NI PASS PROTOCOL

TITLE:	**MABTHERA DRUG UTILISATION STUDY AND PATIENT ALERT CARD EVALUATION IN NON-ONCOLOGY PATIENTS IN EUROPE: AN INFUSION CENTRE–BASED APPROACH**
PROTOCOL NUMBER:	BA28478
VERSION NUMBER:	3.0
DATE OF LAST VERSION:	8 September 2015
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FINAL PROTOCOL APPROVAL

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EU PAS REGISTER NUMBER:	To be determined
ACTIVE SUBSTANCE:	L01XC02: Rituximab
MEDICINAL PRODUCT:	MabThera®
PRODUCT REFERENCE NUMBER:	RO 45-2294
PROCEDURE NUMBER{S}:	[redacted]
MARKETING AUTHORIZATION	Roche Registration Ltd

HOLDER (MAH):	6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted]
RESEARCH QUESTION AND OBJECTIVES:	This protocol addresses the 2 European Union (EU) follow-up measures (FUMs) following approval of Variation EMEA/H/C/165/II/65 for MabThera use in RA (1) FUM no. 68 (Clinical): Drug Utilisation Study (DUS) to Assess Off-Label Use and (2) FUM No, 71.1 (Pharmacovigilance): Evaluation of Receipt, Use, and Impact of the Patient Alert Card (PAC) on Infections, Including Progressive Multi-focal Leukoencephalopathy (PML).
COUNTRIES OF STUDY:	United Kingdom, Germany, France, Italy, and Spain

PROTOCOL ACCEPTANCE FORM

TITLE:	**MABTHERA DRUG UTILISATION STUDY AND PATIENT ALERT CARD EVALUATION IN NON-ONCOLOGY PATIENTS IN EUROPE: AN INFUSION CENTRE–BASED APPROACH**
PROTOCOL NUMBER:	BA28478
VERSION NUMBER:	3.0
EU PAS REGISTER NUMBER:	To be determined
MEDICINAL PRODUCT:	MabThera®
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
SPONSOR:	F.Hoffmann-La Roche Ltd

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

_____

Lead Scientific Responsible's Name (print)

_____ _____

Lead Scientific Responsible's Signature Date

Please return the signed original of this form to the [redacted] CRA assigned to your site or to the [redacted] Project Team a [redacted]. Please retain a copy for your study files.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	ANCA-associated vasculitis
AE	adverse event
ANCA	anti-neutrophil cytoplasmic autoantibody
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COX	Cyclooxigenase
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Even
CTMS	Clinical Trial Management System
DAS28	28-joint Disease Activity Score
DUS	Drug Utilisation Study
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FUM	follow-up measure
GMA	Global Medical Affairs
GPA	granulomatosis with polyangiitis
GPP	Good Pharmacoepidemiological Practice
GVP	EU Guideline on Good Pharmacovigilance Practices
HCP	health care provider
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
JAK	janus kinase
LN	lupus nephritis
MPA	microscopic polyangiitis
NCI	National Cancer Institute
NO	Non-oncology conditions
NSAID	Non-steroidal anti-inflammatory drugs

Abbreviation	Definition
PAC	Patient Alert Card
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation reports
PIL	Patient information leaflet
PML	Progressive Multi-focal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
Q	Quarter
QC	quality control
RA	rheumatoid arthritis
[redacted]	[redacted]
SAE	Serious adverse event
SDV	Source data verification
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TNF	tumour necrosis factor
UAT	user acceptance testing
UK	United Kingdom
US	United States

2. RESPONSIBLE PARTIES

- Roche is the sole sponsor of the study. Scientists from Real World Data Science, Safety Science, Global Medical Affairs and Regulatory departments have collaborated in the design and will be responsible for evaluating the implications of the results to future patient and physician communications regarding MabThera® treatment in non-oncology indications.
- [redacted] epidemiologists were the main party responsible for developing this protocol. [redacted] epidemiologists have also contributed to the development of this protocol.
- [redacted], a contract research organisation (CRO), will be responsible for the conduct, analysis and scientific oversight of the study. This will include site and physician recruitment, monitoring of sites for patient recruitment, data collection, cognitive pretesting and ethics committee submissions.
- Local investigators at each infusion centre will be responsible for abstraction of medical records and distribution of the self-administered patient questionnaire. If local investigators require support for medical record abstraction, support could be provided by [redacted] However, medical record abstraction will be conducted always at the local site; medical record data, including patient identifiers, will never leave the infusion centre.
- The study team will be responsible for reporting any possible adverse drug events to the Roche local affiliate using the processes outlined in Section 10.
- Roche will assess the information for possible adverse events and product complaints (see Section 10) and forward for processing to the company safety database and/or to the Product Complaints group as applicable through Roche's usual processes and standard operating procedures.
- Roche will be responsible for fulfilling any responsibilities for reporting results to regulatory agencies.

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3. SYNOPSIS

TITLE:	**MABTHERA DRUG UTILISATION STUDY AND PATIENT ALERT CARD EVALUATION IN NON-ONCOLOGY PATIENTS IN EUROPE: AN INFUSION CENTRE–BASED APPROACH**
PROTOCOL NUMBER:	BA28478
VERSION NUMBER:	3.0
DATE OF PROTOCOL:	8 September 2015
EU PAS REGISTER NUMBER:	To be determined
MEDICINAL PRODUCT:	Rituximab (generic name); Mabthera® (brand name)
INTERNATIONAL MEDICAL DIRECTOR:	[redacted]
MAIN AUTHOR:	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Rheumatoid arthritis (RA); granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA)
MARKETING AUTHORIZATION HOLDER:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

Rationale and Background

Rituximab (MabThera) received European Medicines Agency (EMA) approval in June 2006 for the treatment in combination with methotrexate of adult patients with severe, active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies. In March 2013, the EMA approved a new non–oncology-related indication, allowing the use of MabThera in combination with glucocorticoids for the induction of remission in adult patients with severe, active GPA (Wegener's) and MPA. This protocol addresses the 2 European Union (EU) follow-up measures (FUMs) following approval of Variation EMEA/H/C/165/II/65 for MabThera use in RA (1) FUM no. 68 (Clinical): Drug Utilisation Study (DUS) to Assess Off-Label Use and (2) FUM No, 71.1 (Pharmacovigilance): Evaluation of Receipt, Use, and Impact of the Patient Alert Card (PAC) on Infections, Including Progressive Multi-focal Leukoencephalopathy (PML).

Research Question and Objectives

A single study is proposed to address both EU FUMs with the following objectives:

1. To quantify and characterise off-label use through an evaluation of the disease and characteristics of patients treated with MabThera for non-oncology conditions.
2. To evaluate the extent to which patients receive and read the PAC, knowledge of the PAC content among patients receiving MabThera for non-oncology conditions at infusion centres, and whether distribution of the PAC may influence patient actions.

Study Design

A geographically dispersed and diverse set of infusion centres in the United Kingdom (UK), Germany, France, Italy, and Spain will be recruited to participate in the study. At each participating centre, de-identified data will be retrospectively abstracted from medical records on

non-oncology treatment indication and patient and disease characteristics for all patients receiving MabThera. In addition, a self-administered patient questionnaire will be employed to collect information on patient knowledge about the risk of infections including PML, patient receipt and review of the PAC, and any actions the patient has taken as a result of receiving the PAC.

Description of Study:

Data from medical records will be retrospectively abstracted over a 12-month look back period in the participating infusion centres. Patients will be recruited in the same infusion centres to participate in the patient survey during a 10-month data collection period.

Start Date of Study:

The study start date will be the date of the first data collection: the date on which information on the first study patient from the survey is recorded in the study database or, the date on which retrospective data extraction starts**.**

End of Study:

The end of the study will be the date on which the last information of the last patient is recorded in the study database.

Population

Patients must meet the following inclusion criteria for study entry:

- Patient is in the centre to receive an infusion for MabThera for a non-oncology indication during the study period
- Patient is aged 18 years or older
- Patient provides informed consent for medical record abstraction and/or survey participation
- Patient participating in the survey can read and understand English, Spanish, Italian, French, or German, according to the country

No Exclusion criteria will apply for medical record abstraction participation although patients who meet any of the following criteria will be excluded from the survey participation:

- Patient has previously already completed the MabThera survey
- Patient has participated in the past 12 months in a clinical trial in which MabThera was one of the treatments being evaluated

Variables

Medical record data:

- Patient demographics
- Indication for which MabThera has been prescribed
- Disease severity
- Treatment history

Patient questionnaire data:

- Patient demographics
- Patient awareness of potential risk factors
- Receipt and reading of the PAC

- Additional safety-related materials

Data Sources

Patient medical records; self-administered patient questionnaire.

Study Size

Based on the results of a feasibility evaluation, it is estimated that 1,000-1,500 medical records of patients receiving MabThera will be abstracted during the study period and that 500-700 patients will complete the questionnaire at participating infusion centres.

Data Analysis

Analysis of MabThera off-label use and evaluation of PAC knowledge and utilisation will be descriptive in nature and will entail the tabular display of summary statistics and the frequency distribution of item responses. A detailed analysis plan describing methods of analysis and presentation, as well as table shells, will be developed prior to starting analysis of data. All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS Institute Inc., Cary, North Carolina, USA).

Milestones

Milestone	Planned Date
Protocol approval by an IRB/EC	Q3 2015
Start of data collection	Q4 2015
End of data collection	Q3 2016
Registration in the ENCePP EU PAS register	Q3 2015
Final report of study results	Q2 2017

4. PROTOCOL AMENDMENTS AND UPDATES

Protocol version 1.0: 27 July 2012
Protocol version 2.0: 24 June 2014
Protocol version 3.0: 8 September 2015
Protocol amendments/updates so far: see table below

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
2.0	24 June 2014	Background, on-label use definition, off-label use definition	Added information on addition to the Summary of Product Characteristics (SPC) of the indication for severe, active granulomatosis with polyangiitis (Wegener's) (GPA) or microscopic polyangiitis (MPA). Likewise, added to diseases defining on-label use and deleted from the list of diseases defining off-label use.	To reflect up-to-date approved indications
2.0	24 June 2014	Feasibility assessment, analysis and interpretation, strengths and limitations	The supplementary analysis of off-label use to be performed using existing registry data is no longer included as part of the study. References in the text to additional analysis of off-label use using registries data have been deleted.	The marketing authorisation holder has already completed activities, and others are ongoing, outside the scope of this study.

