EU RISK MANAGEMENT PLAN FOR MABTHERA®/RITUXIMAB

RMP version to be assessed as part of this application:

RMP version number: 25.1

Data lock point for this RMP: 17 November 2023

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
08-Mar-2024 08:08:48	Deputy QPPV	PPD
08-Mar-2024 09:03:14	Company Signatory (PV)	

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Rationale for submitting an updated RMP: The Pharmacovigilance Risk Assessment Committee (PRAC) requested to re-evaluate the need for the educational materials (EMs) in the final PRAC assessment report (AR) EMEA/H/C/PSUSA/00002652/202211, which was received for the 12th Periodic Safety Update Report (PSUR). This European Union Risk Management Plan (EU RMP) is updated to remove the EMs [additional risk minimization measures; progressive multifocal leukoencephalopathy (PML) and infections (including serious infections), off-label use of the subcutaneous (SC) formulation and administration route error] and consequently the respective associated important potential risks. Addressing questions from the PRAC assessment (EMEA/H/C/000165/II/0201/G), the MAH has provided additional justification with reference to the safety data to remove the two important potential risks "Off-label use of the SC formulation [Non-Hodgkin's Lymphoma (NHL)/Chronic Lymphocytic Leukemia (CLL), SC formulations]" and "Administration route error (NHL/CLL, SC formulations)". As the additional risk minimization measures have been removed, the risks of "Off-label use of the SC formulation (NHL/CLL, SC formulations) and Administration route error (NHL/CLL, SC formulations)" would no longer "qualify" as risks for the EU RMP as per the GVP Module V rev. 2 guidelines. The routine risk minimization measures, specifically clear package differentiation, peel-off sticker included on the individual vials, and SC and intravenous (IV) formulations covered by separate summary of product characteristics (SmPC) (which include specific warning against incorrect route of administration) will remain. The Marketing Authorization Holder (MAH) continues to keep the Patient alert card (PAC) as additional risk minimization measure for the risk of PML and the risk of infections, including serious infections in non-oncology indications. The PAC aims to provide the patients with important safety information on PML and infections, especially new patients.

Based on the PRAC assessment (EMEA/H/C/000165/II/0201/G), the MAH has reassessed the following important identified risks "Hepatitis B reactivation (All indications)" and "Hypogammaglobulinemia (non-oncology indications)" and concluded that these risks are well characterized and there are no additional activities/measures needed. The MAH proposes to remove these risks from the EU RMP. The MAH continues routine pharmacovigilance activities including signal detection and will continue to present these important risks in the upcoming PBRERs.

Furthermore, three guided questionnaires (GQs) [routine pharmacovigilance activities; PML, off-label use in pediatric patients, malignant events and second malignancies] have been removed. Based on an extensive analysis of rituximab safety data gathered over the course of last 20 years, these EMs and GQs are no longer considered to be of additional benefit beyond the existing routine risk minimization activities.

Also, the discontinuation of the routine pharmacovigilance activity to expedite all cases of PML to PRAC is reflected in this update as confirmed by PRAC.

In this consolidated version, the MAH has taken the opportunity to reflect the changes approved in the RMP V24.0 via procedure EMEA/H/C/000165/II/0199 and to implement the changes in response to PRAC assessment on V25.0 via procedure EMEA/H/C/000165/II/0201/G. The significant changes made in this RMP are provided below:

Summary of Significant Changes in this RMP

- Part I "Product Overview" has been updated to reflect the updated ATC code.

- Part II: Module SII – The discussion sections in "1.1.1 Single- and repeat-dose toxicity studies" and "1.1.2 Toxicology studies" has been updated to improve readability.

- Part II: Module SIV – Use in pregnant or breastfeeding women was no longer considered missing information.

- Part II: Module SV and Annex 7 – 'Post-authorization experience' section was updated as per the most recent PBRER 1126778 with the data lock point (DLP) of 17 November 2023.

- Part II: Module SVII.2 – 'New Safety Concerns and Reclassification with a Submission of an Updated RMP' was updated with a justification and arguments to remove the two important potential risks "Off-label use of the SC formulation (NHL/CLL, SC formulations)" and "Administration route error (NHL/CLL, SC formulations)" and important identified risks "Hepatitis B reactivation (All indications)" and "Hypogammaglobulinemia (non-oncology indications)".

- Part II: Module SVII.3.1 – 'Presentation of important identified risks and important potential risks' has been updated as per the most recent PBRER 1126778 with a DLP of 17 Nov 2023. Additionally, the data for PML has been updated with cut-off date 17 Nov 2023.

- Part II SVII.3.1.1.1, SVII.3.1.2.1, SVII.3.1.2.2, Part V.2, Part V.3 have been updated to reflect the removal of the EMs (and consequently the respective associated risks) and the GQs (from routine pharmacovigilance activities).
- Part II SVII 3.1.2, Part II: Module SVIII - Summary of the safety concerns, Part V.1 Routine risk minimization measures, Part V.2 Additional risk minimization measures and Part V.3 Summary of risk minimization measures has been updated with the removal of important identified risks "Hepatitis B reactivation (All indications)" and "Hypogammaglobulinemia (non-oncology indications)" and important potential risks "Off-label use of the SC formulation (NHLL/CLL, SC formulations) and Administration route error (NHL/CLL, SC formulations)".
- Part III.1 Routine pharmacovigilance activities – has been updated with removal of GQs and discontinuation of expedited reporting for PML.

- Annex 4 "Specific Adverse Drug Reaction Follow-up Forms" has been updated to remove the three GQs.
- Annex 6 “Details of proposed additional risk minimization activities” has been updated with the removal of EMs and the text related to PAC has been updated in line with the integrated format EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.
- Annex 7 ‘Other Supporting Data’ has been updated with cumulative post-authorization exposure data from IBD until data cut-off date 30 September 2023 and pregnancy exposure outputs have been updated for the reporting interval (PBRER 1126778 cover period: 18 November 2022 to 17 November 2023).
- Annex 8 “Summary of Changes to the Risk Management Plan Over Time” has been updated to summarize the changes done to the RMP.

Other RMP versions under evaluation: Not Applicable
Details of Currently Approved RMP:

Version number: 24.0

Approved with procedure EMEA/H/C/000165/II/0199

Date of approval (opinion date): 30 November 2023

See page 1 for signature and date

PPD (Deputy QPPV)	Date

See page 1 for signature and date

PPD	Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Rituximab
Pharmacotherapeutic group(s) (ATC Code)	L01FA01
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	MabThera® (rituximab)
Invented name(s) in the European Economic Area (EEA)	MabThera
Marketing authorization procedure	Centralised Procedure
Brief description of the product including:	Chemical Class: chimeric mouse/human monoclonal antibody
	Summary of mode of action: Rituximab binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on hemopoietic stem cells, pro-B-cells, normal plasma cells or other normal cells. Following antibody binding, CD20 is not internalized or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding. Rituximab is believed to exert its therapeutic effect by promoting B-cell lysis. It binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and induction of apoptosis. The CD20 antigen is expressed on > 95% of all B-cell non-Hodgkin's Lymphomas (NHL). *In vitro* studies have demonstrated that rituximab sensitizes drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents. In rheumatoid arthritis (RA), B-cells are thought to play a central role in the RA disease process through secretion of pro-inflammatory cytokines, antigen presentation, and auto-antibody production. Hence, selective depletion of CD20-positive B-cells (with rituximab) offers a rational approach to the treatment of RA.

