TITLE:	**LONG-TERM SURVEILLANCE STUDY OF RITUXIMAB (MABTHERA)-TREATED PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS (GPA) OR MICROSCOPIC POLYANGIITIS (MPA)**
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EU PAS REGISTER NUMBER:	EUPAS16359
ACTIVE SUBSTANCE:	L01XC02: Rituximab
MEDICINAL PRODUCT:	MabThera®
PRODUCT REFERENCE NUMBER:	EMEA/H/C/165
PROCEDURE NUMBER:	EMEA/H/C/165/MEA/093
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Deutschland
MAH CONTACT PERSON:	████████
RESEARCH QUESTION AND OBJECTIVES:	RIVAS is a secondary use of data study aimed to provide long-term safety data from the use of rituximab (MabThera) and other available therapies for patients with GPA or MPA.

	The primary objective of this study is to provide long-term safety data on rituximab (MabThera)-treated patients with GPA/MPA. The secondary objectives are (1) to estimate the incidence of serious adverse events (SAEs), including infections, cardiovascular events and malignancies, following MabThera or other available treatments in patients with GPA/MPA, and (2) to compare the incidence of each safety event over time between the MabThera-treated cohort and the cohort treated with other available therapies.
COUNTRY OF STUDY:	United Kingdom

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2.   LIST OF ABBREVIATIONS

AAV	ANCA-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
BVAS	Birmingham Vasculitis Activity Score
CI	Confidence Interval
CYC	Cyclophosphamide
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GPA	Granulomatosis with polyangitis
GVP	Guideline on good pharmacovigilance practices
CHMP	Committee for Medicinal Products for Human Use
IgG	Immunoglobulin G
MAH	Marketing Authorisation Holder
MPA	Microscopic polyangiitis
NI-PASS	non-interventional post-authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PI	Principal Investigator
RIVAS	Rituximab surveillance study in VASculitis
RMP	Risk Management Plan
RTX	Rituximab
UKIVAS	The UK and Ireland vasculitis registry
SAE	Serious Adverse Event
VDI	Vasculitis Damage Index

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4. <u>ABSTRACT</u>

Rituximab (MabThera) is a licensed therapy for the induction of remission in granulomatosis with polyangitis (GPA) and microscopic polyangitis (MPA). There is a paucity of data on the long term safety of rituximab (MabThera) for this indication. The UK and Ireland vasculitis registry (UKIVAS) is a nation-wide independent registry collecting long-term observational data on patients with vasculitis across 85 sites. The Vasculitis and Lupus clinic at Addenbrooke's Hospital Cambridge UK is one of the 85 UKIVAS centers providing data into UKIVAS, data of which will be used for the Rituximab (MabThera) surveillance study in VASculitis (RIVAS).

RIVAS aims to include all GPA/MPA patients who received rituximab (MabThera) in Cambridge at any time since 2003 and all GPA/MPA patients treated with other agents (estimated total sample size 400).

An annual data set will be extracted from the UKIVAS database (hosted in Oxford, UK) to include the following:

- Serious adverse events – including patient and renal survival, hospitalization, infections
- Other events including cardiovascular events – malignancies, vasculitis relapse, cumulative 'all cause' damage
- Concomitant therapy
- Lab abnormalities: neutropaenia and hypogammaglobulinaemia.

The Addenbrooke's Hospital Cambridge UK will retrospectively analyze the extracted data and provide an annual report with aggregated safety data to the Marketing Authorisation Holder (MAH), which will be submitted to the European Medicines Agency (EMA) through the Periodic Benefit Risk Evaluation Report (PBRER).

5.   AMENDMENTS AND UPDATES

Amendment 1: 18th July 2018: Substantial amendment. Change from prospective to retrospective study design. Milestone, data analysis and SAP sensitivity analysis updated. MAH and study team updates. Clarification of data/event data collection period being from time of first rituximab (MabThera) exposure to defined end of data extraction date as specified in Milestone section. Reduction of target recruitment numbers from 500 to 400. Clarification of collection of data following rituximab biosimilar exposure. Clarification of exclusion criteria based on the routine use of biosimilars since first approval.

Amendment 2: 25th March 2020: Non-substantial amendment. Changes in PIS to allow for postal consent. Minor edits to protocol for clarification.