2.0	24 June 2014	Study population, patient eligibility for medical record abstraction, patient eligibility for survey participation, medical record abstraction, informed consent	The period of recruitment and implementation of the medical record abstraction component will be extended in France and Italy. The eligibility criterion of patient informed consent has been added as inclusion criteria for study patients in France and Italy. A specific process in France and Italy for obtaining patient informed consent in France and Italy to abstract their medical records is added to the text.	New local regulations in France and Italy require patient informed consent procedures for medical record abstraction.
2.0	24 June 2014	Patient eligibility for survey participation, medical record abstraction, strengths and limitations	A reference has been added to the plan for medical record abstraction recruitment logs in France and Italy. The text describing the use of recruiting log data to compare characteristics of study participants and non-participants has been changed to reflect that linking of survey and medical record	Linkage of data would require patient informed consent process.

			abstraction data will not take place during the study. References in the text to the use of linkage of medical record abstraction and survey data to compare characteristics of study participants and non-participants have been deleted.	
3.0	8 September 2015	Synopsis (Section 3) and Population (Section 8.2)	Patient eligibility criteria have been amended and now include an exclusion criteria section that only applies to participants who take part in the survey. The inclusion criteria now includes the following criterion: patient provides informed consent for medical record abstraction and/or survey participation.	Distinction between inclusion and exclusion criteria enhances clarity, and now the text reflects the updated consent requirements for patients i.e. patients in all countries will provide informed consent to participate in either/both components of the study.
3.0	8 September 2015	Overview of Study Design (Section 8.1.1)	Study design clarified to reflect that retrospective chart review of patient medical records will be performed within a 12-month period prior to the index date (start date of medical record	This study design will ensure that data collected are fully reflective of real-world use of MabThera and not influenced by study awareness.

			abstraction). The patient survey will be performed after the index start date.	
3.0	8 September 2015	Informed Consent (Section 9.2)	Informed consent is now required for either/both medical record abstraction and survey participation, in all study countries.	To reflect latest ethical requirements.
3.0	8 September 2015	Data Management - Electronic Case Report Forms (Section 8.7.2)	Text has been amended to indicate that both medical record data and patient questionnaire data will be abstracted into eCRF.	To clarify data management.

5. MILESTONES

Milestone	Planned Date
Protocol approval by an IRB/EC	Q3 2015
Start of data collection	Q4 2015
End of data collection	Q3 2016
Registration in the ENCePP EU PAS register	Q3 2015
Final report of study results	Q2 2017

6. RATIONALE AND BACKGROUND

6.1 RHEUMATOID ARTHRITIS, GRANULAMATOSIS WITH POLYANGIITIS, AND MICROSCOPIC POLYANGIITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation of the membrane lining the joints (the synovium) (Klarenbeek et al. 2010). The inflamed synovium causes a loss of joint shape, function, and alignment that can eventually lead to complete destruction of the involved joints. Patients with RA have pain, redness, swelling, stiffness, and restricted movement around the joints of the hands, feet, elbows, knees, and neck that lead to loss of function and deformity. Additional common manifestations of RA include fatigue, anaemia, and osteoporosis. Extra-articular manifestations of RA may affect major organ systems, and along with complications of long-term treatment, can lead to a decreased life expectancy.

Approximately 2.8 million Europeans are affected by RA (Alamanos et al. 2006), and more than 20 million people are affected worldwide (Business Wire, 2004). The prevalence of RA is higher in women than in men, and estimates of the prevalence from European studies range from 1 to 6 cases per 1,000 men and 3 to 12 cases per 1,000 women (European Commission, 2010). Southern European countries have lower median incidence and prevalence rates than northern European countries (Alamanos et al. 2006).

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are rare small-vessel vasculitides that are characterized by the presence of circulating anti-neutrophil cytoplasmic autoantibodies (ANCAs) in 80–94% of affected patients (Finkielman et al. 2007; Guillevin et al. 1999). The prevalence of ANCA-associated vasculitis (AAV) has increased in recent years, in part due to increased recognition of these complex diseases. AAVs have an annual incidence of 20 per million population (Ntatsaki et al. 2010). GPA and MPA are severe, progressive diseases that, left untreated, can lead to death from multisystem organ failure. Disease recurrence and drug-related toxicity continue to produce significant morbidity and mortality, and remain the main challenges in patient management (Hoffman et al. 1992).

6.2 MABTHERA

Rituximab (MabThera®) is a genetically engineered chimeric murine/human monoclonal antibody, which binds specifically to CD20, a B-lymphocyte differentiation antigen on pre-B and mature B-lymphocytes. In June 2006, the United States (US) Food and Drug Administration had approved MabThera for RA (Food and Drug Administration, 2006). In June 2006, the European Medicines Agency (EMA) approved the use of rituximab for the same indication. The RA indication was updated by Variation EMEA/H/C/165/II/65 (EMA, 2010). The current European Union (EU) approved label authorises MabThera in combination with methotrexate for the treatment of adult patients with severe, active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies.

In March 2013, the EMA approved a new non–oncology-related indication, allowing the use of MabThera in combination with glucocorticoids for the induction of remission in adult patients with severe, active GPA (Wegener's) and MPA (EMA, 2013a). Rituximab is also approved for several oncology conditions, but these indications are not the focus of this study.

This protocol addresses the 2 EU follow-up measures (FUMs) following approval of Variation EMEA/H/C/165/II/65 for MabThera use in RA.

1. FUM no. 68 (Clinical): Drug Utilisation Study to Assess Off-Label Use

There is concern regarding off-label use of MabThera, in particular that rheumatologists and other physicians may prescribe MabThera for systemic lupus erythematosus (SLE) and lupus nephritis (LN). The EMA Committee for Medicinal Products for Human Use (CHMP) FUM (Clinical) No. 68 from Procedure No. EMEA/H/C/165/II/65 states, *'Given the extensive off-label potential of MabThera, the MAH [Marketing Authorisation Holder] should submit a European drug utilisation study protocol to the CHMP'.*

2. FUM No, 71.1 (Pharmacovigilance): Evaluation of Receipt, Use, and Impact of the Patient Alert Card (PAC) on Infections, Including Progressive Multi-focal Leukoencephalopathy (PML)

As with other immunomodulatory therapies, MabThera use may carry a risk of developing progressive multi-focal leukoencephalopathy (PML). PML is a rare but serious and potentially fatal viral disease characterised by progressive damage of the white matter at multiple locations in the brain. Roche currently provides physicians with PACs to distribute to non-oncology patients to inform them of this potential risk, of risk of infections in general, and of signs and symptoms that should prompt them to seek medical care. In addition, alert cards are supplied in MabThera cartons, attached to the patient information leaflet (PIL).

The PAC text is identical in both the locally distributed PACs and the in-carton PACs, although the appearance of the 2 cards may differ in certain EU Member States, depending on the layout of the locally distributed PAC. It should be noted that the format of the in-carton PAC may be subject to change during the set-up period for this study. EMA will be notified of any change made. No change to the PAC text is foreseen. The PAC version distributed to patients in this study is dependent on distribution by Roche of the non-oncology PAC to centres prior to the study start date. The text for the non-oncology PAC is in Appendix 1. The EMA CHMP FUM (Pharmacovigilance) No. 71.1 in Procedure No. EMEA/H/C/165/II/65 requests:

"... submission of a proposal to conduct patient and physician user acceptance testing of the PML AC [alert card] and an assessment of the proportion of patients who receive the

card, who use it, who use it correctly and whose outcome is improved by the card. This assessment should include reporting milestones."

The User Acceptance Testing (UAT) part of this FUM has already been addressed. The results submitted to EMA in July 2012 and, following EMA endorsement, the resulting text changes were updated into the Product Information Annex IIIA during the Variation EMEA/H/C/65/II/89 approved in April 2014. This study protocol is designed to assess the PAC for its current distribution to patients with RA, GPA and MPA.

6.3 FEASIBILITY ASSESSMENT

[redacted] drafted a previous version of this protocol ([redacted], which has been reviewed by the EMA CHMP. The previous protocol included a feasibility component to guide the final design of the study. An [redacted] study team including researchers in epidemiology, survey research, instrument development, and biostatistics conducted a feasibility evaluation study in 30 infusion centres located in the 5 European countries of interest to assess the centres' interest in participating in this study, clarify local requirements for study approval, and refine the protocol regarding sample size expectations and study procedures ([redacted] The selection of participating centres for the feasibility component was not intended to be representative in each country but merely to guide the design of this study.

The specific goals of the feasibility evaluation were as follows:

- To assess the interest of infusion centres in participating in a research study.
- To obtain estimates of the number of patients treated with MabThera.
- To assess whether the centres meet requirements for both patient enrolment and patient medical record abstraction.
- To evaluate the characteristics of infusion centres.
- To obtain input from the infusion centres about patient flow, centre processes, feasibility of the study procedures, and how to minimise impact on day-to-day activities.
- To assess whether infusion centre records provide the patient disease information needed for the medical record abstraction.
- To ascertain the current counselling practices of health care providers (HCPs) at the centre to evaluate whether the patient questionnaire can be completed prior to the provision of any new counselling regarding the MabThera PAC content.
- To collect information about EC requirements for the medical record abstraction and patient survey.
- To evaluate the optimal time window for medical record abstraction, the target number of patients per centre to be recruited into the survey, and survey enrolment periods.