Active Substance(s) (INN or common name)	Rituximab
	Due to its specific mode of action, the use of rituximab has also been explored in several other autoimmune disorders impacted by B-cell function, including Granulomatosis with Polyangiitis (GPA)/Microscopic Polyangiitis (MPA) and pemphigus vulgaris (PV).
	<u>Important information about its composition:</u> Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.
Hyperlink to the Product Information	
Indication(s) in the EEA	Current: <u>MabThera Intravenous:</u> **Rheumatoid Arthritis** MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARD) including one or more tumor necrosis factor (TNF) inhibitor therapies. **Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)** MabThera in combination with glucocorticoids is indicated for the treatment of adult patients with severe, active GPA and MPA. **GPA/MPA Pediatric patients:** MabThera in combination with glucocorticoids is indicated for the induction of remission in pediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA. **Pemphigus vulgaris:** MabThera is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV). **Non-Hodgkin's Lymphoma** MabThera is indicated for the treatment of previously untreated adult patients with stage

Active Substance(s) (INN or common name)	Rituximab
	III – IV follicular lymphoma in combination with chemotherapy. MabThera maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy. MabThera monotherapy is indicated for treatment of adult patients with stage III – IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera is indicated for the treatment of adult patients with CD20 positive diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy. **Non-Hodgkin's Lymphoma Pediatric patients:** MabThera in combination with chemotherapy is indicated for the treatment of pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL). **Chronic Lymphocytic leukemia** MabThera in combination with chemotherapy, is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic Leukemia (CLL). <u>MabThera Subcutaneous:</u> **Non-Hodgkin's Lymphoma** (Single dose vials contain 1400 mg/11.7 mL (in 15 mL vial) Subcutaneous MabThera is indicated for the treatment of previously untreated patients with stage III – IV follicular lymphoma in combination with chemotherapy. Subcutaneous MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. Subcutaneous MabThera is indicated for the treatment of patients with CD20 positive diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. **Chronic Lymphocytic Leukemia** (Single dose vials contain 1600 mg/13.4 mL (in 20 mL vial)) In combination with chemotherapy, subcutaneous MabThera is indicated for the treatment of patients

Active Substance(s) (INN or common name)	Rituximab
	with previously untreated and relapsed/refractory CLL.
	Proposed: N/A
Dosage in the EEA	Current: <u>MabThera Intravenous:</u> **Rheumatoid Arthritis** A course of MabThera consists of two 1000 mg intravenous infusions separated by a 2-week interval. The need for further courses should be evaluated 24 weeks following the previous course. **Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)** *Adult Induction of remission* The recommended dosage of MabThera for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion once weekly for 4 weeks (four infusions in total). *Adult Maintenance treatment* Following induction of remission with MabThera, maintenance treatment in adult patients with GPA and MPA should be initiated no sooner than 16 weeks after the last MabThera infusion. Following induction of remission with other standard of care immunosuppressants, MabThera maintenance treatment should be initiated during the 4-week period that follows disease remission. MabThera should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. **GPA/MPA Pediatric patients** *Induction of remission* The recommended dosage of MabThera for induction of remission therapy in pediatric patients with severe, active GPA or MPA is 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks. The safety and efficacy of MabThera in pediatric patients (≥ 2 to < 18 years of age) has not been established in indications other than severe, active GPA or MPA. MabThera should not be used in pediatric patients less than 2 years of age with severe, active GPA or MPA as there is a possibility of an inadequate

Active Substance(s) (INN or common name)	Rituximab
	immune response towards childhood vaccinations against common, vaccine preventable childhood diseases (e.g. measles, mumps, rubella, and poliomyelitis). **Pemphigus vulgaris** The recommended dosage of MabThera for the treatment of PV is 1000 mg administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids. *Maintenance treatment* A maintenance infusion of 500 mg IV should be administered at months 12 and 18 and then every 6 months thereafter based on clinical evaluation. *Treatment of relapse* In the event of relapse during the course of MabThera therapy, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion. **Non-Hodgkin's Lymphoma** *Follicular non-Hodgkin's lymphoma* Combination therapy The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 BSA per cycle, for up to 8 cycles. Maintenance therapy • Previously untreated follicular lymphoma The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 BSA once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 infusions in total). • Relapsed/refractory follicular lymphoma The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2

Active Substance(s) (INN or common name)	Rituximab
	BSA once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 infusions in total). Monotherapy • Relapsed/refractory follicular lymphoma The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 BSA, administered as an intravenous infusion once weekly for four weeks. For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 BSA, administered as an intravenous infusion once weekly for four weeks. *Adult Diffuse large B cell non-Hodgkin's lymphoma* MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. **Non-Hodgkin's Lymphoma Pediatric Patients:** Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera. In pediatric patients with NHL, premedication consists of paracetamol and H1 antihistamine (=diphenhydramine or equivalent) administered 30 to 60 minutes before the start of the infusion of MabThera. In pediatric patients from ≥ 6 months to < 18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, MabThera should be used in combination with systemic Lymphome Malin B chemotherapy. The recommended dosage of MabThera is 375mg/m^2 BSA, administered as an IV infusion. No MabThera dose adjustments, other than by BSA, are required. The safety and efficacy of MabThera in pediatric patients ≥ 6 months to < 18 years of age has not been established in indications other than

Active Substance(s) (INN or common name)	Rituximab
	previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. MabThera should not be used in pediatric patients from birth to < 6 months of age with DLBCL. **Chronic Lymphocytic Leukemia** For CLL patients whose lymphocyte counts are $>25 \times 10^9$/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 BSA administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion. <u>MabThera Subcutaneous:</u> **Non-Hodgkin's Lymphoma** The recommended dosage of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's BSA. *Follicular non-Hodgkin's lymphoma* Combination therapy: The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 BSA, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8 cycles. Maintenance therapy: • Previously untreated follicular lymphoma The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 administrations