6.   MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Start of study (first patient enrolled)	7th October 2016
End of patient inclusion (i.e. the last date that a patient will receive study drug)	30 September 2017
End of data extraction for any patient	30 September 2018
End of study	As soon as all eligible patients are consented and data extraction is complete
First cumulative report by PI to MAH	October 2016
First cumulative report in PBRER	January 2017
Second cumulative report by PI to MAH	October 2017
Second cumulative report in PBRER	January 2018
Third cumulative report by PI to MAH	October 2018
Third cumulative report in PBRER	January 2019
Fourth cumulative report by PI to MAH	October 2019
Fourth cumulative report in PBRER	January 2020
Fifth cumulative report by PI to MAH	October 2020
Fifth cumulative report in PBRER	January 2021
Registration in the EU PAS register	23 November 2016
Final report of study results	31 October 2021

7.   RATIONALE AND BACKGROUND

GPA and MPA are the two major forms of systemic vasculitis associated with the presence of ANCA [1]. These conditions are termed ANCA-associated vasculitis (AAV) because of their strong association with highly specific autoantibodies. AAV encompasses autoimmune disorders in which tolerance for one of two self-antigens, proteinase 3 (PR3) or myeloperoxidase (MPO), has been lost, leading to the production of PR3- or MPO ANCAs. Animal models, in vitro experiments, and many clinical observations in humans suggest that endothelial injury and tissue damage are dependent upon the pro inflammatory effects of ANCAs that result from the interaction of these specific antibodies with their target antigens on the surface of activated neutrophils and monocytes.

The prognosis for untreated GPA is poor with a low likelihood of survival (much less remission) in the absence of conventional treatment with cyclophosphamide (CYC) [2]. Regimens involving CYC and high doses of glucocorticoids have led to successful control of the disease and, in most cases, the prevention of death from overwhelming AAV [3,4,5]. Current available therapies are associated with significant toxicities, as well as disease relapses when therapy is tapered or discontinued, and therefore novel and targeted mechanism–based treatment approaches are needed. There is strong support for a crucial role for B lymphocytes in the pathogenesis of GPA and MPA [4, 6, 7] and, therefore, a clear rationale for the use of a B-cell depleting therapy such as rituximab.

This rationale led to the first published account of RTX therapy in an AAV patient (Specks et al. 2001). Subsequent investigator-initiated studies (Eriksson 2005; Keogh et al. 2005, 2006; Omdal et al. 2005; Aries et al. 2006; Smith et al. 2006; Stasi et al. 2006; Brihaye et al. 2007; Sanchez-Cano et al. 2008; Seo et al. 2008; Jones et al. 2009; Lovric et al. 2009) have demonstrated induction of remission in severe and often refractory patients.

Rituximab has been investigated in one multi-center, active-controlled, non-inferiority trial of rituximab vs CYC (RAVE) [8], as well as in a number of smaller investigator-initiated studies and case series. Results of the RAVE study support the conclusion that rituximab is non-inferior to CYC over 6 months of treatment; a higher percentage of patients in the RTX arm (64%) achieved complete remission at 6 months compared with patients in the CYC arm (55%). The lower limit of the 95.1% CI for the absolute difference, – 4.3%, was greater than the non-inferiority margin of – 20% and thus met the protocol-specified non-inferiority criterion. Non-inferiority to CYC was observed consistently across secondary and exploratory endpoint and across subgroups defined by demographic and disease characteristics. At 18 months, efficacy findings were similar to those

observed at 6 months. The proportion of patients who maintained their complete remission at 12 months and 18 months was similar across treatment groups.

Overall tolerability at 6 months was comparable between RTX and CYC treatment in RAVE: the proportions of patients experiencing any AE, any severe (Grade $\geq$ 3) AE, or any serious AE were similar between the RTX and CYC groups, as were the overall rates of any AE and serious AE per patient-year. The most frequently reported type of AE and serious AE were infections, comprising most commonly upper respiratory tract infections. The incidence of these and other events of special interest for rituximab, such as serious cardiac adverse events and malignancies, were similar across treatment groups over 6 months of treatment. No serious IRRs were reported. The overall profile of adverse events reported over 18 months and out to the common closeout date of RAVE was similar to that observed at 6 months. The rates (95% CI) of malignancy in the RTX and CYC groups were 2.00 (0.90−4.46) and 0.73 (0.18−2.91) per 100 patient-years, respectively. Overall, however, rates of death, serious infection, and malignancy were within those expected for AAV populations. Safety events in the investigator-initiated studies reported in the literature are limited. However, these data are generally consistent with those reported in the RAVE study. The most common type of adverse event reported was infection, particularly respiratory infection.

