in 25 paediatric patients (≥ 2 to < 18 years old) with active GPA or MPA. The median age of patients in the study was: 14 years (range: 6-17 years) and the majority of patients (20/25 [80%]) were female. A total of 19 patients (76%) had GPA and 6 patients (24%) had MPA at baseline. Eighteen patients (72%) had newly diagnosed disease upon study entry (13 patients with GPA and 5 patients with MPA) and 7 relapsing disease (6 patients with GPA and 1 patient with MPA).

The study design consisted of an initial 6-month remission induction phase, with a minimum 18-month follow-up, up to a maximum of 54 months (4.5 years) overall. Patients were to receive a minimum of 3 doses of IV methylprednisolone (30 mg/kg/day, not exceeding 1 g/day) prior to the first MabThera IV infusion. If clinically indicated, additional daily doses (up to three), of IV methylprednisolone could be given. The remission induction regimen consisted of four once weekly IV infusions of MabThera at a dose of 375 mg/m2 BSA, on study days 1, 8, 15 and 22 in combination with oral prednisolone or prednisone at 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6. After the remission induction phase, patients could, at the discretion of the investigator, receive subsequent MabThera infusions on or after Month 6 to maintain PVAS remission and control disease activity (including progressive disease or flare) or to achieve first remission.

All 25 patients completed all four once weekly IV infusions for the 6-month remission induction phase. A total of 24 out of 25 patients completed at least 18 months of follow-up.

The objectives of this study were to evaluate safety, PK parameters, and efficacy of MabThera in paediatric GPA and MPA patients (≥ 2 to < 18 years old) in the induction of remission setting. The efficacy objectives of the study were exploratory and principally assessed using the Pediatric Vasculitis Activity Score (PVAS).

3.2. Favourable effects

The CHMP considered the dosing regimen proposed by the MAH for the induction of remission acceptable. The PK and PD effects of the proposed dose were evaluated in study WA25165 and the paediatric data were included in a popPK model with adults from the RAVE study.

Twenty-four out of 25 patients (96%) in Study WA25615 achieved oral glucocorticoid taper to 0.2 mg/kg/day (or less than or equal to 10 mg/day, whichever was lower) at or by Month 6 during the protocol-defined oral steroid taper. A decrease in median overall oral glucocorticoid use was observed from Week 1 (median = 45 mg prednisone equivalent dose [IQR: 35 – 60]) to Month 6 (median = 7.5 mg [IQR: 4-10]), which was subsequently maintained at Month 12 (median = 5 mg [IQR: 2-10]) and Month 18 (median =5 mg [IQR: 1-5]).

Clinically encouraging results were observed in terms of PVAS and BVAS. The proportion of patients with PVAS remission was 52% at month 6, 72% at month 12 and 72% at month 18. The mean duration of response 71.67 weeks. The number of number of major and minor PVAS relapses/flares at different time-points decreased over time, as expected. By month 12 no patients has PVAS flares. Similar results were observed in terms of BVAS.

Looking at other exploratory efficacy endpoints, the median oral glucocorticoid use declines rapidly over the first weeks of treatment, and by month 6 it reaches a very low plateau, median 7.5 mg. Patients were subsequently maintained on 5 mg as per protocol.

3.3. Uncertainties and limitations about favourable effects

The majority of the patients are diagnosed with GPA, while only 6 patients had MPA. Furthermore, most patients were newly diagnosed. However, the CHMP acknowledged that MPA and GPA overlap as disease entities.

The popPK analysis predicted the exposures in paediatric and adult patients adequately; however, only patients ≥ 6 years of age were enrolled in the study and pharmacokinetics of rituximab in patients ≥2 years of age and < 6 years of age are missing. Simulations of rituximab exposure in ≥ 2 to < 6 years old children and older patients with GPA or MPA with different methods to estimate PK parameters also indicated similar exposure across age groups. Rituximab PK data in children down to 3 years of age in

other indications have also indicated comparable PK in the youngest children. Therefore, the CHMP considers that it has been adequately justified that a body size-based dosing regimen in GPA/MPA will provide similar and acceptable exposure in the youngest children ≥ 2 to < 6 years of age even though no clinical data in this age group are available.

3.4. Unfavourable effects

Overall, all patients have been exposed to rituximab and followed for a sufficient period of time in order to allow an assessment of safety in the induction of remission setting. There was no malignancies, no deaths or discontinuations due to AEs. No new safety findings.

Limited data shows there was no trend observed in the adverse reactions reported in ADA positive patients. There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the paediatric GPA and MPA clinical trials.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited, but the observed findings are in line with the well-known safety profile of rituximab in the induction of remission setting.

The lack of data on long-term safety in the maintenance setting was of major concern to the CHMP. The MAH was asked repeatedly to make a proposal, present the outline and commit to conducting a PASS study post-approval in order to address the concerns related to long-term safety in the maintenance setting. Regrettably, the MAH could not commit to conducting a PASS study in the maintenance setting. Section 4.1. has been limited to the induction setting.

3.6. Effects Table

Table 57: Effects Table for Mabthera for paediatric patients with GPA/MPA in the Remission-Induction Phase (data cut-off: 10 May 2018).