Active Substance(s) (INN or common name)	Rituximab
	in total). • Relapsed/refractory follicular lymphoma The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 administrations in total). *Diffuse large B cell non-Hodgkin's lymphoma* MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle, MabThera intravenous formulation: 375 mg/m^2 BSA, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles. **Chronic Lymphocytic Leukemia** The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1600 mg irrespective of the patient's BSA. The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is: MabThera intravenous formulation 375 mg/m^2 BSA administered on day 0 of the first cycle of treatment followed by MabThera subcutaneous formulation injected at a fixed dose of 1600 mg per cycle, on day 1 of each subsequent cycle (in total: 6 cycles).
	Proposed: N/A
Pharmaceutical form(s) and strength(s)	Current: *MabThera 100 mg and 500 mg concentrate for solution for infusion* Each mL of solution contains 10 mg of rituximab Each single use vial contains 100 mg or 500 mg of rituximab. *MabThera 1400 mg solution for subcutaneous injection* Each mL of solution contains 120mg of rituximab. Each single use vial contains 1400mg/11.7mL of rituximab. *MabThera 1600 mg solution for subcutaneous*

Active Substance(s) (INN or common name)	Rituximab
	injection Each mL of solution contains 120mg of rituximab. Each single use vial contains 1600mg/13.4mL of rituximab.
	Proposed: N/A
Is or will the product be subject to additional monitoring in the EU?	No

BAL = Burkitt leukaemia (mature B-cell acute leukaemia), BL = Burkitt lymphoma, BLL = Burkitt-like lymphoma, BSA = body surface area, CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone, CLL = chronic lymphocytic Leukemia, DMARD = disease modifying anti-rheumatic drugs, EEA = European economic area, EU = European Union, GPA=granulomatosis with polyangiitis, MPA = microscopic polyangiitis, N/A = not applicable, NHL = non-Hodgkin's Lymphomas, PV = Pemphigus Vulgaris; RA = rheumatoid arthritis, TNF = tumor necrosis factor.

ABBREVIATIONS

Abbreviation	Definition
AAV	ANCA (Anti-Neutrophil Cytoplasmic Antibody) Associated Vasculitis
AE	Adverse Event
AI	Autoimmune
B-AL	Burkitt Leukemia
BL	Burkitt Lymphoma
BLL	Burkitt-like lymphoma
B-NHL	B-cell Non-Hodgkin’s Lymphoma
CCO	common closeout
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
CSR	Clinical Study Report
CV	Cardiovascular
CYC	Cyclophosphamide
DLP	Data Lock Point
DMARD	Disease-Modifying Anti-Rheumatic Drug
DSR	Drug Safety Report
EEA	European Economic Area
EM	Educational Material
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EULAR	European League Against Rheumatism
GI	Gastrointestinal
GPA (WG)	Granulomatosis with polyangiitis (Wegener's Granulomatosis)
GQ	Guided questionnaire
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IBD	International Birth Date
IgG	immunoglobulin G

Abbreviation	Definition
IRR	Infusion-Related Reaction
IV	Intravenous
LMB	Lymphome Malin B
MAH	Marketing Authorization Holder
MPA	Microscopic Polyangiitis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NHL	Non-Hodgkin's Lymphoma
NMSC	Non-melanoma Skin Cancer
NS	Nephrotic Syndrome
PBRER	Periodic Benefit Risk Evaluation Report
PAC	Patient Alert Card
PCP	Pneumocystis Jiroveci Pneumonia
PF	Pemphigus Foliaceus
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PSUR	Periodic Safety Update Report
PV	Pemphigus Vulgaris
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SC	Subcutaneous
SEER	Surveillance Epidemiology and End Results
SLE	Systemic Lupus Erythematosus
SLL	Small Lymphocytic Lymphoma
SMR	Standardized mortality rate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TB	Tuberculosis
TNF	Tumor Necrosis Factor
UK	United Kingdom
US(A)	United States (of America)

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 RHEUMATOID ARTHRITIS

- Incidence:

The incident rate is 45/100,000 person-years, in a population of 18 years and older; out of which 73% are female, 27% are male (Gabriel et al. 2003).

- Prevalence:

Overall rheumatoid arthritis (RA) prevalence in industrialized countries is between 0.3% and 1% (Wolfe et al. 2003); 14/1,000 female, 7.4/1,000 male population (Gabriel et al. 2003), with the lifetime risk of RA in adults in the US being 3.6% (1 in 28) for women and 1.7% (1 in 59) for men (Crowson et al. 2011). The incidence and prevalence of RA increases with age. Pooled estimates of prevalence in European populations are as follows (males/females per 1,000): ages 5 – 14, 0/0.05; ages 15 – 44, 1/6; ages 45 – 59, 5.3/12; ages 60 and over, 12/26 (Lau et al. 1996). Age and sex distribution is largely similar across American and European populations (Abdel-Nasser et al. 1997).

- Demographics:

New-onset RA occurs in a wide range of ages, the majority of patients are females with a rate of approximately 3:1(Lau et al. 1996; Abdel-Nasser et al. 1997). Rheumatoid Arthritis patients in the United Kingdom(UK), who began using biological therapy (anti-tumor necrosis factor [TNF]), had a mean age of 56 years, younger than patients on non-biological Disease-Modifying Anti-Rheumatic Drug (DMARD) therapy (mean 60 years) (Dixon et al. 2006). Standard deviation of the age in these groups was 12 and 13 years, respectively, showing that patients in a wide age range are treated with biologic and non-biologic DMARD therapies.

- Main existing treatment options:

Recommendations for the management of RA have been developed by major professional organizations, including the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). These guidelines recommend that patients diagnosed with RA should be started on disease-modifying antirheumatic drug (DMARD) therapy as soon as possible following diagnosis, and that treatment should be aimed at reaching a target of sustained remission or low disease activity. There are a number of efficacious DMARDs, including conventional synthetic DMARDs (methotrexate, leflunomide, sulfasalazine), biological DMARDs (TNF inhibitors, IL-6 inhibitor, abatacept, rituximab) and targeted synthetic DMARDs (Jak inhibitors).

EULAR guidelines recommend treatment start with a conventional DMARD, with methotrexate being part of the first treatment strategy, in combination with short-term glucocorticoids if necessary. For patients responding insufficiently to methotrexate with poor prognostic factors, or who respond insufficiently to a combination of conventional DMARDs, biological DMARDs or targeted synthetic DMARDs are treatment options.

- Risk factors for the disease:

Gender-specific, genetic and environmental risk factors for RA have been identified:

  - Female sex: Women are two to three times more likely to develop RA than men. Gender-specific factors affecting the susceptibility remain incompletely understood, maybe due to stimulatory effects of estrogen on the immune system. Various reproductive factors may contribute to the cause of RA, it has been observed that the risk of RA is increased by nulliparity, and pregnancy is often associated with disease remission in the last trimester (Gabriel et al. 2017, Crowson CS et al. 2011, Ansar Ahmed et al. 1985).
  - Genetic risk factors: Twin and sibling studies implicate genetic factors in the susceptibility for RA, and there is a significant overlap with genes identified as risk factors for other autoimmune (AI) diseases. A number of genes and genetic makers have been identified, with the human leucocyte antigen (HLA) being the major genetic susceptibility factor (Gabriel et al. 2017, Jawaheer D et al. 2001, de Vries N et al. 2002).
  - Environmental risk factors are smoking and obesity. Multiple studies show that cigarette smoking increases a person's risk of developing RA and for greater disease severity. Studies examining the role of obesity also found that the more overweight a person was, the higher his or her risk of developing RA became (Gabriel et al. 2017, Liao KP et al. 2009).