Based on the results from RAVE study, rituximab (MabThera) was licensed for the induction of remission for patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) by the FDA in 2011 and the EMA in 2013. The MabThera CHMP Type II variation assessment report for GPA/MPA application (EMEA/H/C/165/II/79) requires that long-term safety in GPA/MPA patients, which is identified in the Risk Management Plan (RMP) as missing information, should be addressed via data from identified EU registries and should be included in the next version of the RMP as an additional pharmacovigilance activity. The MAH will fulfill this RMP commitment by collaborating with one of the centers within UKIVAS to obtain aggregated long-term safety data in GPA/MPA patients.

This proposed observational pharmacovigilance study aims to better characterize the risk profile of rituximab (MabThera) by collecting safety-focused data in patients with GPA/MPA who have been treated with rituximab (MabThera) or other available therapies. The study is a European Medicines Agency (EMA) post-authorization commitment and represents a non-interventional post-authorization safety study (NI-PASS, as defined by Directive 2001/83/EC [DIR] Art 1[15], E.U. Pharmacovigilance Legislation, and the Guideline on Good Pharmacovigilance Practice Module VIII).

The UK and Ireland vasculitis registry (UKIVAS) is a national independent registry collecting long term observational data on patients with vasculitis. This registry had its early origins in the "Lockwood Club" which was a pioneering vasculitis study group established in 1995 by Dr Martin Lockwood (Cambridge), Dr David GI Scott (Norwich), and Dr Richards Watts (Ipswich). Since then the club has grown in size and scope and is now UKIVAS. The Vasculitis Rare Disease Group evolved from UKIVAS, a steering group set up to develop the national Vasculitis registry. Its aims are

- to create a database of Vasculitis patients in the British Isles
- to build-up longitudinal clinical data to create a picture of the patient's clinical course
- to link the clinical information to biological samples

This will enable large-scale genetics and epidemiology studies, identify cohorts of patients to recruit for clinical trials and biomarker studies, allow multi-centre audit of novel biological therapies and inform logical service delivery. There are currently 85 UK and Ireland sites involved in enrolling patients in the UKIVAS database. The registry is curated in Oxford UK by Raashid Luqmani and has an established clinical governance system supervised by a management committee chaired by Mark Little (Dublin) and Richard Watts (Ipswich).

The Vasculitis and Lupus clinic at Addenbrooke's Hospital Cambridge UK is one of the 85 UKIVAS centers. It was established in 1987 and currently cares for over 400 patients with GPA/MPA. The center in Cambridge has led studies of rituximab in GPA/MPA since 2003. Data from the Addenbrooke's Hospital submitted to the UKIVAS will be the data source for the rituximab (MabThera) surveillance study in VASculitis (RIVAS).

8.   RESEARCH QUESTION AND OBJECTIVES

Research question

RIVAS is a secondary use of data study aimed to provide long-term safety data from the use of rituximab (MabThera) and other available therapies for patients with GPA or MPA.

Objectives

The primary objective of this study is:

- To provide long-term safety data on rituximab ((MabThera)-treated patients with GPA/MPA.

The secondary objectives are:

- To estimate the incidence of serious adverse events (SAEs), including infections, cardiovascular events and malignancy, following rituximab (MabThera) or other available treatments in patients with GPA/MPA
- To compare the incidence of each safety event over time between the rituximab (MabThera)-treated cohort and the cohort treated with other available therapies

9.   RESEARCH METHODS

9.1   STUDY DESIGN

This study is a non-interventional secondary data safety study in patients with GPA/MPA exposed to rituximab (MabThera) or other available treatments as part of their standard clinical care. Data will be extracted from the Cambridge site within UKIVAS database. Patients in each treatment cohort (rituximab (MabThera) or other available treatment regimens) will be followed from time of disease flare or disease diagnosis since 2003 (year of first use of rituximab (MabThera) in Cambridge, (total target study sample size approximately 400). Patients who switch treatment regimens during the course of their registry follow-up will continue to be followed with date of switching recorded. Data will be extracted to the end of study, loss to follow-up or to withdrawal of consent or death and will be evaluated and patients treated according to physician's standard practice.