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
PVAS remission at each time-point	Paediatric Vasculitis Activity Score	N(%) number of patients in remission	6 months: 13 (52%) 12 months: 18 (72%) 18 months:18 (72%)	Small paediatric study.	
PVAS DOR	Mean PVAS duration of remission	Weeks	71.67 Min-max: 6.9 – 193.4	Small paediatric study.	
BVAS remission at each time-point	Birmingham Vasculitis Activity Score	N(%) number of patients in remission	6 months: 9 (36%) 12 months: 16 (64%) 18 months:17 (68%)	Small paediatric study.	
Unfavourable Effects					
IRR (overall study period)	Infusion related reactions	N(%)	17 (68%)		

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Serious infections (overall study period)		N(%)	7 (28%)		
AESI of induction of remission	Infections	N(%)	17 (68%)		
	Serious inf.	N(%)	3 (12%)		
	IRRs	N(%)	15 (60%)		
	Hypogammaglobulineamia	N(%)	3 (12%)		
	Cardiac event	N(%)	0		
	Malignancy	N(%)	0		

Abbreviations: AESI Adverse event of special interest

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Childhood onset GPA/MPA is rare and serious disease. The current treatment options include high dose glucocorticoids in combination with cyclophosphamide. There is a high unmet need in this patient population.

Study WA25615 shows that rituximab seems to offer paediatric patients with GPA/MPA a valuable treatment option, where fast and sustained remission induction is achieved by 4 doses. However, this comes at cost of risk of IRR and serious infections, but these risks do not outweigh the benefits. The safety profile of rituximab is well-known due to wide clinical use in both malignant and benign conditions, and the majority of the AEs related to rituximab are clinically manageable. This is also supported by the fact that no patients discontinued treatment due to AEs.

The majority of the patients had severe disease; however, the MAH applied for an indication in "active" GPA (Wegener's) and MPA. Since the disease can present itself in different degree of severity, no solid arguments have been provided by the MAH to treat paediatric patient with slow and few symptoms. B-cell depletion is a serious matter and it would be inappropriate to start with rituximab in patients with few and mild symptoms. The inclusion criteria of study WA25615 appropriately describe children with 'active severe' GPA/MPA. Mabthera is indicated in severe, active GPA / MPA in the adult population. Therefore, at the CHMP's request, the MAH has revised the indication accordingly.

Study WA25615 main objectives were safety and PK/PD. Efficacy objectives were exploratory. The study was not designed to evaluate rituximab in the maintenance setting, but only the induction of remission.

3.7.2. Balance of benefits and risks

The CHMP considers a body size-based dosing regimen in GPA/MPA will provide similar and acceptable exposure even in the youngest children ≥ 2 to < 6 years of age although no clinical data in this age group are available.

The totality of evidence, including Mechanism of Action, disease pathophysiology, approved use in adults and the observed efficacy results in Study WA25615 can be considered clinically meaningful. Although the efficacy outcomes for this study were exploratory, they were as expected and in line with the results observed in the adult population.

The safety profile of MabThera in paediatric GPA or MPA patients in the induction of remission setting was consistent in type, nature and severity with the known safety profile in adult patients in the approved autoimmune indications with approved autoimmune diseases, including adult GPA or MPA.

3.8. Conclusions

The overall B/R of rituximab is positive in the indication "*MabThera, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ⩾ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA*".

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the induction of remission in paediatric patients (aged ⩾ 2 to <18 years old) with severe, active GPA (Wegener' s) and MPA; as a consequence sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.5, 8 of the SmPC are updated for MabThera 100 mg and 500mg concentrate for solution for infusion. The PL was updated accordingly.

In addition, the product information for the MabThera 100 mg and 500mg concentrate for solution for infusion have been combined.

The RMP version 21.1 has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent

updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Educational Material for Healthcare Professionals, Educational Material for Patients and Patient Alert Card (non-oncology indications) for the safety concerns

1. Infections, including serious infections
2. Progressive Multifocal Leukoencephalopathy

Educational Material for Healthcare Professionals for the safety concerns

1. Administration Route Error (NHL/ CLL, SC formulations)
2. Off-label Use of the Subcutaneous Formulation (NHL and CLL Subcutaneous Formulations)

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
WA29330 (PEMPHIX): A randomized, double-blind, double-dummy, active-comparator, multicenter study to evaluate the efficacy and safety of rituximab versus MMF in patients with pemphigus vulgaris.	Final study report: Q4 2020

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0060/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the induction of remission in paediatric patients (aged ≥ 2 to <18 years old) with severe, active granulomatosis with polyangiitis (GPA) (Wegener's) and microscopic polyangiitis (MPA); as a consequence sections 1, 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.5, 8 of the SmPC are updated for MabThera 100 mg and 500mg concentrate for solution for infusion. The PL was updated accordingly.

In addition, the product information for the MabThera 100 mg and 500mg concentrate for solution for infusion have been combined.

The RMP has been updated to version 21.1.

Summary

Please refer to Scientific Discussion ‘Mabthera-H-C-165-II-162’.