- Natural history of the indicated condition in the untreated population:

Mortality: In RA populations, elevated Standardized Mortality Rates (SMR) of 1.23 – 2.03 were reported (Gabriel et al. 2003, Young et al. 2007, Björnadal et al. 2002, Kapetanovic et al. 2011c, Kim et al. 2012). Coronary artery disease is a major cause of death in RA, SMR 1.79 (Björnadal et al. 2002). RA patients, compared to the general population, have elevated all-cause and cardiovascular (CV) mortality rates (Dixon et al. 2006, Young et al. 2007). Early functional disability (Farragher et al. 2007) and persistent inflammatory state (inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, were found to be predictors of CV death (Symmons et al. 2006, Maradit-Kremers et al. 2005).

Morbidity: Decreased life expectancy is usually due to morbidity associated with RA such as CV disease, or to iatrogenic effects of therapy, in particular infections and gastrointestinal (GI) bleeding related to long-term use of anti-inflammatory drugs (Dixon et al. 2006).

Outcome of the (untreated) target disease: Destruction of joint capsules, tendons and ligaments lead to deformed joints that have restricted range of motion. Extra-articular manifestations of RA may affect major organ systems.

Adverse pregnancy outcomes: RA has consistently been associated with increased risks of adverse pregnancy outcomes compared with the general population, especially preterm birth, cesarean sections and delivery of children small for gestational age. A study in the US (2003- 2011) reported that women diagnosed with RA had higher rates of obstetric complications than did the control group. The rates of adverse pregnancy outcomes compared to matched control reported were premature rupture of membranes

(PROM) (5.4% vs 3.4%), antepartum hemorrhage (3% vs 2%), preterm delivery (10.2% vs 6.6%), and cesarean section (35% vs 28%) (Kishore et al. 2019). The rates of adverse pregnancy outcomes in RA women compared to matched cohort in a study from Canada (2004-2013) were gestational hypertension (4.12% vs 3.25%), pre-eclampsia (6.8% vs 4.1%), PROM (16.28% vs 9.9%), postpartum hemorrhage (3.11% vs 2.9%), small for gestational age (4.6% vs 2.1%), congenital anomalies (1.02% vs <1%), intrauterine fetal deaths (<1% vs <1%) and preterm births (12.2% vs 7.2%) (Aljary et al. 2020).

- Important co-morbidities:

As RA is associated with inflammation and changes of immunity, various co-morbidities may be present. Several organ systems may be affected, such as the skin (vasculitis, rheumatoid nodules), eye (episcleritis), pulmonary (interstitial pneumonia), neurological, musculoskeletal (e.g., osteoporosis) and hematological (anemia) (Wasko et al. 2004, Robbins et al. 2005). Occurrence of CV disease, malignant events, and infections are especially important.

RA patients have an increased risk of 30%-60% for CV disease (Watson et al. 2003), elevated relative risk (RR) of 1.76-2.00 for MI (Turesson et al. 2004; Solomon et al. 2003), elevated risk of 1.41 (95% CI 1.31-1.51) for atrial fibrillation (Lindhardsen et al. 2012) and elevated RR of 1.32-1.48 for stroke (Solomon et al. 2003 ; Solomon et al. 2006; Watson et al. 2003; Lindhardsen et al. 2012).

RA patients remain at increased risk for overall malignancy with standardized incidence ratios (SIR) of 1.20, having a higher risk of lymphoma (SIR 2.60), lung cancer (SIR 1.66), and non-melanoma skin cancer (NMSC) (SIR 1.72-1.83) (Smitten et al. 2008b; Simon et al. 2014; Mercer et al. 2012). The risk of lymphoma is directly related to the degree and duration of inflammation in RA (Baecklund et al. 2006). Increased RR were reported for RA patients on TNF inhibitors: RR 1.37-2.02 - for NMSC (Lopez-Olivo et al. 2012, Askling et al. 2011), 1.08 - for skin cancer, 2.14 - for lymphoma, and 1.13 for solid tumors (Lopez-Olivo et al. 2012).

Patients with advanced RA are at a higher risk of infection than the general population, largely because of altered immunological function, other disease-related factors such as decreased mobility, and therapies used to treat the underlying disease (steroids, immunomodulating agents). Compared to non-RA group, the hazard ratio (HR) was 1.70 for incident objectively confirmed infection (Doran et al. 2002). Treatment with anti-TNF-α agents appears to increase the risk of infection, especially during the initial phase of therapy Curtis et al. (2007) and Askling et al (2007).

SI.2 GRANULOMATOSIS WITH POLYANGIITIS AND MICROSCOPIC POLYANGIITIS

- Incidence:

Adult Patients

The overall incidence rate of Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis (AAV) in Europe is between 13 and 20 per million population per year. The incidence rate of Granulomatosis with Polyangiitis (GPA) in the European Union (EU) ranges from 0.7 to 11.9 per million population and the incidence rate of Microscopic Polyangiitis (MPA) in the EU ranges from 0.5 to 13.4 per million population (Watts et al. 2015). The incidence rate of GPA in the UK has been calculated to be 11.8 (95% CI: 10.7, 12.9) per million person-years, as assessed in a study using 462 cases diagnosed between 1997 and 2013 (Pearce 2017).

There are geographic differences in the incidence of GPA/MPA in Europe with GPA being more common in Northern Europe and MPA being more common in Southern Europe (Ntatsaki 2010, Watts, 2001). There are also age differences in Europe with GPA being most prevalent in younger patients (i.e. <65 years old) than in older patients in Southern Greece (Panagiotakis et al. 2009). A study from a mixed-ethnicity population from the UK indicates that the incidence rates of GPA and MPA were 8.2 per million (95% CI: 5.8, 11.3) and 13.4 per million (95% CI: 10.3, 17.2), respectively (Pearce et al. 2016), and that across all types of AAV there were no statistically significant racial/ethnic differences (incidence rate ratio 0.7, 95% CI: 0.3, 1.5, p=0.3).

Pediatric Patients

Among the population aged <18 years, there is limited data on the incidence of GPA and MPA.

The mean incidence of GPA in this population was 1.2 per million (Watts et al. 2012), study period: 1988-2010 and study period 1996-1999 in the UK (Gardner-Medwin et.al. 2002). The annual incidence in Poland and Sweden was 1.0 (2004-2010) and 1.4 (2004-2014) per million respectively (Kanecki et al. 2014, Mossberg et al. 2018). The mean incidence of MPA across age group <18 years was 1.0 per million (Watts et al. 2012) in the UK (study period: 1988-2010), while the annual incidence in Sweden was 1.4 (Mossberg et al. 2018) per million (study period: 2004-2014). Seven publications on the pediatric population (five were from Europe) from 2000-2018 were identified (search terms in Embase.com database included were: ‘MPA’, ‘wegener granulomatosis’ and ‘ANCA associated vasculitis’) which estimated the combined annual incidence (proportion) of GPA and MPA, ranging from 0.9 to 1.4 cases per million and a prevalence (2013) of 4.2 per million.
The evidences suggest that GPA and MPA are extremely rare in the population <18 years. No information on mortality and risk factors were available from epidemiological studies. Since very few cases were identified in the studies, extrapolation of incidence and prevalence could have led to risk of bias and discrepancy

resulting from use of different statistical methodologies hence need to be interpreted with caution.