AAV patients with minimum disease duration of six months who are under the care of the Cambridge Vasculitis Clinic will be invited to participate. Potential patients will be given or posted

a study participant's information sheet to read, prior to signing informed consent once any of their questions have been satisfactorily answered by the study team. Study data, reflecting safety events occurring in the duration of the study will be collected as per Appendix 1. Immunosuppressive, rituximab (MabThera) and glucocorticoid exposure will be calculated from date of diagnosis (Section 9.3) to date of assessment using data derived from the hospital patient record. The rituximab (MabThera) group will comprise patients who have received rituximab (MabThera) at any time since diagnosis of GPA/MPA. The control group will comprise patients who have never received rituximab (MabThera). Aggregated summary results will be prepared by the PI every 12 months and submitted to the MAH.

9.2   SETTING

Patients must meet the following criteria for study entry:

1. Clinical diagnosis of GPA/MPA through use of the consensus algorithm for the classification of ANCA vasculitis and polyarteritis nodosa (European Medicines Agency, Abdulkader et al 2013)
2. Age ≥ 18 years
3. Have given informed consent to participate in the UKIVAS registry
4. Have given informed consent to participate in the RIVAS study
5. Any patient with GPA/MPA who has received rituximab (MabThera) for vasculitis since 2003 (rituximab (MabThera) group)
6. Any GPA/MPA patient with disease flare since 2003 who has not received rituximab (disease control group)

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

- Patients with eosinophilic granulomatosis with polyangitis (EGPA/Churg-Strauss)
- Unwilling or unable to provide written informed consent for the UKIVAS registry
- Unwilling or unable to provide written informed consent for the RIVAS study

Patients with significant concomitant disease (e.g. cancer, HIV/AIDS) will not be excluded from the study. Significant concomitant diseases will be considered at the analysis stage.

9.3   VARIABLES

Primary variables
- Baseline demography

- o Diagnosis GPA or MPA
- Status at time of evaluation
  - o Date of rituximab (MabThera) administration
  - o Onset date of event
  - o Occurrence of serious adverse events (SAE) in last 6-12 months
    - Type of event (MedDRA code)
    - Outcome of event
  - o All malignancies in the last 6-12months

Secondary variables

- Baseline demography
  - o Age, gender, ethnicity (Caucasian Y/N)
  - o Height and weight
  - o ANCA at diagnosis (PR3-ANCA/ MPO-ANCA or ANCA negative)
  - o Date of diagnosis
  - o Drug exposure
    - Cyclophosphamide, g
    - Glucocorticoids, months
    - Prior azathioprine, methotrexate or mycophenolate
    - Number and type of other immunosuppressives
  - o Co-morbidities (cardiovascular disease, chronic pulmonary disease, malignancy, diabetes)
- Status at time of evaluation
  - o Vasculitis activity
    - Disease state (active/remission/low disease activity state)
    - Severe disease flare (one or more BVAS/WG new/worse 'major' items) over past 6-12 months
  - o GFR, IgG, CD19 count (if measured), neutrophil count (if measured)
  - o Pregnancy and contraception status (for women of childbearing potential) (if available)
  - o Concomitant glucocorticoid and immunosuppressive therapy
  - o Occurrence of lab abnormalities (neutrophil count < 1.5 x 109 /L, IgG < 3g/L and < 5g/L, in last 6-12 months (note: lab abnormalities will be reported as adverse events if treatment is required or treatment has been changed)
  - o Vasculitis Damage Index (VDI)

Information will be collected as per local standard of practice.

9.4 DATA SOURCES AND DATA MANAGEMENT

All data included in RIVAS are obtained by the investigational site and entered in the UKIVAS registry. MAH does not have any influence in the data collection nor the registry design. MAH will not receive any patient-level data nor have direct access to registry data. RIVAS will include data from all consented GPA/MPA patients who have received rituximab (MabThera) in Cambridge at any time since 2003 and all consented GPA/MPA patients treated with other agents (total target study sample size approximately 400). There will be no patient selection (see 9.1).

Data extraction commences at the time of enrolment into RIVAS (and into UKIVAS if not already registered). The data observational window (data extraction period) will be from the participant's first exposure to rituximab (MabThera) or flare of vasculitis requiring an alternative immunosuppressive to rituximab (MabThera), up to 30th September 2018; therefore data extracted is retrospective. Data will be extracted at least annually.