The feasibility component also evaluated the potential for using existing registries of biological agents in the 5 European countries to capture off-label use of MabThera. The goal was to evaluate registries of biological therapies as a source of supportive data in

addition to the drug utilisation study (DUS). Registry data could complement the study design included in the current draft of the infusion centre study protocol, assuming that the registries capture MabThera use for both RA and other autoimmune diseases, their data can be accessed for research purposes, and they collect a minimum set of variables necessary to classify use as on- or off-label. This revised version of the protocol removes the supplementary analysis of off-label use using those registries. This change has been implemented because the marketing authorisation holder has submitted assessments of rituximab off-label usage in autoimmune indications from a health care claims database and cumulative post-authorisation exposure in the EU MabThera Risk Management Plan version 13 (Section SV.4, submitted in October 2014) and periodic benefit-risk evaluation reports (PBRER) 1058003 (submitted January 2015 covering the period from 18 November 2012 to 17 November 2014, Sections 5.2.1.2, 5.2.1.3, 5.2.2.3, 5.2.3.1). Should further information be required, the marketing authorisation holder may conduct additional investigations using biologic registries and submit these in future PBRERs.

The feasibility evaluation ([redacted] was completed in April 2012 and was submitted to EMA, as was the final version (V1) of this protocol, which incorporates the results of the feasibility evaluation and its recommendations. The outcome of the EMA review of V1 final was described in EMA/411582/2014.

6.4 STUDY RATIONALE

Administration of MabThera takes place in special settings, primarily infusion centres. For study purposes, we define an infusion centre as a location—doctor's office, clinic, hospital, one or more sites within a health care building—where infusions of MabThera might take place. The above FUMs require close coordination of activities to avoid duplication of effort and minimise the administrative burden on participating infusion centres. Therefore, this protocol plans for a single study to address both FUMs, with the exception of the UAT, which has previously been evaluated and shown to be acceptable.

The study will be conducted in infusion centres to (1) characterise the indications for which MabThera is being used and (2) evaluate the use of the PAC in patients receiving the medication for non-oncology conditions at infusion centres.

The feasibility assessment conducted by [redacted] identified some variability in the distribution of the PAC across centres in the 5 European countries and indicated that some centres are providing educational information on safe use of MabThera other than the PAC. The small number of centres (N = 30) participating in the feasibility study was not selected to be representative of all treatment facilities in each country. Therefore, this study will determine via the patient questionnaire whether additional information is provided to the patient. Additional input regarding these materials can arise in communications with study sites during the course of the study.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 OBJECTIVES

- Specific aim 1: To quantify and characterise off-label use through an evaluation of the disease and characteristics of patients treated with MabThera for non-oncology conditions.
- Specific aim 2: To evaluate the extent to which patients receive and read the PAC, knowledge of the PAC content among patients receiving MabThera for non-oncology conditions at infusion centres, and whether distribution of the PAC may influence patient actions.

8. RESEARCH METHODS

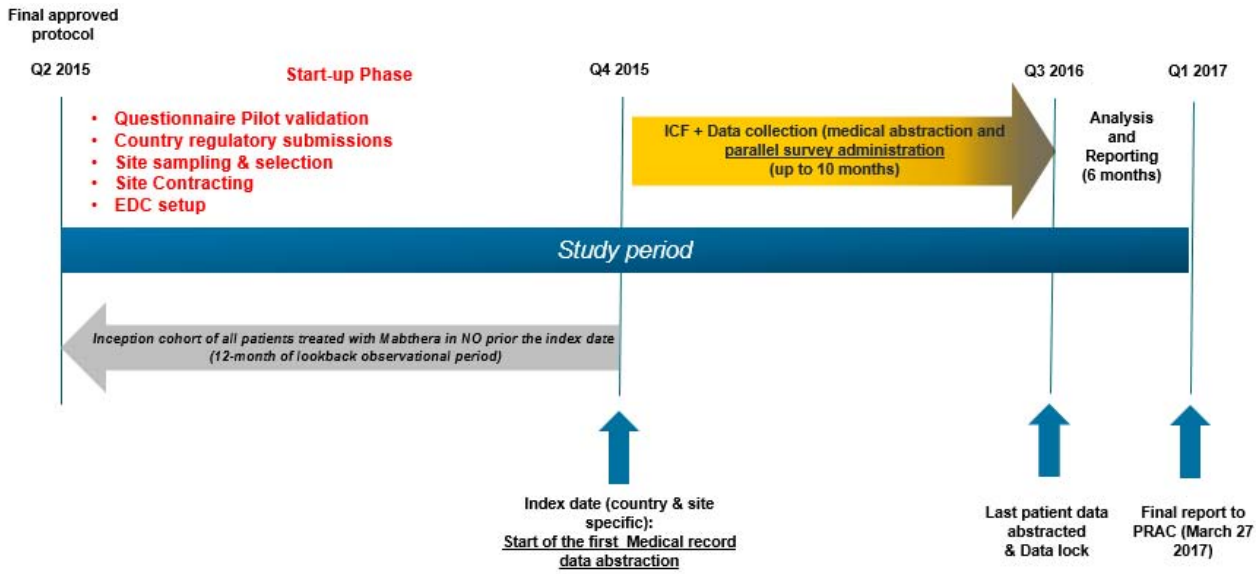
8.1 STUDY DESIGN

8.1.1 Overview of Study Design

This DUS is a multinational, multicentre study involving the retrospective chart review of MabThera users' medical records in non-oncology indications (Figure 1). Nested in the study, a cross-sectional survey of patients receiving MabThera will be performed starting from the date of the first medical record data abstraction (Figure 1).

A geographically dispersed and diverse set of infusion centres in the United Kingdom (UK), Germany, France, Italy, and Spain will be recruited to participate in the study. At each participating centre, de-identified data will be retrospectively abstracted from medical records on treatment indication (RA, SLE/LN, other) and selected patient and disease characteristics for all patients receiving MabThera for a non-oncology condition, during a 10-month data collection period. The survey will also be conducted during the same 10-month period, and will prospectively collect information on patient characteristics, and will include questions about patient knowledge on the risk of infections including PML, patient receipt and review of the PAC, and any actions the patient has taken as a result of receiving the PAC.

Figure 1: DUS and PAC Survey Overview



ICF: Informed Consent Form; NO: non-oncology conditions; PRAC: Pharmacovigilance Risk Assessment Committee; Q: quarter.

Drug Utilisation Study

The index date (start date of medical record abstraction for the first patient) for the study will be selected for each country and correspond to the date when a site becomes aware of the study objectives. After all approvals from national EC and regulatory authorities have been granted, all medical record data will be retrospectively reviewed until the index date; this approach will ensure the data collected are fully reflective of real world administration of MabThera and not influenced by study awareness. The retrospective review of medical records will occur within a 12-month “look-back” period prior the selected index date (i.e., the eligibility period). The observation period for consenting patients corresponds to the interval between the first and last infusion dates of MabThera, if treatment is discontinued before the index date. If the patient is still on MabThera at the index date, then the observation period is the interval between the first infusion date and index date. Furthermore, if a patient stops and re-starts MabThera during the observation period, all repeated treatment intervals will be captured.

Patient Alert Card survey

The PAC survey will be conducted after the index data and concomitantly with the medical record abstraction process. The PAC survey will be completed once by each patient after informed consent has been provided.

Duration of the study

The planned duration of the study (i.e., both medical record and survey data collection) is approximately 16 months after the recruitment of the first patient. This period takes into account 10 months of data collection and a 6 month period between last patient recruited and final study report.

[redacted] will closely monitor inclusion rates. If projected recruitment rates indicate that patient targets may not be achieved in the planned recruitment period, consideration will be given to extending the recruitment period, initiating additional sites within the 5 existing countries, and/or expanding the study into additional EU countries.

8.1.2 Number of Patients Observed in the Study

Based on the results of a feasibility evaluation, it is estimated that 1,000-1,500 medical records (200-300 per country) of patients receiving MabThera will be abstracted and 500-700 patients (approximately 100 per country) will complete the questionnaire at participating infusion centres.

8.1.3 Centres

This study will be conducted at approximately 10-15 centres in approximately 5 countries, in order to recruit the estimated number of patients for medical record abstraction and survey participation, as described in Section 8.1.2. Additional countries and centres may be added or substituted if underperforming.

8.2 POPULATION

Infusion centres that are representative of the non-oncology use of MabThera in the UK, Germany, France, Italy, and Spain will be recruited to participate in the study. Each centre will be expected to retrospectively abstract data from medical records for non-oncology MabThera patients and to enrol an appropriate number of patients who will complete the patient questionnaire component of the study; the target is a total of 100 survey participants per country. The survey participants will be recruited during a 10-month period concomitantly with the medical record abstraction process.

Infusion Centre Eligibility

To participate in the study (DUS and PAC survey), each infusion centre must meet all of the following criteria:

1. Administer MabThera to a least 20 patients who would meet the eligibility criteria in the past 12 months; and

2. Be able to provide a semi-private space for patient recruitment, the consent process, and completion of the patient questionnaire; and

3. Have a staff member available to coordinate study activities.

Patient Eligibility for the study

Patients must meet the following inclusion criteria for study entry:

1. Patient is in the centre to receive an infusion for MabThera for a non-oncology indication during the study period

2. Patient is aged 18 years or older

3. Patient provides informed consent for medical record abstraction and/or survey participation

4. Patient participating in the survey can read and understand English, Spanish, Italian, French, or German, according to the country.

No Exclusion criteria will apply for medical record abstraction participation although patients who meet any of the following criteria will be excluded from the survey participation:

1. Patient has previously already completed the MabThera survey

2. Patient has participated in the past 12 months in a clinical trial in which MabThera was one of the treatments being evaluated.

Study coordinators at infusion centres will be responsible for identifying and recruiting patients as they are scheduled or come to the site for their MabThera infusion. For the patient survey, patients meeting the eligibility criteria who visit the participating infusion centres during the data collection period will be given the opportunity to participate in the patient survey until the infusion centre recruitment goal is met. Sites will keep a simple log with information on the number of patients approached about the survey and reasons for refusal for those who refuse to participate. Sites will also keep a log of all eligible patients from whom consent is requested whether they participate or not to the study, and reason for refusal for those who refuse to give consent. The logs will also include minimal information such as age, sex, and clinical indication for MabThera depending on country data privacy policies. The logs will not include any patient identifier and will be kept separate for the survey and medical record abstraction components.

Infusion Centre Recruitment

Approval from each relevant IRB/independent EC will be obtained prior to study start in each country and documented in a letter to the centre specifying the date on which the IRB/EC met and granted approval. Centres will be contacted to confirm their eligibility, assess their interest in participating in the study, and assess the feasibility of implementing data collection.