- Prevalence:

Adult and Pediatric Patients:

The prevalence of GPA ranges from a low of 23.7 per million population in Paris (Mahr 2004) to a high of 160 per million population in Sweden (Mohammad 2007), with intermediate prevalence rates reported in north Germany (Herlyn 2014), Norway (Koldingsnes 2000), and Turkey (Pamuk 2016). The point prevalence of GPA in Turkey was higher in men (50.9/1,000,000, 95 % CI 26–75.8) than in women (32.7/1,000,000, 95 % CI 12.4–53; Pamuk 2016). A recent study reports that in 2013 the prevalence of GPA in the UK was 134.9 (95% CI: 121.3, 149.6) with statistically significant lower prevalence in women than men (OR = 0.79, 95% CI: 0.64, 0.97, p = 0.027) and in black/minority ethnic than White populations (OR = 0.57, 95% CI: 0.39, 0.84, p = 0.002).

The prevalence of MPA ranges from 9 to 94 per million population in the UK (Watts et al. 2012), Paris (Mahr 2004), Germany (Reinhold-Keller et al. 2000, Herlyn 2014), and Sweden (Mohammad 2007). The point prevalence of MPA in Turkey was higher in women (29.4/1,000,000, 95 % CI 10.2–48.6) than in men (9.5/1,000,000, 95 % CI 0–20.3; (Pamuk 2016).

- Demographics:

Mean age onset for GPA is 50 years, for MPA 60 – 70 years, (Koldingsnes et al. 2008). In pediatric patients, incidence of GPA and MPA is low (see information on reported incidence above) and hence, prevalence is expected to be significantly lower than in adults.

- Main existing treatment options:

Treatment strategies for patients with GPA or MPA generally follow the recommendations provided by the European Alliance of Associations for Rheumatology (Hellmich et al. 2023).

The EULAR 2022 recommendations for the management of ANCA-associated vasculitis recommend that induction of remission therapy for newly diagnosed organ- or life-threatening disease or a major relapse typically consists of high-dose glucocorticoids combined with either rituximab or cyclophosphamide in order to rapidly reduce inflammation, induce disease remission, and prevent permanent organ damage.
In relapsing disease, rituximab is preferred. For induction of remission of non-organ-threatening or non-life-threatening GPA or MPA, treatment with a combination of glucocorticoids and rituximab is recommended. Methotrexate or mycophenolate mofetil can be considered as alternatives to rituximab.

For maintenance of remission of GPA and MPA, after induction of remission with either rituximab or cyclophosphamide, EULAR guidelines recommend treatment with rituximab.

Azathioprine or methotrexate may be considered as alternatives. This recommendation was changed towards favoring rituximab in the 2022 update, in view of consistent results from two high-quality randomized controlled trials confirming a higher efficacy of rituximab compared with azathioprine and other recent prospective trials on the use of rituximab for maintenance of remission. Therapy to maintain remission for GPA and MPA is recommended to be continued for 24–48 months following induction of remission of new-onset disease. Longer duration of therapy should be considered in relapsing patients or those with an increased risk of relapse, but should be balanced against patient preferences and risks of continuing immunosuppression (Hellmich et al. 2023).

- Risk factors for the disease

GPA and MPA are two types of ANCA-associated vasculitides. Infectious, genetic, and environmental risk factors (and combinations of all three) have been described as being involved in either creating the environment for inducing ANCA production or inducing ANCA themselves (De lind Van Wijngaarden RA et al. 2008).

No epidemiology studies were identified describing the mortality and risk factors associated with GPA and MPA in pediatric patients. However, increased silica exposure has been observed to increase GPA/MPA cases, though exact association could not be established.

- Natural history of the indicated condition in the untreated population:

Mortality: SMR is 2.6 – 4.8 (Flossman et al. 2011). The increased mortality risk is persisting over time, HRs are 1.68 – 4.4 (Luqmani et al. 2011). An analysis by the European Vasculitis Study Group (EUVAS) of ANCA-AAV patients enrolled in four trials reported a SMR of 2.6 (95% CI: 2.2; 3.1) when compared to age- and sex-matched general population controls. The most common causes of death within the first year were infection (48%) and active vasculitis (19%). After the first year, the major causes of death were CV disease (26%), malignancy (22%), and infection (20%) (Flossman et al. 2011).

The increased mortality in GPA patients has also been shown to be elevated and to persist over time in a UK study with HRs of 1.68 (95% CI: 1.08; 2.60), 2.41 (95% CI: 1.43; 4.07), and 4.4 (95% CI: 2.0; 9.8) at 1 – 5 years, 5 – 10 years, and 10 – 15 years, respectively. Microscopic polyangiitis (MPA), disease activity, sepsis, and CV disease are the primary causes of death, with malignancy being an additional late cause (Luqmani et al. 2011).

In GPA, the early causes of death are sepsis, disease activity and acute renal failure; the late causes include all listed above plus malignancy being an additional contributing cause (Philip et al. 2008).

In MPA, the primary causes of death are disease activity, sepsis, and CV disease, and malignancy is an additional late cause (Philip et al. 2008).

Outcome of the (untreated) target disease:

If untreated, GPA and MPA progress from limited disease processes (e.g., inflammation centered on the upper respiratory tract or lung) to a generalized phase characterized by multiple complications of small-vessel vasculitis (e.g., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar hemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis) (Walton 1958; Fienberg 1981; Hoffman et al. 1992; Guillevin and Lhote 1995; Reinhold-Keller et al. 2000). End stage renal disease occurs in about 20% of patients with GPA/MPA (Koldingsnes et al. 2002, Jayne D. 2000). The prognosis for untreated GPA is poor, with a low likelihood of survival (Walton 1958).

Adverse pregnancy outcomes: Pregnancy outcomes of patients with vasculitis, especially small vessel vasculitis (GPA, MPA), are unknown because of the relative rarity of pregnancies among these patients. A retrospective survey in the US reported 496 pregnancies before and 74 pregnancies after the diagnosis of vasculitis. The rate of pregnancy loss (including miscarriages and stillbirths) was higher among women who conceived after a diagnosis of vasculitis compared to those who conceived prior to diagnosis (33.8% vs 22.4%). The rate of preterm births increased significantly for pregnancies conceived after a diagnosis of vasculitis relative to those conceived before diagnosis (23.3% vs 11.4%). Only 18% of women reported worsening of vasculitis during pregnancy, but those who experienced increased vasculitis activity were more likely to deliver preterm (Clowse et al. 2013).