All baseline data, and event data between assessment time points, will be derived from information routinely collected in the Hospital Patient Record with the exception of VDI. The investigational site will be responsible for management of the data they extract, including quality checking of the individual data points. Aggregate data reports will be transferred to the MAH at annual intervals as specified in the Statistical Analysis Plan. Patient confidentiality will be respected and all data transmitted to the study database will be anonymous. Quality control will be achieved by back checking periodically from the UKIVAS registry against a sample of primary data sheets (See Section 9.7).

9.5 STUDY SIZE

All patients with GPA/MPA who are managed by the Vasculitis and Lupus Clinic at Addenbrooke's Hospital, Cambridge, U.K., who fulfill the eligibility criteria, and who have received rituximab (MabThera) or other available treatments during the study period will be invited to participate without further restrictions. A formal study size calculation has therefore not been performed. The observational period for each patient varies depending on when they were first exposed to rituximab (Mabthera) up to 30th September 2018; the longest observational period for a patient may therefore be approx. 15 years (from 2003 to 2018). A previous long-term follow-up study of rituximab (MabThera) treated AAV patients from Cambridge reported serious adverse events occurring in 37%, and infections occurring in 24%, of patients treated with rituximab (MabThera) over a mean follow-up period of 104 months.

9.6 DATA ANALYSIS

The Principal Investigator will retrospectively analyze a pre-specified data-cut within the Cambridge center every 12 months for the cumulative study reports. For each patient cohort, variables will be summarized using mean, median, standard deviation and range for continuous data, and counts and percentages for categorical data.

Following the methodology used in rheumatoid arthritis, two main analytical approaches will be used depending on the outcome of interest. For analyses of risk of malignancy, the primary analysis will use an ever-exposed model that includes all person-time since the first drug dose in the study. For all SAEs except malignancy, the primary analysis will be based on a time-on-drug approach that uses a pre-defined risk window after the last administration of rituximab (MabThera) or other available therapies. An outcome of interest occurring during the defined risk window period will be allocated to the preceding treatment identically for both drug regimens. Details of how the study will account for treatment switching can be found in the Statistical Analysis Plan (SAP).

Sensitivity analyses will be performed to assess how dependent the conclusions are to the methods and assumptions used to deal with switching. The sensitivity analyses will include, but not be limited to: varying the duration of the risk windows; censoring at the first switch (in both drug regimens); and down-weighting observations from switchers. All methods of analysis will be systematically applied to each event definition.

The analysis of the primary endpoint will be stratified by enrolment period (pre-consent versus post-consent) to assess robustness of conclusions from primary analysis due to change in study design.

The PI will provide yearly cumulative study reports with aggregated data on safety events that occur in each patient cohort. The total number of safety events and unadjusted incidence rates per 1000 patient-years and 95% confidence intervals (CIs) will be provided for each patient cohort, as well as for males and females within each cohort (Appendix 2). Incidence rates will be calculated using Poisson regression model and the CI provided, assuming the estimated parameters follow a normal distribution.

In addition to these yearly cumulative reports, the PI will provide a final report at the end of data extraction and analysis. The study final report will also contain event rates per 1,000 patient-years and 95% CIs: First, event rates including all events reported within the qualifying exposure window will be presented, assuming that the inter-event time observations are exchangeable within patients, and do not depend on the number of times the event has recurred within a

patient. The rates will then be re-presented using first events only, censoring at first switching. Subsequent recurrent events will be summarized by presenting Kaplan-Meier curves for the time from 1st to 2nd event, and generally the time from n^{th} to $(n+1)^{th}$ event, until the number of events falls below 10; the times will be censored at the first switching, and survival curves provided separately for the two drug regimens.

The hazard ratio between the rituximab (MabThera) and control group (males and females combined) with associated 95% CIs will be estimated using Cox-proportional hazards models. Patients (in both cohorts) are enrolled over a period of time and the study will end on a specific calendar date . Thus, patients who enroll later will be observed for a shorter period than patients who enroll early. Therefore the time-to-event analyses, e.g. Cox regression model, where patients without an event of interest will be censored at the last date known to be followed-up, will applied. A comparison will only be made only when a minimum of 10 events across both groups has been observed with at least one event in each cohort. Unadjusted and adjusted hazard ratios will be presented, taking into account potential confounders, including age, disease duration, ANCA type, co-morbidities (eg, diabetes, cardiac disease, malignancy, pulmonary disease), etc. Subgroup analyses will be performed according to specific co-morbidities and categories of VDI. The extended Cox Proportional Hazard Model will be used to account for treatment switching.