Approximately 10-15 infusion centres in each country will be recruited to participate in this study. As part of the feasibility evaluation, Roche provided lists of infusion centres for potential participation. If the target number of participating infusion centres is not achieved, national study coordinators may be required to update and supplement the site lists. The final infusion centres recruited are not intended to reflect a random sample of all infusion centres for biologic treatments in the target countries but rather a generally representative sample of centres administering MabThera. Several factors will be evaluated to ensure a diverse representation of sites, including geographic location, infusion centre type (e.g., outpatient clinic or hospital-based infusion centre), medical specialty of physicians treating the patients (e.g., rheumatology vs. internal medicine), research experience (e.g., academic centre vs. community health centre), and casuistic purpose (e.g., centres that treat mainly off-labels patients vs. centres that treat mainly patients with RA). In addition, during site recruitment, data on site characteristics that may influence patients and their knowledge of the PAC will be collected (e.g., whether or not the PAC is being distributed at the infusion centre and counselling practices at the centre).

Following study start, information will be collected about the distribution or not of the MabThera PAC within each centre. For those infusion centres that are unable to participate or are not interested in participating, reasons for their refusal to participate in the study will be documented as part of the recruitment process.

Patient Selection and Recruitment

As patients come in for their MabThera infusions or shortly before the visit, the study coordinator at each site will confirm whether selected patients meet eligibility criteria for the study as specified in the study protocol. According to the eligibility criteria, a patient may be invited to participate in either the medical record abstraction component of the study, or both the medical record abstraction and survey components of the study; patients eligible for the latter may choose to participate in either or both components of the study. The study coordinator will present eligible patients with information about the study using a patient recruitment card and instructions. The study coordinator will invite interested and eligible patients to participate in the study, describe the nature of their participation, and obtain informed consent from patients willing to participate.

It is estimated that 20-30 patients will participate to the medical record abstraction in order to yield between 1000-1500 medical records in the DUS. For the patient survey, it is estimated that each infusion centre will recruit 10-14 patients, with the goal of 500-700 patients (approximately 100 patients per country) completing the survey. The estimates are based upon the anticipated number of eligible patients for participation identified in the feasibility evaluation and an adequate level of precision for the estimates (see Section 8.6). This final number of study participants depends on the actual number of patients filling a prescription within the established time frame and on actual response rates for the study.

For centres with a large volume of patients that will most likely reach the maximum number of patients, a patient sampling methodology will be considered to select the specific patients that will participate in the study. The sampling methodology will be designed with the goal of maximising the probability that each patient treated with MabThera will have an equal opportunity to be selected. In some sites, it is likely that all treated patients will be selected. The sampling approach for those sites with larger numbers of patients will be customised for the site (based on patient volume) and will be devised to achieve an efficient method of obtaining a representative patient sample in centres with varying patient administration systems. The sites will be asked to recruit patients for the study when the patients are at the physician practice for a scheduled visit.

Patient Alert Card Distribution

The PAC will be distributed to all patients receiving MabThera for non-oncology indications, as stated on the card.

8.3 VARIABLES

Medical Record Data

The site will abstract information from the medical record for each of the DUS consenting patients and will enter the abstracted information in an electronic case report form (eCRF):

- Study ID (identification), age, sex
- Condition for which MabThera has been prescribed (via checklist):

  - RA
  - Ankylosing spondylitis
  - Psoriatic arthritis
  - Undifferentiated spondyloarthritis
  - Juvenile idiopathic arthritis
  - SLE
  - Systemic vasculitis
  - Inflammatory myopathies
  - Behçet disease
  - Sjögren syndrome
  - Nephrotic syndrome
  - Glomerulonephritis
  - Multiple sclerosis/neuromyelitis optica
  - Pemphigus vulgaris
  - Polydermatomyositis
  - Mixed connective tissue disease
  - Wegener's GPA/ MPA
  - Eosinophilic GPA
  - Other (specify)
- Reason for MabThera prescription:
  - Failure of previous treatment
  - Adverse events (AEs) under previous treatment
  - Compassionate use
- Date of first diagnosis of the condition
- For patients with RA, severity of RA as measured with the DAS28 (28-joint Disease Activity Score). To calculate the DAS28, the following items will have to be abstracted from the medical record:
  - C-reactive protein level
  - Erythrocyte sedimentation rate
  - Number of tender joints
  - Number of swollen joints
  - Global assessment of patient's general health on the visual analogue scale (VAS) (0–100)
  - Presence of extra-articular involvement
- MabThera dosage for the most recent infusion and number of MabThera infusions in the past 2 years
- Other current and previous anti-inflammatory medication including biological agents other than MabThera
  - Methotrexate (key variable for on- or off-label classification of MabThera use)

- Immunosuppressives: prednisolone, glucocorticoid bolus therapy, methylprednisolone, methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, intravenous immunoglobulin, plasmapheresis, other immunosuppressives (specify)
- Non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxigenase (COX)-2 inhibitors
- Biological agents:
    - TNF-alpha inhibitors (key variable for on- or off-label classification of MabThera use): etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, ocrelizumab
    - Interleukin inhibitors: tocilizumab, anakinra
    - Abatacept
    - Janus kinase (JAK) inhibitor: tofacitinib
    - Other biological agents (specify)

A “data not available” response will be available where appropriate for those record abstraction items for which data may be missing from patient records. This type of response will help reduce missing data and will document the overall gaps in record keeping.

A brief pilot test of the translated version of the abstraction form will be conducted in each country, and the abstraction form in one or more countries may be adjusted based on the results of this pilot.

A draft version of the medical record abstraction form is included with this document (Appendix 1).

Off-Label Use Definition

The definition of off-label use of MabThera will be based on the use for a non-oncology disease or medical condition other than RA and GPA/MPA covered by MabThera SPC.

In absence of labelled indications, potential off-label use could include, but is not limited to, the following conditions:

- Ankylosing spondylitis
- Psoriatic arthritis
- Undifferentiated spondyloarthritis
- Juvenile idiopathic arthritis
- SLE
- Systemic vasculitis

- Eosinophilic GPA
- Inflammatory myopathies
- Behçet disease
- Sjögren syndrome
- Nephrotic syndrome
- Glomerulonephritis
- Multiple sclerosis/neuromyelitis optica
- Pemphigus vulgaris
- Polydermatomyositis
- Mixed connective tissue disease

Patient Survey data

The patient questionnaire has been developed following standard survey methodological principles and will be cognitively tested with patients in each of the target countries. Modifications will be made to the questionnaire based on the results of testing, and some variations to the questionnaire are anticipated based on country-specific requirements.

The questionnaire will include an introductory section with questions to confirm eligibility. The majority of the questionnaire items will be closed ended, ensuring that the resulting data are easy to analyse and interpret. Closed-ended questions are generally more efficient than open-ended questions (or open-ended text fields) and more conducive to summarisation and statistical analyses.

The questionnaire will collect the following information (please refer to Appendix 1 for the draft questionnaire):

- Demographics (e.g., age, sex, ethnicity)
- Patient previous history of PML or other serious infectious diseases
- Whether the patient has received a previous treatment with MabThera, if so, number of prior infusions during the last 12 months
- Patient understanding or awareness of the following:
  - Known and potential risks of infection associated with MabThera including the risk of PML
  - Symptoms of infection, including PML, and what actions patients should take
  - Who should not be treated with MabThera
  - What medication information patients should tell their doctor
  - Any other counselling received for the infections covered in the PAC
- Patient receipt and reading of the PAC

  - How often has the patient received the PAC?
  - Does the patient currently have a PAC?
- Has the patient received a package leaflet (i.e., PIL)? Does the patient currently have one?
- Patient receipt of additional safety-related information about MabThera
- Patient actions and any changes in behaviour triggered by the PAC (for example, if the patient consulted another physician following the first MabThera treatment or if the patient showed the card to a doctor other than one associated with the MabThera treatment).

Other descriptive information about the patient will be collected to enable stratification of results and facilitate comparison of study participants with the total sample of patients receiving MabThera at participating sites.

Patient Questionnaire Administration

The questionnaire will be completed after the patient arrives at the centre and before the start of the infusion to make sure the questionnaire is completed before any additional counselling regarding the content of the PAC is provided by the site. According to the responses to the feasibility evaluation, all sites considered this to be feasible considering their infusion and counselling practices.

The patient questionnaire will be self-administered (closed-ended questions with predefined answers) on a hard-copy form at the site. The questionnaire will be translated into each local language (English, French, German, Italian, and Spanish) and pretested. Although there are a number of advantages to using an electronic format for questionnaire administration, based on the results of the feasibility evaluation, paper data collection forms are the most efficient approach for this study given the centres' preferences, infrastructure, and the number of patients per centre. Written informed consent will be obtained from each patient prior to completion of this questionnaire.

Patients will be asked to complete the questionnaire in a private setting within the infusion centre. Sites will provide patients with appropriate privacy so there is no influence by the physician (or patient perception thereof) in this process. Patients will place their completed questionnaires in an envelope and give the sealed envelope to a study coordinator or designee. Although participating physicians will be informed of the purpose of the study, they will be counselled not to alter routine practice and patient education so as not to influence the study results. Physicians will be advised that the ultimate goal of the study is to evaluate the use of the PAC.

Pretesting of the Patient Questionnaire

To evaluate the patient questionnaires before fielding the study, cognitive pretesting with physicians and patients will be conducted in each country and in each local language. Cognitive pre-test interviewing is a well-established qualitative research methodology

used to identify problems with survey questions and response options (Groves, 2009). Specifically, trained interviewers will ask pre-test participants to complete the questionnaire while thinking aloud or describing their thought processes as they answer the questionnaire items. Pre-test interviewers will use an interview guide that includes probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaires. The pre-test interviews will be designed to help identify problems with survey questions, wording, response choices, etc., and ensure that respondents understand the questions. The pre-test interview data will be used to optimise the language used in the questionnaire prior to implementing the patient surveys.