- Important co-morbidities:

Major categories of comorbidities are CV disease, malignancies, and infections (Kallennberg CG. 2014).

In patients with AAV, the risk of coronary heart disease is 2-4 times higher, and stroke is also more frequent compare to the general population (Faurschou et al. 2009 , Morgan et al. 2009). Within 5-years of diagnosis of GPA or MPA, 14% of patients will suffer from a CV event (Suppiah et al. 2011).

Patients with GPA or MPA are at higher risk of overall malignancy compared to the general population (SIR 1.6-6.02) (Faurschou et al. 2008). This increased risk of overall malignancy in GPA/MPA patients is mainly driven by the increased risk of bladder cancer, Leukemia, NMSC and lymphoma (Pankhurst et al. 2004; Knight et al. 2002; Stone et al. 2006).

Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents. Infection is implicated in death in up to 48% of cases short-term (within 6 months) and long-term (≥5 years survival) (Flossman et al. 2011; Luqmani et al. 2011; Phillip et al. 2008).

SI.3 PEMPHIGUS VULGARIS

- Incidence and Prevalence:

Pemphigus Vulgaris (PV) is the most common form of pemphigus and comprises around 80% of cases (range 70-90%) in both Europe and US (Baican et al. 2010; Woldegiorgis and Swerlick 2001; Micali et al. 1998; Simon et al. 1980). The condition is rare with a

prevalence of approximately 1 in 2,630. Regardless of the patient's geographic location, pemphigus patients present with the same clinical, histological, immunological, and disease course characteristics. Men and women are equally affected, although there may be a slight female predominance.

Seven epidemiological studies have assessed the incidence of PV in Europe. One retrospective study of patients in the northern region of Greece from 1985 to 2004 identified an average annual incidence of 8 new patients per year (Michailidou et al. 2007). Two studies in Germany found that PV was rare, with one prospective study reporting only one case in 17 months yielding an incidence of 0.5 new cases per million population per year (Bertram et al. 2009) and another retrospective study reporting 14 patients with PV between 1989 and 1997 yielding an overall crude incidence of 0.98 (95% CI: 0.02; 5.54) cases per million population per year (Hahn-Ristic 2002). A more recent analysis of German insurance claims data of 9.5 million individuals representing 12% of the population of Germany identified 7,699 patients with an ICD10 code (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification) for PV (L10.0), yielding an estimated prevalence of 94.82 per million population (Hubner et al. 2016), with a higher prevalence observed in women (108 per million population) than in men (81 per million population). A prospective study of patients with AI blistering diseases in Northwest Romania between 2001 and 2007 identified 55 patients with PV over the course of the study (Baican A et al. 2010). A 13.5 year retrospective chart review from 1982 to 1996 in Italy observed 85 PV cases yielding an incidence rate of 0.25 per 100,000 inhabitants per year, and a prevalence rate of 3.38 per 100,000 inhabitants (Micali et al. 1998). A ten year retrospective historical cohort study of the general population in the UK from 1996 to 2006 identified 138 patients with PV yielding a crude incidence of PV of 0.68 (0.58 to 0.80) per 100,000 person years (Langan et al. 2008). In summary, seven studies conducted in five European countries indicate that PV is a rare disease with a low incidence. Orphanet (a reference portal for information on rare diseases and orphan drugs) has estimated the PV prevalence to be approximately 1/2,630 (Orphanet, Accessed on 21 Feb 2017).

There is very limited information on the incidence and prevalence of PV in the United States of America (USA) with only 2 small studies identified in the literature search through May 2017. In Hartford County, Connecticut, 12 cases of pemphigus were identified during 1972-1977, yielding an estimated crude average annual incidence of 4.2 (95% CI: 2.2 to 7.3) new cases of pemphigus per million population (around 92% of these cases were PV) (Simon D.G et al. 1980). In Olmsted County, Minnesota, 6 cases of PV were identified during 1950-2000, yielding an estimated incidence of 3.5 (95% CI: 1.5 to 5.4) new pemphigus cases per million population (Alhashimi et al. 2005).

Globally, published incidence estimates in general populations range from around <1 to 6.8 new cases per million population per year (Simon D.G et al. 1980, Alhashimi et al. 2005, Hahn-Ristic, K. et al. 2002, Langan S. et al. 2008); with higher rates reported in some settings (eg, 27 per million in Ashkenazi Jews in Israel (Pisanti, S. et al. 1974).

- Demographics:

The onset of PV generally occurs in middle age, affects men and women equally, and occurs less commonly in children. PV occurs in all races, although there seems to be a genetic predisposition link to Human Leukocyte Antigen (HLA) Class II alleles, and the disease is thus more common in people of Eastern European Jewish and Mediterranean descent (Hertl et al. 2006, Feldman and Ahmed 2011).

- Main existing treatment options:

Despite the serious nature of PV and the potentially fatal prognosis if untreated, before rituximab became available as approved treatment option, only corticosteroids had regulatory approval in the EU and US. The lack of data from large, high-quality prospective trials comparing different therapeutic options for PV, in addition to variability in study protocols, outcome measures and results, had made it difficult to make definitive conclusions on the best approach to PV treatment (Gregoriou et al. 2015), and there are well-known side effects associated with high dose, chronic corticosteroid use that can result in morbidity involving multiple organ systems, and in some cases, mortality.

The main objective in the treatment of PV is to control the disease, achieve complete remission, and prevent relapses, while minimizing treatment-related adverse effects.

The AI blistering diseases Task Force of the European Academy of Dermatology and Venereology (EADV) has published recommendations for the management of patients with pemphigus (Joly et al. 2020). The guideline recommends the following first-line therapies of moderate and severe pemphigus: rituximab (2 infusions of 1 gm two weeks apart) in combination with systemic corticosteroids, or systemic corticosteroid alone or in combination with an immunosuppressive drug as corticosteroid-sparing agent (if rituximab is not available or contra-indicated). After the initial cycle of rituximab, maintenance treatment with rituximab is recommended, and the rituximab dosing and timing of dosing depends on patient characteristics (initial disease severity, rate of anti-desmoglein (DSG) antibodies, patients with or without complete remission off therapy). The EADV guideline also include rituximab as first-line treatment option for mild PV.

Recommendations of an international panel of experts on diagnosis and management of pemphigus are also available (Murrell et al. 2020), and include intravenous (IV) CD20 inhibitors and specifically rituximab as a first-line therapy option for moderate to severe pemphigus.

- Risk factors for disease:

PV has a complex etiology involving interplay of genetic as well as environmental factors, most of which remain unknown. Several human leukocyte antigen (HLA) alleles have been identified as risk factors for the disease (Firooz et al. 1994, Animesh et al. 2011). Environmental factors such as viral infections, certain food compounds and drugs, pesticide, and ionizing radiation have been suggested.