Full details of planned statistical summaries including mapping of the adverse events, treatment switching and adjusted analysis will be specified in a Statistical Analysis Plan which will be developed before the first cumulative report.

9.7 QUALITY CONTROL

Serious adverse event episodes will be notified to the study team when they occur. In addition, the occurrence of any episodes in the previous six months will be recorded from the routine visits. Where there is a discrepancy in notification a query will be raised by the study team and the hospital charts examined.

9.8 LIMITATIONS OF THE RESEARCH METHODS

This observational, longitudinal, non-interventional study design aims to evaluate the risk profile of rituximab and other available treatment regimens in patients with either GPA or MPA in a real-world setting. Choice of therapy is at the discretion of the treating physician and this may introduce selection bias which that could lead to an imbalance of baseline patient demographics and/or confounding variables between treatment cohorts. It is possible that patients with GPA or

MPA who participate in this single-center study may not be representative of the population as a whole, however, both indications are relatively rare and this may mitigate any lack of representativeness. The statistical methods used in the generation of the cumulative and final report provided to the MAH are intended reduce the possibility of the introduction of bias or error into the findings by adjusting for baseline covariates and potential confounders. Nevertheless, residual bias could still persist due to unmeasured or imprecisely measured confounding factors.

10. PROTECTION OF HUMAN SUBJECTS

Patients are treated according to the principles decided by the responsible physician, not influenced by the study. Patient confidentiality will be respected and all data transmitted to the study database will be anonymous. MAH will not receive any patient-level data nor have direct access to registry data. All patient data will be submitted into the UKIVAS registry after written informed consent by the patient. The registry operates under relevant ethical approvals from the United Kingdom and Ireland.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2012) distinguishes between non-interventional studies that are based on primary data collection directly from consumers and HCPs and study designs that are based on the secondary use of data, such as the use of data from existing registries.

EMA GVP Module VI states that
"*For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarised in the study report, where applicable*" (EMA, 2012, section VI.C.1.2.1.).

Therefore, the responsibility for adverse event reporting will remain with the treating physician. The MAH will receive only anonymized aggregated data from the registry, which will be summarized in the annual and overall final study reports.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The MAH will review all study reports and then submit them to the Health Authorities through the PBRER. Results might be published by the PI independently of Roche.

13. REFERENCES

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Appendix 1 - Data Extraction Overview (as per Standard of Care)

Data Extraction (available data will be extracted, no additional diagnostic or monitoring procedures shall be applied to the patients outside routine clinical practice)	Screening and/or baseline visit[a]	Every 6-12 Months (±45 days) Data Collection[b]
Informed consent for UKIVAS[c]	x	
Review patient eligibility (inclusion/exclusion criteria)	x	
Demographic data[d]	x	
Date diagnosis of GPA/MPA	x	
Previous GPA/MPA treatment	x	x
Co-morbidities	x	
Current GPA or MPA disease status[f]	x	x
Vasculitis Damage Index (VDI)	x	x
GFR, neutrophil count, IgG, CD19 (if measured)	x	x
Current medication	x	x
Occurrence of severe flare since last data collection time point[g]	x	x
Height and weight[h]	x	x
Pregnancy status (if available)	x	x
SAEs	x	x
Malignancies, including NMSC	x	x
Laboratory abnormalities - Neutrophil count <1.5 x 10^9/L, IgG < 3g/L (if measured)	x	x

[a] Screening and baseline visits may be performed on the same day
[b] Patients will be evaluated and treated according to their physician's standard practice and discretion at their standard-of-care visits. Data will be extracted every 6-12 months (± 60 days) from patients' medical records. All data collection dates should be projected on the basis of the date of the patient's baseline office visit.
[c] Written informed consent must be obtained before any data collection.
[d] Patient demographic information includes the extraction of date of birth, sex, and race/ethnicity
[e] Record the reason the patient did not enroll, the dose of RTX prescribed, and concomitant GPA or MPA therapy, if any.
[f] Provide the details of tests and information extracted (including renal involvement)
[g] defined as one or more new/worse 'major' items on the BVAS/WG
[h] Height and weight will be recorded at screening/baseline visit. At all subsequent visits, only weight will be collected.