8.4 PATIENT, STUDY, AND SITE DISCONTINUATION

8.4.1 Withdrawal from Study

Patients may withdraw consent and discontinue participation from the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study, any known reason for withdrawal should be documented in the eCRF. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

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

8.4.2 Study and Site Discontinuation

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

- Patient enrolment is unsatisfactory
- Other reasons

The CRO will notify the physician if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The CRO may replace any site as needed. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

8.5 STUDY SIZE

The results from the feasibility evaluation showed that some large centres recruited more than 100 patients. To avoid large centres being overrepresented in the study population, it is planned to put a cap of 30 patients as the maximum number of patients that a single centre can recruit for either the medical record abstraction component or survey component of the study. To compensate for the 30-patient cap, the recommendation in the feasibility evaluation was to recruit 10-15 infusion centres per country in order to accomplish the recruitment targets for both components of the study.

Medical Record Abstraction Component Study Size

From the estimates obtained in the feasibility evaluation, the Sponsor projects that 20-30 patients per infusion centre will be recruited for the medical record abstraction component of the study, yielding a total of between 1,000 and 1,500 medical records collected during the 10-month period. Because the sample size for the medical record abstraction component of the study will be larger than that for the survey component, there will be greater precision around the estimates of MabThera use by whether the disease indication (RA, SLE/LN, other) represents on-label or off-label use. For example, with a sample of 1,500 patients, if 75% those abstracted are identified as on-label use, then the 2-sided 95% confidence interval (CI) will be 72.8% to 77.2%.

Survey Component Study Size

Considering the estimates of the volume of patients available that were provided by the feasibility evaluation, during a 10-month period, a maximum of 720 patients could be recruited for the survey component in the 5 countries, assuming a mean (median) of 23-24 (13-18) patients per centre and 30 participating centres. However, the mean is based on some large centres recruiting more than 100 patients. To avoid large centres being overrepresented in the study population, it is planned to put a cap of 30 patients as the maximum number of patients that a single centre can recruit. The final study size has been set at 500 completed surveys across all countries, with an estimated 10-14 patients recruited per infusion centre for the survey; this will allow reasonable precision around estimates of patient knowledge and understanding of the PAC at the study level. Since it is planned to recruit up to 10-14 patients per infusion centre for the survey, the responses from patients within the infusion centre may be correlated. Assuming no correlation and the percentage of correct responses to a question (or the percentage with off-label use) is 75%, then for a sample of size 500, the 2-sided 95 CI will be 71.2% to 78.8%; whereas the corresponding CI will be 68.3% to 81.7% if there are on average 8 patients per infusion centre with an intra-class correlation of 0.3. A correct response rate of 50% yields the widest possible CI and thus the least precision; the farther the percentage is from 50%, the greater the precision. Table 1 shows 95% confidence limits assuming various combinations of sample size, percentage with correct response, and intra-class correlation coefficients.

Table 1 Confidence Limits for Various Combinations of Sample Size and Correct Response Percentage

Patient Sample Size	Intra-class Correlation Coefficient[a]	Correct Response[b] (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	0	25	16.5	33.5
100	0	50	40.2	59.8
100	0	75	66.5	83.5
100	0	90	84.1	95.9
100	0.15	25	12.8	37.2
100	0.15	50	36.0	64.0
100	0.15	75	62.8	87.2
100	0.15	90	81.6	98.4
100	0.3	25	10.1	39.9
100	0.3	50	32.7	67.3
100	0.3	75	60.1	89.9
100	0.3	90	79.6	100.0
500	0	25	21.2	28.8
500	0	50	45.6	54.4
500	0	75	71.2	78.8
500	0	90	87.4	92.6
500	0.15	25	19.6	30.4
500	0.15	50	43.7	56.3
500	0.15	75	69.6	80.4
500	0.15	90	86.2	93.8
500	0.3	25	18.3	31.7
500	0.3	50	42.3	57.7
500	0.3	75	68.3	81.7
500	0.3	90	85.4	94.6
1500	0	25	22.8	27.2
1500	0	50	47.5	52.5
1500	0	75	72.8	77.2
1500	0	90	88.5	91.5
1500	0.15	25	21.9	28.1

Patient Sample Size	Intra-class Correlation Coefficient[a]	Correct Response[b] (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
1500	0.15	50	46.4	53.6
1500	0.15	75	71.9	78.1
1500	0.15	90	87.8	92.2
1500	0.3	25	21.1	28.9
1500	0.3	50	45.5	54.5
1500	0.3	75	71.1	78.9
1500	0.3	90	87.3	92.7

Note: Table calculations assume an average of 8 patients from each practice (cluster).
[a] With an average cluster size of 8 patients, correlation coefficients of 0.15 and 0.30 correspond with design effects of 2.05 and 3.1, respectively.
[b] The percentage in this column does not need to represent only the percentage of correct responses; it can represent any percentage, for example percentage of abstractions that were identified as off-label use or percentage of abstractions that had systemic lupus erythematosus (SLE).
Calculations performed using SISA software, prevalence module. Uitenbroek DG. Binomial. SISA. 1997. Available at: http://www.quantitativeskills.com/sisa/calculations/preval.htm. Accessed 11 June 2012.

8.6 DATA ANALYSIS

Analysis of MabThera off-label use and evaluation of PAC knowledge and utilisation will be descriptive in nature and will entail the tabular display of summary statistics and the frequency distribution of item responses.

A detailed analysis plan describing methods of analysis and presentation, as well as table shells, will be developed prior to starting analysis of data. In addition to describing the analysis of off-label use, for the questionnaire data, the analysis plan will describe any planned comparisons of participants and non-participants. The analysis plan will also describe the following:

- Analysis of subgroups
- Methods for handling missing data
- Level of statistical precision

All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS Institute Inc., Cary, North Carolina, USA). Programs, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

The analysis of off-label use will be descriptive and will present MabThera utilisation by indication (RA, SLE/LN, other). Results will be evaluated by site characteristics, including country and geographic region within country, to ascertain any patterns of prescribing by specific indication. The main analysis will be to estimate (with 95% CIs)

the proportion of off-label use among users of MabThera during the entire study period in the 5 European countries of interest. The proportion of each of the most common off-label use indications will be described among the entire off-label use group. In addition, an estimate of off-label usage will be determined amongst prevalent (i.e., repeat infusions) and incident (i.e., patients attending for their first MabThera infusion) patients to the extent that incident use can be accurately determined. Characteristics of patients meeting the definitions for both strict and broad on-label use will also be evaluated. The dosage of MabThera used by infusion will also be estimated in the on- and off-label groups.

To evaluate the differences between subgroups by indication, with 95% CIs, proportions for categorical variables and means for continuous variables will be estimated within each subgroup. If appropriate, medians will be used instead of means when the variables of interest do not assume a normal distribution.

It is anticipated that the analyses of the PAC knowledge and utilisation will focus on summarising the results of the questionnaire data (e.g., percentage confirming receipt of the PAC, percentage demonstrating correct knowledge of the PAC, percentage correctly identifying the appropriate actions they should take under different scenarios). Tables will include frequencies and percentages for categorical variables and descriptive statistics (e.g., median, means and standard deviations or 95% CIs) for continuous variables (e.g., scales or composite variables created from summation of several items). Results will be grouped by key variables that could be related to patient awareness, such as recency of the first treatment with MabThera and whether the participant reported reading the PAC. Results will also be grouped by the clinical condition for which the patient received MabThera (RA, other autoimmune diseases) in a subset of patients who provided consent for both the questionnaire and medical record abstraction (since information on clinical condition is only provided by the latter). Open-ended responses (if any) will be listed and categorised as appropriate, but will not be analysed quantitatively. In the study report, results will be provided in aggregate form only.

The number of patients who were invited to participate in the survey but declined will be tracked, and the analyses will describe selected key general characteristics of non-respondents (e.g., reason for refusal). Based on the information available on the recruiting logs (i.e., age, sex, and clinical indication), the analysis will compare characteristics of survey respondents with characteristics of patients who refused to participate in the survey. Also, characteristics of the infusion centres participating in the study will be compared with characteristics of the overall set of infusion centres from the final list of infusion centre used, based on the information available for all centres on the list, e.g., geographic location, centre type (clinic, hospital), and physician specialty (internal medicine, rheumatology).

Exploratory analyses will be conducted to examine low awareness of key safety elements based on patients who read the PAC vs. those who did not; patients who were

infused in-office vs. infused at independent infusion centres; and incident MabThera patients (i.e. patients receiving their first course of MabThera) compared with patients who had received 2 or more courses.

Results of both components of the study will be examined to assess any implications for the MabThera communication and education activities, including the PAC, and for physicians and patients on the appropriate use of MabThera. If any findings suggest extensive off-label use or suboptimal patient knowledge of the PAC or patient-reported practice patterns, root cause analyses may be explored, as appropriate (e.g., additional exploratory analyses, follow-up discussions), with infusion centres that participated in the survey. Follow-up contact with infusion centres might examine differences in practices by site type. Results of the study and root cause analyses can be used as input into potential modifications to the MabThera communication and education activities, including the PAC programme.

8.7 DATA MANAGEMENT

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. The eCRF will be used for both medical record data abstraction and questionnaire completion by patients. The forms will be sent to a data processing centre. Once the forms are received, they will be single-entered into the database. The CRO will follow standard procedures for ensuring accurate data entry, including performing an audit (i.e., a comparison of data on paper to data in the database) of a subset of data entered. Edit and logic checks will be conducted and queries resolved to ensure high-quality data. However, for the patient questionnaire, due to the self-reported nature of the data, some such resolutions may not be possible.

Data managers will conduct UAT of the data entry system and will sign the UAT report before the paper forms are used in the field. Site staff will be trained on data collection forms before the study is fielded. Specialised data managers will approve the data management plan, all annotated data collection forms, data entry system data dictionaries, the data cleaning specifications document, and the testing of summary reports before authorising the data systems to go “live.” Data managers will ensure that the paper data systems are tested and valid and will require that testing documentation, database documentation, and change control documentation be created and maintained.

Once the systems are in the field, data management activities will include programming edit checks in preparation for statistical analysis and merging of datasets if required.

Any paper data files collected in the EU will be maintained within the EU. Only de-identified data with case identification numbers will be transferred to the US for data analysis and generation of the final report. Data analysis and storage of de-identified data sets will be in the US.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control (QC) checks of all programs. Each database custodian will maintain any patient-identifying information securely on site according to internal Standard Operating Procedures (SOPs).