Environmental factors such as drug intake, viral infections, physical agents, contact allergens and diet, as well as endogenous factors (e.g. emotional stress, hormonal disorders) have been described to act as inducing or triggering factors (IPPF website).

- Natural history of the indicated condition in the untreated population:

Mortality: A life-table analysis was conducted to estimate the 5-year prevalence of PV in the US and predicted mortality using data from a larger, more contemporary study carried out using UK electronic medical records that reported age- and sex-specific incidence rates for PV during 1996-2006 (overall crude incidence was 6.8 [95% CI: 5.8, 8.0] per million population per year) (Langan et al. 2008). It is reasonable to use this UK data for the US life-table analysis because the overall incidence rate, frequency of HLA class II antigen alleles, and prevalence of ethnicities at potentially higher risk of PV (e.g., Asian, Ashkenazi Jewish) are likely comparable between the UK and US. Because there were no studies identified that reported mortality rates in US patients with PV, the life-table analysis used the Kaplan-Meier survival estimates reported in the UK study (e.g., 65% survival after 5 years) (Langan et al. 2008) and applied these and the age- and sex-specific incidence rates to the 2017 US census population (2012 National Projections, Middle Series [United States Census Bureau]). These results indicate that in 2017, 137 individuals with PV in the US are predicted to die, leaving a predicted 1,800 surviving incident cases.

Adverse pregnancy outcomes: The occurrence of PV during pregnancy is rare and evidence is limited to case series and single case reports (Daneshpazhooh et al. 2011). In a study, a retrospective search of Medline was conducted for case reports and series on PV during pregnancy. A total of 38 reports that described 49 pregnancies complicated with PV were identified. Exacerbation of PV was reported in 11 (22%) of the 49 cases and stillbirths were recorded in 5 (10%) patients. Of the 44 live births, 20 (45%) neonates had PV lesions at birth and 24 (55%) were lesion-free (Kardos et al. 2009). A similar study in Iran identified 52 pregnancies in 48 women with pemphigus (including 41 women with PV) between 1984 and 2006. Exacerbation of pemphigus was reported in 28 cases (58%), abortion in 5 cases (9.6%) and postpartum flare in 23 cases (44%) (Daneshpazhooh et al. 2011).

- Important comorbidities:

PV is associated with corticosteroid-related comorbidities such as infections, Cushing syndrome (hypercortisolism), adrenal insufficiency and osteoporosis (Hsu et al. 2016). PV has also been correlated with other AI diseases, such as AI thyroid diseases (Graves

disease and Hashimoto thyroiditis), RA and type 1 diabetes mellitus (Leshem et.al 2011, Parameswaran et al 2015).

SI.4 NON-HODGKIN'S LYMPHOMA

Adult Patients

- Incidence:

  The non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of malignancies arising from lymphoid tissue. The most common types of NHL are diffuse large B-cell lymphoma (DLBCL), which accounts for 30–40% of lymphomas in western countries, and follicular lymphoma (FL), which accounts for approximately 20 – 30% (Jaffe et al. 2001). The incidence rate of NHL increased in the Western world between 1970 and 1990, but has stabilized since the late 1990s. The annual percentage increase in incidence rate in the US was 3.7% between 1975 and 1991 and 0.5% in the period 2002 – 2011 (Howlader et al. 2014). Recent review of cancer statistics in the US showed an annual percentage change in observed incidence rate of -2.1 between 2009 and 2013 (Howlader et al. 2016) See Figure 1 (worldwide) and Figure 2 (Europe) below for age-adjusted incidence rates for NHL.

Figure 1 (a) Age-Standardized Incidence Rates (ASR) of NHL per 100,000 population, Worldwide. Figure prepared by Cancer Research UK, original data source (Ferlay et al. 2010)

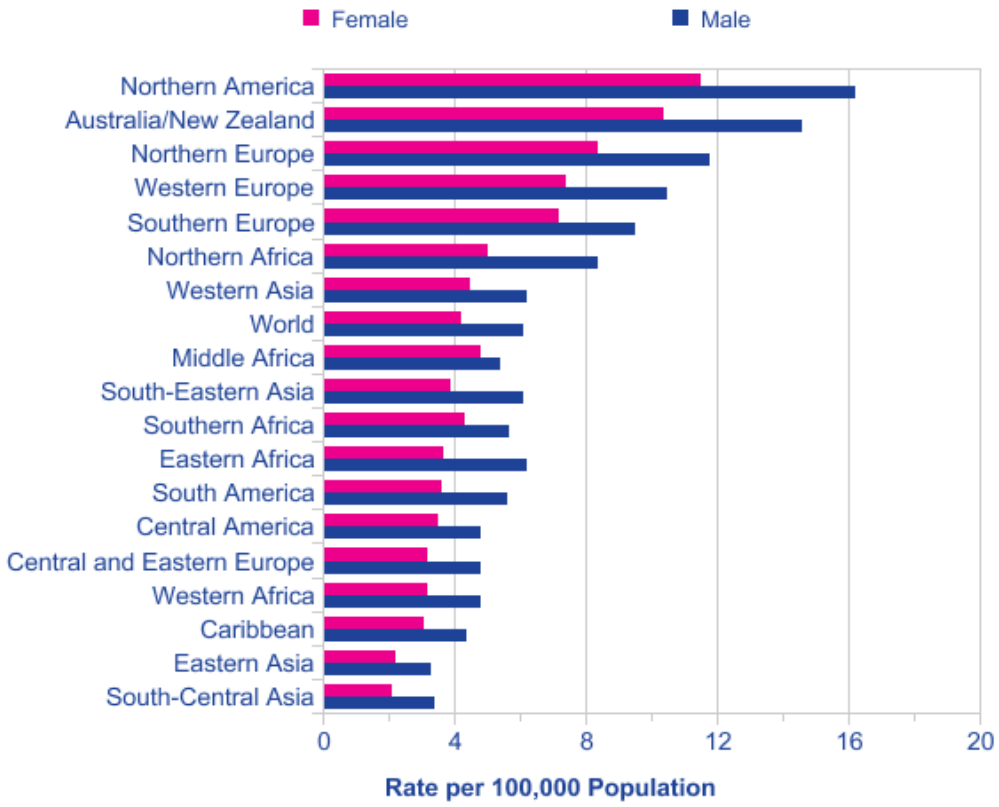
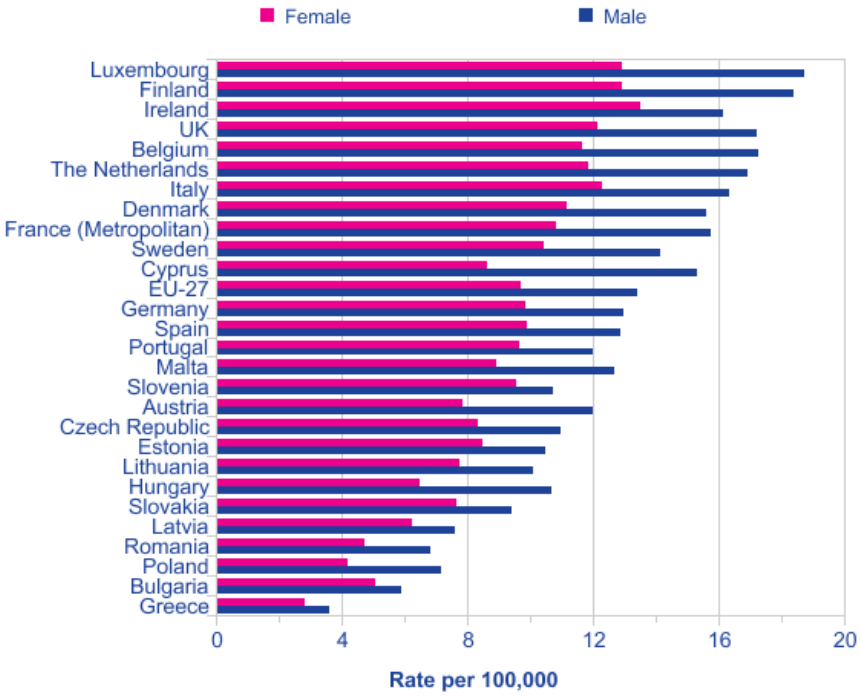