APPENDIX 2 – DRAFT ANNUAL SAFETY REPORTING TEMPLATE

The table shell below should be generated for each treatment cohort (ie, rituximab and other available treatment regimens)

Table 1   Patient Demographics

Start of observation		
Number of new registrations (dd.mm.yyyy to dd.mm.yyyy, dates to be determined)		
Cumulative number of registrations (since date of first registration)		
Cumulative number by gender	Male	
	Female	
Cumulative number by age at registration	18–29	
	30–39	
	40–49	
	50–64	
	65–74	
	≥ 75	

Table 2   Baseline Characteristics

					Mean			SD (not applicable for all variables)		
		GPA	MPA	Total	GPA	MPA	Total	GPA	MPA	Total
Age (years)	Male									
	Female									
	Total									
Clinical diagnosis (GPA/MPA, No/%)	Male									
	Female									
	Total									
Time since diagnosis (months)	Male									
	Female									
	Total									
Disease duration prior to first RTX infusion (months)	Male									
	Female									
	Total									
Ethnicity (Caucasian, No/%)	Male									
	Female									
	Total									
Vasculitis Damage Index (VDI)	Male									
	Female									
	Total									
Active vasculitis in last year (BVAS/WG >/= 1) (No/%)	Male									
	Female									
	Total									
ANCA type (PR3-ANCA, MPO-ANCA, ANCA negative, No/%)	Male									
	Female									
	Total									
Prior use of rituximab for GPA/MPA (No/%)	Male									
	Female									
	Total									
Rituximab exposure (g)	Male									
	Female									
	Total									
Time since first rituximab for GPA/MPA (months)	Male									

						Mean			SD (not applicable for all variables)		
		GPA	MPA	Total	GPA	MPA	Total	GPA	MPA	Total	
	Female										
	Total										
Prior exposure to CYC (g)	Male										
	Female										
	Total										
Prior duration of glucocorticoids (months)	Male										
	Female										
	Total										
Prior exposure to azathioprine (No/%)	Male										
	Female										
	Total										
Prior exposure to methotrexate (No/%)	Male										
	Female										
	Total										
Prior exposure to a mycophenolate preparation (No/%)	Male										
	Female										
	Total										
Number of non-glucocorticoid immunosuppressives or non rituximab biologics (median)	Male										
	Female										
	Total										
GFR at time of first RTX (ml/min, median)	Male										
	Female										
	Total										
Proportion receiving ongoing glucocorticoids (No/%)	Male										
	Female										
	Total										
Proportion receiving ongoing non-glucocorticoid immunosuppressive or non-rituximab biologic (No/%)	Male										
	Female										
	Total										
Comorbidity * specificity	Male										
	Female										
	Total										

* Comorbidity defined as diabetes, cardiac disease, non-skin malignancy or chronic pulmonary disease occurring before first rituximab treatment

Table 3   Cumulative Listing and Incidence Rates of Adverse Events after RTX Infusion (or Other Treatment Depending on Patient Cohort)

	Males		Females		Total	
Event	Events (N)	Rate (95% CI)	Event (N)	Rate (95% CI)	Events (N)	Rate (95% CI)
Serious Infection						
Septicaemia						
HBV reactivation						
Herpes infection						
Opportunistic infection (including TB)						

	Males		Females		Total	
Event	Events (N)	Rate (95% CI)	Event (N)	Rate (95% CI)	Events (N)	Rate (95% CI)
Upper respiratory tract infections						
Lower respiratory tract infections						
Total Serious Infection						
Cardiovascular Disorders						
Congestive heart failure (new or worsening)						
Coronary artery disease						
Myocardial infarction						
Stroke (ischemic, haemorrhagic, or undetermined origin)						
Venous thrombotic event (DVT,PE)						
Cardiovascular death						
Other cardiovascular events (not mentioned above)						
Total cardiovascular disorders (any of above)						
Haematological Events						
Agranulocytosis						
Aplastic anaemia						
Neutropenia (ANC <1500µl)[†]						
Other dyscrasia						
Pancytopaenia						
Thrombocytopenia						
Total haematologic events (any of above)						
Malignant Events						
Leukaemia						
Lymphoproliferative disorder						
Lymphoma (NHL, Hodgkin, diffuse large b-cell lymphoma (DLBCL))						
Myeloma						
Non-melanoma skin cancer						
Other malignant solid tumours						
Total malignant events (any of above)						
Renal Insufficiency						