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore electronic files in the event of a hardware or software failure.

8.7.1 Data Quality Assurance

The Sponsor will supply eCRF specifications for this study. The CRO will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via Electronic Data Capture (EDC) using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor standard procedures will be used to handle and process the electronic transfer of these data.

CRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures.

8.7.2 Electronic Case Report Forms

Medical record data will be recorded via eCRF. Patient questionnaires will be self-report, paper-based forms, and data from these forms will be abstracted into eCRF. The source documents will be transcribed by the site on the eCRF. In no case is the eCRF to be considered as source data for this study.

Accurate and reliable data collection will be assured by verification and cross check of the eCRFs against the physician's records and patient questionnaires by the study monitor (source data verification [SDV]). A comprehensive validation check program

utilizing back-end checks in the clinical database will verify the data, discrepancies and queries will be generated accordingly and data clarification from the sites will be requested. Queries will be transferred (e.g., via fax or electronic mail) to the site for resolution by the physician.

8.7.3 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs and Informed Consent Forms (ICFs), must be retained by the physician for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8.8 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

8.8.1 Study Documentation

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

8.8.2 Site Audits and Inspections

Site visits will be conducted by the Sponsor or an authorized representative for audit of study data, patients' medical records, and eCRFs.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Selection bias is a distortion of evidence or data that arises from the method of collecting samples and data, in other words, resulting from the method by which study patients are selected. The selection bias may undermine the external validity (generalizability) of the study data and results. In this study, a selection bias may arise from:

1. The method study sites are selected

2. The method patients at the individual sites are selected.

In order to minimize selection bias, the following site and patient selection methods are used. Ten (10) to 15 infusion centres in the participating European countries, preferably from diverse geographical regions within a country, that have prescribed MabThera to patients with non-oncology conditions during the (country-specific) eligibility period will be chosen (see also Section 8.2). A list of potential sites will be reviewed, and in situations where the number of identified sites is greater than the number required for the study, the selection of sites will be randomized. The process of site selection will be carefully documented.

Possible selection bias occurring at the patient level will be minimized by the following selection methods (see also Section 8.2):

- If a site had administered MabThera during the country-specific observation period to not more than 30 (eligible) patients, all these patients will be included in the study.
- If a site had prescribed MabThera during the (country-specific) observation period to more than 30 (eligible) patients, 30 (eligible) patients will be randomly selected from this site to avoid any potential clustering or period effect.

As is the case with all voluntary surveys, invited patients will self-select into the study, and volunteer bias may lead to an underestimate or overestimate of the level of patient awareness.

9. PROTECTION OF HUMAN SUBJECTS

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including, where applicable, the Declaration of Helsinki. EC approvals will be obtained in accordance with applicable national and local regulations in each country.

9.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study is a post-authorization safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EU *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2013b), and with the 2012 EU pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII section VIII.B.6.3.1. “Progress reports” and VIII.B.6.3.2. “Final study Report” of the *Guideline of Good Pharmacovigilance Practices* (EMA, 2013b).

The study will be conducted under *GPP* (International Society for Pharmacoepidemiology [ISPE], 2007) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2013a). The completed ENCePP *Checklist for Study Protocols* (ENCePP, 2013b) is in Appendix 1.

Approval from the appropriate independent EC will be obtained before starting the study and will be documented in a letter to each centre specifying the date on which the EC met and granted approval.

The study will be registered in the ENCePP EU PAS Register (ENCePP, 2014) before the study implementation commences.

The study will be entered and tracked in the Roche Clinical Trial Management System (CTMS) and follow data collection and AE reporting guidance outlined in the *GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2012).

9.2 INFORMED CONSENT

The Sponsor's approved ICF will be provided to each site in all 5 countries. The ICF will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before EC submission. The final Consent Forms approved by the EC must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in either or both components (medical record abstraction and/or survey participation) of the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

9.3 ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the EC by the CRO or infusion centres' staff and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.

The CRO or infusion centres' staff is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the EC of any protocol amendments.

9.4 CONFIDENTIALITY

The research team will not have access to any participant identifying information. No personal identifying information will be removed from the infusion centres. Only de-identified data will be made available to the research staff and Roche. Thus, any reports that are generated will *not* contain any participant identifiers. Data will be provided to Roche in aggregate only and will not be linked to individual patients or HCPs.

For the survey, sites will maintain a patient log with only the names of patients who completed the study and HCPs involved in the study. Site logs will be maintained at the site and will never be shared with the research team, third parties, or the Sponsor. Additionally, data from the patient survey and abstraction form will *not* be linked to any patient log or any other patient identifying information.

9.5 FINANCIAL DISCLOSURE

Infusion centre investigators will be paid nominal fees to compensate them for the time spent recruiting patients, obtaining patient consent and instructing patients on questionnaire completion, and abstracting medical records. The amount and payment methods will be reviewed and approved by the EC to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

Patients participating in the survey will be paid nominal fees as allowed by local regulations to compensate them for their time in completing the study questionnaires. As with the site compensation, the amount and payment methods will be reviewed and approved by the EC to ensure that payments are commensurate with the time needed to complete the forms, not coercive, and made according to local regulations in each country.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

The medical chart abstraction component of this study is classified as secondary data usage and therefore individual adverse event reporting is not required.

10.1 ADVERSE EVENTS SOLICITED VIA THE PATIENT QUESTIONNAIRE (MABTHERA)

The patient questionnaire component of the study is classified as primary data collection. Therefore, individual adverse event information solicited for MabThera via the Patient Questionnaire must be reported to Roche as the Marketing Authorisation Holder.

The Investigational Site Staff must review these Patient Questionnaires and should complete an Adverse Event Reporting Form if there are any adverse events captured. This should then be reported to Roche within the following timelines:

- Serious Adverse Events (SAEs) - 24 hours of awareness
- Non-Serious Adverse Events - 30 calendar days of awareness

10.2 OTHER ADVERSE EVENTS

Healthcare professionals are reminded to spontaneously report any adverse reactions (for any Roche or non-Roche medicinal product) identified during the course of the study but not captured as part of the patient questionnaire to:

- Roche, if they suspect a causal role of a Roche medicine.

- The relevant marketing authorisation holder, if the suspected medicinal product is a non-Roche medicine.

The final study report will include a full summary of all safety data received from HCPs at site or documented on the Patient Questionnaire. A safety tabulation of AEs and SAEs will be provided for team and safety science review and evaluated by the Roche Safety Science Leader for inclusion in the rituximab PBRER.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The protocol, study status, and report(s) will be included in regulatory communications in line with the EU MabThera Risk Management Plan, PBRERs, and other regulatory milestones and requirements, including communications with the CHMP.

In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the ISPE (2007) and the International Committee of Medical Journal Editors (2013).

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

1. **MabThera Patient Alert Card Text for Non-Oncology Indications**
2. **Medical Record Abstraction Form – Draft**
3. **Patient Questionnaire – Draft**
4. **ENCePP Checklist for Study Protocols**

1. MabThera Patient Alert Card Text for Non-Oncology Indications

MabThera Alert Card for patients with non-oncology diseases

Why have I been given this card?

This medicine may make you more likely to get infections. This card tells you:

• What you need to know before having MabThera

• What the signs of an infection are

• What to do if you think you might be getting an infection.

It also includes your name and doctor's name and phone number on the back.

What should I do with this card?

• Keep this card with you all the time - such as in your wallet or purse.

• Show this card to any doctor, nurse or dentist you see - not just the specialist who prescribes your MabThera.

Keep this card with you for 2 years after your last dose of MabThera.

What else do I need to know?

Rarely MabThera can cause a serious brain infection, called "Progressive Multifocal Leukoencephalopathy" or PML. This can be fatal.

• Signs of PML include:

- Confusion, memory loss or problems thinking

- Loss of balance or a change in the way you walk or talk

- Decreased strength or weakness on one side of your body

- Blurred vision or loss of vision.

If you get any of these, tell a doctor or nurse straight away. You should also tell them about your MabThera treatment.

Where can I get more information?

See the MabThera package leaflet for more information.

Treatment start date and contact details

Date of most recent infusion: _____

Date of first infusion: _____

Patient's Name:_____

Doctor's Name:_____

Doctor's contact details:_____

This is because side effects can develop several months after you have had treatment. **When should I not have MabThera?** Do not have MabThera if you have an active infection or a serious problem with your immune system. Tell your doctor or nurse if you are taking or have previously taken medicines which may affect your immune system this includes chemo-therapy. **What are the signs of getting an infection?** Look out for the following possible signs of infection: • Fever or cough all the time • Weight loss • Pain without injuring yourself • Feeling generally unwell or listless. **If you get any of these, tell a doctor or nurse straight away.** **You should also tell them about your MabThera treatment.**	Make sure you have a list of all your medicines when you see a health care professional. Please talk to your doctor or nurse if you have any questions about the information in this card.

2. Medical Record Abstraction Form – Draft

Patient ID:

Medical Record Abstraction Form—Draft

1. Date of abstraction: / / (dd/mm/yyyy)

2. Date of patient's most recent visit to infusion centre:

   / / (dd/mm/yyyy)

3. Patient's age:

   - ☐ 18-25 years
   - ☐ 26-35 years
   - ☐ 36-45 years
   - ☐ 46-55 years
   - ☐ 56-65 years
   - ☐ 66-75 years
   - ☐ 76-85 years
   - ☐ > 85 years

4. Patient's gender:
   - ☐ Male
   - ☐ Female

5. Date of patient's first MabThera infusion: / /
   (dd/mm/yyyy)

6. Date of patient's most recent MabThera infusion:

   / / (dd/mm/yyyy)

Patient ID:

Medical Record Abstraction Form—Draft

7. Primary condition for which patient was prescribed MabThera:
(Select one answer.)

- ☐ Rheumatoid arthritis*
- ☐ Ankylosing spondylitis
- ☐ Psoriatic arthritis
- ☐ Undifferentiated spondyloarthritis
- ☐ Juvenile idiopathic arthritis
- ☐ Systemic lupus erythematosus
- ☐ Systemic vasculitis
- ☐ Inflammatory myopathies
- ☐ Behçet disease
- ☐ Sjögren syndrome
- ☐ Nephrotic syndrome
- ☐ Glomerulonephritis
- ☐ Multiple sclerosis/neuromyelitis optica
- ☐ Pemphigus vulgaris
- ☐ Polydermatomyositis
- ☐ Mixed connective tissue disease
- ☐ Wegener's granulomatosis/microscopic polyangiitis
- ☐ Eosinophilic granulomatosis with polyangiitis
- ☐ Other (specify) _____

* Complete the Supplemental Form for Patients Receiving MabThera for Rheumatoid Arthritis.

8. Date of first diagnosis for primary condition:

/ / (dd/mm/yyyy)

9. Reason for MabThera prescription:
- ☐ Failure of previous treatment
- ☐ Adverse events under previous treatment
- ☐ Compassionate use
- ☐ Other, please specify: _____
- ☐ Data not available

10. Total number of MabThera infusions in the past 2 years: infusions

11. MabThera dosage for <u>most</u> <u>recent</u> infusion: mg

12. Medications patient has taken within the past 12 months. (Select all that apply.)

Immunosuppressives

- ☐ Azathioprine
- ☐ Cyclophosphamide
- ☐ Intravenous immunoglobulin
- ☐ Methotrexate
- ☐ Methylprednisolone (oral or in bolus)
- ☐ Prednisolone (oral or in bolus)
- ☐ Glucocorticoid (in bolus)
- ☐ Mofetil mycophenolate
- ☐ Plasmapheresis
- ☐ Other immunosuppressive, please specify:

Non-steroidal anti-inflammatory drugs (NSAIDS)

- ☐ NSAIDS including COX-2 inhibitors

Biological agents

Tumour necrosis factor-alpha inhibitors

- ☐ Adalimumab
- ☐ Certolizumab pegol
- ☐ Etanercept
- ☐ Golimumab
- ☐ Infliximab
- ☐ Ocrelizumab

Interleukin inhibitors

- ☐ Anakinra
- ☐ Tocilizumab

Other biological agents

- ☐ Abatacept
- ☐ Janus kinase inhibitor: Tofacitinib
- ☐ Other, please specify: _____

Patient ID:

Medical Record Abstraction Form—Draft

Supplemental Form for Patients Receiving MabThera for Rheumatoid Arthritis

RA1. Is the patient currently taking methotrexate?

- ☐ Yes
- ☐ No

If yes to question RA1, continue with RA1a. If no, go to RA2.

RA1a. Please indicate the start date for methotrexate use:

/ / (dd/mm/yyyy)

RA2. Prior to the first infusion in the patient's current treatment cycle, did the patient ever take any tumour necrosis factor–alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)?

- ☐ Yes
- ☐ No

For questions RA3 through RA8a, please provide results for tests performed closest in time and prior to the date of the first MabThera infusion in the patient's current treatment cycle.

RA3. C-reactive protein (CRP) level at first MabThera infusion in the current treatment cycle: mmol/L

RA3a. Date of CRP test: / / (dd/mm/yyyy)

RA4. Erythrocyte sedimentation rate (ESR) at first MabThera infusion in the current treatment cycle: mm/hr

RA4a. Date of ESR: / / (dd/mm/yyyy)

Medical Record Abstraction Form—Draft

RA5. Tender joint count (0 – 28) at first MabThera infusion in the current treatment cycle: joints

RA5a. Date of tender joint count: / / (dd/mm/yyyy)

RA6. Swollen joint count (0 – 28) at first MabThera infusion in the current treatment cycle: joints

RA6a. Date of swollen joint count: / / (dd/mm/yyyy)

RA7. Presence of extra-articular involvement at first MabThera infusion in the current treatment cycle:

- ☐ Yes
- ☐ No

RA8. Global assessment of patient's general health on visual analogue scale (VAS) (0 – 100) at first MabThera infusion in the current treatment cycle: mm

RA8a. Date of global health assessment: / / (dd/mm/yyyy)

Patient ID:

Medical Record Abstraction Form—Draft

For questions RA9 through RA14a, please provide results for tests performed on or nearest to the date of the patient's most recent MabThera infusion (Q6).

RA9. C-reactive protein (CRP) level at most recent MabThera infusion:

mmol/L

RA9a. Date of CRP test: / / (dd/mm/yyyy)

RA10. Erythrocyte sedimentation rate (ESR) at most recent MabThera infusion:

mm/hr

RA10a. Date of ESR: / / (dd/mm/yyyy)

RA11. Tender joint count (0 – 28) at most recent MabThera infusion: joints

RA11a. Date of tender joint count: / /
(dd/mm/yyyy)

RA12. Swollen joint count (0 – 28) at most recent MabThera infusion: joints

RA12a. Date of swollen joint count: / /
(dd/mm/yyyy)

RA13. Presence of extra-articular involvement at most recent MabThera infusion:

- ☐ Yes
- ☐ No

Medical Record Abstraction Form—Draft

RA14. Global assessment of patient's general health on visual analogue scale (VAS) (0 – 100) at most recent MabThera infusion:

mm

RA14a. Date of global health assessment: / /
(dd/mm/yyyy)

3. Patient Questionnaire - Draft

MabThera Risk Minimisation Programme Evaluation

Patient Questionnaire—Draft

Thank you for agreeing to participate in this study.

The questionnaire should take approximately 10 to 15 minutes to complete. Your responses will be kept confidential and will not be shared with your doctor or other health care professionals.

Please answer the following questions to confirm that you are eligible for this study.

Confirmatory Screening Question

S1. Are you 18 years of age or older?

- ☐ Yes
- ☐ No (If no, please speak with your nurse or doctor to confirm your eligibility.)

Questionnaire

The purpose of the study is to learn more about patients' understanding of the important safety information related to MabThera (rituximab). As we are trying to find out your current understanding, please do not look at the MabThera patient alert card or other materials while answering the following questions. The information gathered from this study will help to improve communication about the safe use of MabThera (rituximab).

Note: For review purposes, an asterisk (*) indicates correct responses.

Q1. Approximately when was your first infusion of MabThera (rituximab)? (Select the one answer that best applies to you.)

- ☐ This is my first infusion
- ☐ Less than 3 months ago
- ☐ Between 3 months and 9 months ago
- ☐ More than 9 months ago
- ☐ I don't know

Q2. During the past 12 months, approximately how many times have you received MabThera (rituximab), which is always given by an IV (intravenous) infusion?

- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 times
- ☐ More than 4 times
- ☐ I don't know

Q3. Where do you get most of your information about MabThera (rituximab)? (Select the one most correct answer.)

- ☐ From my doctor who prescribed MabThera (rituximab)
- ☐ From another doctor at the infusion centre
- ☐ From the nurse at the infusion centre
- ☐ From my chemists/pharmacy[1]
- ☐ From a friend or family member (spouse, adult child)
- ☐ From my professional caregiver
- ☐ From the Internet
- ☐ Other, please specify: _____

[1] Use "chemists" for UK and "pharmacy" for other countries.

Risk Assessment

The following questions ask about the risks and side effects that patients could potentially experience when taking MabThera (rituximab). Please note these questions are just to learn more about your knowledge of these risks and not about your specific experiences while taking MabThera (rituximab).

Q4. Has your doctor or other health care professional (e.g., a nurse) ever talked to you about the possible risks of receiving MabThera (rituximab)?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q5. Which of the following side effects can potentially happen in patients who are receiving MabThera (rituximab)?
(Select all that apply.)

- ☐ Hair loss
- ☐ Tooth decay
- ☐ Infections*
- ☐ None of the above
- ☐ I don't know

Q6. Please read each of the following statements and then select "Yes," "No," or "I don't know" for each statement.

Statement	Yes, this is true	No, this is not true	I don't know
Q6a. Patients should not be treated with MabThera if they have an active infection or a serious problem with their immune system.	☐ Yes*	☐ No	☐ I don't know
Q6b. Patients with an infection can be treated with MabThera if they are in a lot of pain.	☐ Yes	☐ No*	☐ I don't know
Q6c. Patients should tell their doctor if they are taking or have previously taken medicines which may affect their immune system, such as chemotherapy or immunosuppressive agents.	☐ Yes*	☐ No	☐ I don't know
Q6d. Patients should not eat or drink anything before receiving their MabThera infusion.	☐ Yes	☐ No*	☐ I don't know

Q7. Which of the following are symptoms of an infection that a patient may experience while undergoing treatment with MabThera (rituximab)? Select "Yes," "No," or "I don't know" for each possible symptom listed below.

Possible Symptom	Yes, this is a symptom of infection	No, this is NOT a symptom of infection	I don't know if this is a symptom of infection
Fever	☐ *	☐	☐
Intense hunger	☐	☐ *	☐
Persistent cough	☐ *	☐	☐
Weight loss	☐ *	☐	☐
Bleeding that takes a long time to stop	☐	☐ *	☐
Listlessness	☐ *	☐	☐

Q8. Very rarely, some patients taking MabThera (rituximab) have had a serious brain infection called progressive multifocal leukoencephalopathy (PML).

- ☐ Yes, this is true*
- ☐ No, this is not true
- ☐ I don't know

Q9. Which of the following are symptoms of progressive multifocal leukoencephalopathy (PML)?
(Select "Yes," "No," or "I don't know" for each possible symptom listed below.)

Possible Symptom	Yes, this is a symptom of PML	No, this is NOT a symptom of PML	I don't know if this is a symptom of PML
Memory loss	☐ *	☐	☐
Swelling or discomfort	☐	☐ *	☐
Problems thinking	☐ *	☐	☐
Unusual bruising	☐	☐ *	☐
Change in the way you walk	☐ *	☐	☐
Loss of vision	☐ *	☐	☐

Q10. Side effects from MabThera (rituximab) can occur even after patients have stopped treatment?

- ☐ Yes, this is true*
- ☐ No, this is not true
- ☐ I don't know

Q11. What should you do if you have symptoms that suggest an infection?
(Select the one most correct answer.)