Event	Males		Females		Total	
	Events (N)	Rate (95% CI)	Event (N)	Rate (95% CI)	Events (N)	Rate (95% CI)
End-stage renal disease (ESRD)						
Dialysis						
Plasma Exchange						
Renal transplantation						
Total renal insufficiency (any of above)						
Progressive multifocal leukoencephalopathy						
PML						
Additional Safety Events						
Serious disease flares i.e major flare						
Serious infusion-related reaction						
Gastrointestinal perforation						
Hypogammaglobulinemia (<300 mg/dL)[†]						
Hypogammaglobulinemia requiring IVIg replacement						
Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (confirmed by skin biobsy)						
All SAEs leading to treatment discontinuation						
Pregnancy						
Vaccination failure						
Posterior reversible encephalopathy syndrome (PRES) or Reversible progressive leukoencephalopathy syndrome (RPLS)						
Any SAEs occurring in either mother, foetus, or baby following exposure of the mother						
Death (all cause)						
All SAEs (any of the above)						

[†] lab abnormalities will be reported as adverse events if treatment is required or treatment has been changed)

Table 4   Cumulative Listing and Incidence Rates of Lab abnormalities after RTX Infusion (or Other Treatment Depending on Patient Cohort)

Lab abnormalities	Males		Females		Total	
	Events (N)	Rate (95% CI)	Event (N)	Rate (95% CI)	Events (N)	Rate (95% CI)
Neutropenia (ANC <1500µl)						
Hypogammaglobulinemia (<300 mg/dL)						

Lab abnormalities	Males		Females		Total	
	Events (N)	Rate (95% CI)	Event (N)	Rate (95% CI)	Events (N)	Rate (95% CI)
Immunoglobulin G (<5g/l)						
Immunoglobulin G (<3g/l)						

APPENDIX 3 – ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENePP

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The <u>European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)</u> welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the <u>ENCePP Guide on Methodological Standards in Pharmacoepidemiology</u> which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the <u>Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies</u>). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Long-term surveillance study of rituximan (MabThera)-treated patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)

Study reference number:
EUPAS16359

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☒	☐	☐	7
1.1.4 Interim progress report(s)	☒	☐	☐	7
1.1.5 Registration in the EU PAS register	☒	☐	☐	7
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10
2.1.2 The objective(s) of the study?	☒	☐	☐	10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10-11
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	10

Comments:

There is no *a priori* hypothesis, as randomised control trials did not report any significant differences in safety profiles between rituximab and comparator arm. (Stone et al. N Engl J Med. 2010; 363(3): 221–232)

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10-11
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	10-12

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[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	10, 13-14

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	10-11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	10-12
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	10-12
4.2.4 Disease/indication?	☒	☐	☐	10-12
4.2.5 Co-morbidity?	☒	☐	☐	12
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	11-13

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	12-13
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	10,12-13
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	13-14
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	10, 13-14
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	10-12

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	11-14
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	11-14

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	10-13
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	10-13
8.1.3 Covariates?	☒	☐	☐	10-13
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	11-13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	11-13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	11-13
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of	☒	☐	☐	11

Section 8: Data sources	Yes	No	N/A	Page Number(s)
Diseases (ICD)-10)				
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	11
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	11
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:
All patients with GPA/MPA who are managed by the Vasculitis and Lupus Clinic at Addenbrookes Hospital, Cambridge, U.K., who fulfill the eligibility criteria, and who have received rituximab or other available treatments during the study period will be invited to participate without further restrictions.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	13-14
10.2 Is the choice of statistical techniques described?	☒	☐	☐	13-14
10.3 Are descriptive analyses included?	☒	☐	☐	13-14
10.4 Are stratified analyses included?	☒	☐	☐	13-14
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	13-14
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	14
11.2 Does the protocol provide information on data	☒	☐	☐	6

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)				
11.3 Are methods of quality assurance described?	☒	☐	☐	14
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	14
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	13-14

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	14
12.1.2 Information biases?				
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	14
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13
12.3 Does the protocol address other limitations?	☒	☐	☐	14

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	15
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	15
13.3 Have data protection requirements been described?	☒	☐	☐	15

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	15
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	15

Comments:

Name of the main author of the protocol: ███████ Addenbrooke's Hospital Cambridge UK

Date: 25/03/2018

Signature: ██████████████████