- ☐ Wait to see if the symptoms go away
- ☐ Seek medical attention immediately*
- ☐ Drink water to help wash the medication out of my system
- ☐ None of the above
- ☐ I don't know

Safe Use

Q12. Please read each of the following statements and then select "Yes," "No," or "I don't know" for each statement.

Statement	Yes, this is true	No, this is not true	I don't know
Q12a. Patients can stop taking MabThera (rituximab) at any time without consulting with their doctor.	☐ Yes	☐ No*	☐ I don't know
Q12b. Patients should show their patient alert card to <u>any</u> doctor, nurse or dentist involved in their treatment, not just their prescribing specialist physician.	☐ Yes*	☐ No	☐ I don't know
Q12d. Patients should have a list of all their medicines with them at any visit to a health care professional.	☐ Yes*	☐ No	☐ I don't know

Q13. One of the side effects of using MabThera (rituximab) is immune system suppression (a lowering of your body's defenses against infections). How long after stopping MabThera (rituximab) can immune system suppression last? (Select the one most correct answer.)

- ☐ A few days
- ☐ Several months*
- ☐ Two or more years
- ☐ None of the above
- ☐ I don't know

Patient Alert Card Receipt and Review

Now we are going to ask you some questions about the Patient Alert Card that you may have received from your doctor or health care professional. This small, pocket-sized card contains important safety information about MabThera (rituximab).

Q14. Have you ever received or been given a Patient Alert Card for MabThera (rituximab)?

- ☐ Yes → Continue with Question 15
- ☐ No → Skip to Question 25
- ☐ I don't know → Skip to Question 25

Answer questions 15-24 only if you have received a Patient Alert Card for MabThera (rituximab). Otherwise, skip to question 25.

Q15. How often have you received or been given a Patient Alert Card for MabThera (rituximab)?

- ☐ Every time I receive a MabThera infusion
- ☐ Some of the times I receive a MabThera infusion
- ☐ Only the first time I received a MabThera infusion
- ☐ I don't know

Q16. Did you have the Patient Alert Card for MabThera (rituximab) with you when you arrived at the centre today?

- ☐ Yes
- ☐ No
- ☐ I'm not sure

Q17. How much of the time do you keep the Patient Alert Card(s) for MabThera (rituximab) with you? (Select one answer.)

- ☐ All the time
- ☐ Some of the time
- ☐ None of the time
- ☐ I don't know

Q18. Have you ever read the Patient Alert Card for MabThera (rituximab)?

- ☐ Yes → Skip to Question 20
- ☐ No → Continue with Question 19
- ☐ I'm not sure → Continue with Question 19

Q19. Is there a reason why you have not read the Patient Alert Card for MabThera (rituximab)?
(Select all that apply.)

- ☐ Someone else explained it to me
- ☐ I lost the Patient Alert Card
- ☐ I already knew the information
- ☐ I sometimes do not read the materials given to me by my doctor
- ☐ Other

Q20. Has someone else, other than the doctor who prescribed MabThera (rituximab) for you, *explained* the information in the Patient Alert Card for MabThera (rituximab) to you?
(Select all that apply.)

- ☐ Yes, a doctor or nurse
- ☐ Yes, a chemist/pharmacist or someone at the chemists/pharmacy[2]
- ☐ Yes, a friend or family member
- ☐ Yes, a professional caregiver
- ☐ No
- ☐ I don't know

Q21. What information should patients record on the Patient Alert Card for MabThera (rituximab)?
(Select all that apply.)

- ☐ Start date and most recent date of MabThera (rituximab) infusion*
- ☐ Patient's name*
- ☐ Doctor's name and phone number*
- ☐ All of the above*
- ☐ None of the above
- ☐ I don't know

Q22. How long should patients keep the Patient Alert Card for MabThera (rituximab) after their last dose?
(Select the one most correct answer.)

- ☐ 1 week
- ☐ 24 months*
- ☐ 5 years
- ☐ None of the above
- ☐ I don't know

[2] Use "chemists" for UK and "pharmacy" for other countries.

Q23. Since starting treatment with MabThera (rituximab), have you seen any doctors for other conditions?

- ☐ Yes → Continue with Question 24
- ☐ No → Skip to Question 25
- ☐ I don't know → Skip to Question 25

Q24. Have you shown the Patient Alert Card for MabThera (rituximab) to doctors treating you for other conditions?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q25. Have you ever received or been given the package leaflet for MabThera (rituximab)?
(Select all that apply.)

- ☐ Yes → Continue with Question 26
- ☐ No → Skip to Question 28
- ☐ I don't know → Skip to Question 28

Q26. Did you have the package leaflet for MabThera (rituximab) with you when you arrived at the centre today?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q27. How much of the time do you keep the package leaflet(s) for MabThera (rituximab) with you?
(Select one answer.)

- ☐ All the time
- ☐ Some of the time
- ☐ None of the time
- ☐ I don't know

Q28. Have you <u>ever</u> received or been given other materials that describe the potential risks of receiving MabThera (rituximab)?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q29. Have you ever experienced an infection while undergoing treatment with MabThera (rituximab)?

- ☐ Yes → Continue with Question 30
- ☐ No → Skip to Question 32
- ☐ I don't know → Skip to Question 32

Q30. Please indicate the most recent infection you experienced while undergoing treatment with MabThera (rituximab)?

- ☐ Progressive multifocal leukoencephalopathy (PML)
- ☐ Other, please specify: _____
- ☐ I don't know

Q31. Which of the following actions did you take when you experienced the most recent infection while undergoing treatment with MabThera (rituximab)? (Select all that apply.)

- ☐ When I noticed symptoms, I talked to my doctor
- ☐ I referred to my Patient Alert Card
- ☐ I told the doctor who treated me for the infection that I was taking MabThera (rituximab)
- ☐ I showed the doctor who treated me for the infection the Patient Alert Card for MabThera (rituximab)
- ☐ None of the above
- ☐ I did something not listed here. Please specify: _____
- ☐ I don't know

Q32. Did you look at the MabThera (rituximab) Patient Alert Card or package leaflet just before or while you were completing this questionnaire?

- ☐ Yes
- ☐ No

Demographics

In this last section, please tell us a little information about yourself to help us describe the participants completing this questionnaire.

Q33. How old are you?

- ☐ 18-25 years
- ☐ 26-35 years
- ☐ 36-45 years
- ☐ 46-55 years
- ☐ 56-65 years
- ☐ 66-75 years
- ☐ 76-85 years
- ☐ > 85 years

Q34. Are you...?

- ☐ Male
- ☐ Female

Q35. What is the highest level of education you have completed? (Select one.)[3]

- ☐ Secondary/high school
- ☐ Professional qualifications (for example, nursing, teaching, accountancy)
- ☐ Other vocational/work-related qualifications gained at college or in employment
- ☐ University – Bachelor's degree
- ☐ University – Master's degree
- ☐ Professional degree (e.g., MD, LLB)
- ☐ Doctorate degree (e.g., PhD)

Thank you again for taking time to participate in this study! Your answers are very important. If you have any questions about the safety of treatment with MabThera (rituximab), you should talk with your doctor or nurse.

Please place your completed questionnaire in the envelope provided to you by the nurse or doctor and seal the envelope. Also, be sure and let them know that you have finished.

[3] Response choices apply to the UK and may need to be adapted for other countries.

5. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoep dem ology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) 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 ENCePP Guide on Methodological Standards in Pharmacoepidemiology 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 Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). 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:
MabThera Drug Utilisation Study and Patient Alert Card Evaluation in Non-Oncology Patients in Europe: An Infusion Centre–Based Approach

Study reference number:
[The EU PAS registry number will be added after registration]

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[4]	☒	☐	☐	20
1.1.2 End of data collection[5]	☒	☐	☐	20
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	

[4] 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.
[5] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.5 Registration in the EU PAS register	☒	☐	☐	20
1.1.6 Final report of study results	☒	☐	☐	20

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)	☒	☐	☐	21-23
2.1.2 The objectives of the study?	☒	☐	☐	25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	21
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a drug utilisation study; no hypotheses will be tested.

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)	☒	☐	☐	25-27
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	30-35
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)	☐	☐	☒	

Comments:

The study is just descriptive. No measures of effect will be estimated (see pages 38-40).

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	27-30
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	27-30
4.2.2 Age and sex?	☒	☐	☐	27-30
4.2.3 Country of origin?	☒	☐	☐	27-30
4.2.4 Disease/indication?	☒	☐	☐	27-30
4.2.5 Co-morbidity?	☒	☐	☐	27-30
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)	☒	☐	☐	27-30

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)	☐	☐	☒	
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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
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:

This is a drug utilisation study; all participants are exposed to MabThera in the course of routine medical treatment. All patients will have received at least a MabThera infusion. Additional exposure information will be obtained from medical records.

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?	☒	☐	☐	32-33
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)	☐	☐	☒	

Comments:

This is a drug utilisation study; the “endpoints” are off-label use of MabThera. Classification of these endpoints will be based on clinical indication derived from the medical record. Knowledge of the PAC will be derived from answers to the patient survey.

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)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a descriptive drug utilisation study.

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.)	☒	☐	☐	30-35
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.)	☒	☐	☐	30-35
8.1.3 Covariates?	☒	☐	☐	30-35
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)	☒	☐	☐	30-35

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	30-35
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	30-35
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	28, 42-45

Comments:

Information on the exposure and the outcome (off-label use) will be derived from the medical record.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	36-38

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	38-40
10.3 Are descriptive analyses included?	☒	☐	☐	38-40
10.4 Are stratified analyses included?	☒	☐	☐	38-40
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Analysis will include only descriptive measures appropriate for the study objectives.

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?	☒	☐	☐	30-32, 38-40
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	38-41
11.3 Are methods of quality assurance described?	☒	☐	☐	41
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	42-43
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	38-40

Comments:

Additional information will be included in the statistical analysis plan.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	42-43
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)	☒	☐	☐	42-43
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23-24
12.3 Does the protocol address other limitations?	☐	☐	☒	

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?	☒	☐	☐	43-45
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	38-41

Comments:

The protocol has not yet been reviewed by an ethics board.

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?	☒	☐	☐	15

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)?	☒	☐	☐	46
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	46

Comments:

Name of the main author of the protocol: [redacted]

Date: 24/June/2014

Signature: _____