Figure 2 European Age-Standardized Incidence Rates of NHL per 100,000 population in EU-27 countries. Figure prepared by Cancer Research UK, original data source (Ferlay et al 2010)



It is estimated that worldwide there were around 386,000 new cases of NHL in 2012 of which 79,000 new cases were in the European Union (EU-28) (Ferlay et al. 2013).

Pediatric Patients:

Non-Hodgkin lymphoma is the fourth most common malignancy in childhood and adolescence. Mature B-cell lymphoma (B-NHL) accounts for approximately 60% of all cases of childhood NHL, of which the majority are a high-grade. Within this group of pediatric B-NHL, the main histological subtypes are BL, B-AL – analogous to acute mature B-cell French-American-British (FAB) L3 leukemia, DLBCL, primary mediastinal large B-cell lymphoma (PMLBL) and aggressive mature B-NHL, not further classifiable (Worch et al. 2013). Compared to adults, the incidence of NHL in childhood and adolescence is low. The incidence rates of pediatric B-NHL in the U.S. by age group is provided in Table 2.

Table 2 Incidence Rates of Newly Diagnosed B-NHL Pediatric Patients in the United States

Age cohorts (years)	Incidence per million	No. of new cases per year in US[a]
< 1	1.59	4
1–4	7.34	81
5-9	11.75	168
10–14	14.21	205
15–19	18.65	275

B-NHL = B-cell non-Hodgkin lymphoma; SEER = Surveillance, Epidemiology, and End Results; US = United States.

Source: SEER database (National Cancer Institute)

[a] Incidence estimates generated using data reported to SEER during 2010-2014

- Prevalence:

  Adult Patients:

  On 1 January 2009, there were approximately 530,919 men and women alive in the US who had a history of NHL – 278,836 men and 252,083 women. This includes any person alive on 1 January 2009 who had been diagnosed with NHL at any point prior to 1 January 2009, and includes persons with active disease and those who are cured of their disease (Howlader et al. 2014).

  Pediatric Patients:

  Pediatric B-NHL represents the fourth most common malignancy in children, has an even higher incidence in adolescents, and is primarily represented by only a few histologic subtypes. B-NHL can occur at any age but it is rare in children younger than 3 years of age (Minard-Colin et al. 2015).

- Demographics:

  Adult Patients:

  The incidence of NHL rises exponentially with age and the median age at diagnosis is 66 years (Howlader et al. 2014). NHL is more frequent in males than females in all age groups and is more common in developed countries (see Figure 1 and Figure 2 above).

  Pediatric Patients:

  Burkitt lymphoma (BL) and Burkitt Leukemia (B-AL) account for 80% of pediatric mature B-NHL. The disease is diagnosed at a median age of 9 years with a predominance in boys (>4:1). Diffuse large B-cell lymphoma accounts for 10-20% of pediatric B-NHL and occurs more frequently in adolescents, with a median age of 11-12 years and a moderate sex ratio towards males (1.7:1). Primary mediastinal large B-cell lymphoma accounts for 2% of B-NHL, typically occurs in older teenagers and affects more females than males (Worch et al. 2013, Minard-Colin et al. 2015, Giulino-Roth 2018).

Main existing treatment options:

- Treatment for NHL in adults ranges from a watch-and-wait approach to aggressive therapy. Radiotherapy is the mainstay of treatment for patients with stage I/II disease, and in a subset of these patients, this may even be curative. Systemic chemoimmunotherapy is indicated for patients with advanced disease who are symptomatic or have adverse prognostic factors and consists of rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine or CVP (cyclophosphamide, vincristine and prednisone), as well as an anthracycline-based regimen in case of (histological or clinical) characteristics of transformation to aggressive lymphoma. Rituximab for 2 years is recommended for maintenance/consolidation. Autologous stem-cell transplantation could be an option for selected cases of relapsing/ progressing disease (Dreyling et al. 2014; Ghielmini et al. 2013)
- For pediatric patients with mature B-NHL, intensive, systemic multi-agent chemotherapy is the cornerstone of therapy. Effective therapy includes the use of intense short courses of non-cross resistant chemotherapy agents, with the specific regimen defined by the patient risk group allocation (limited, intermediate and advanced stages of disease) and including essential CNS prophylaxis. Two highly effective treatment strategies have been established: The French Lymphome Malin B (LMB) protocol and the German, Austrian, Swiss Berlin-Frankfurt-Münster (BFM) protocol (Worch et al. 2013, Minard-Colin et al. 2015, Egan et al. 2019).
- Risk factors for the disease

  Risk factors for NHL include old age, infection with Epstein-Barr virus as an adult, exposure to mutagenic chemicals, radiation exposure and immunodeficiency, among others (Muller et al. 2005). For NHLs in general, severe immunodeficiency is the strongest known risk factor (Morton et al. 2008). FL does not have a distinct risk factor profile or major risk factors; however, a number of potential risk factors may increase the risk for this disease (Morton et al. 2008). Age, gender and ethnicity may also affect a person's likelihood of developing FL (Ma S 2012).

  Environmental risk factors include certain chemicals such as pesticides (Ma S 2012, Roulland et al. 2004). In addition, lifestyle factors such as dietary habits (Ambinder AJ, 2012), smoking (Morton et al. 2005), and alcohol consumption (Casey et al. 2007) are all associated with an increase in FL risk (Ma S 2012). Furthermore, an association between increased body mass index (BMI) and risk of FL has been discussed in a number of studies, albeit with no significant results (Ma S 2012).

  There is also increasing evidence that molecular risk factors may contribute to the risk of FL (Ma S 2012). For example: approximately 85% of patients with FL have a genomic translocation t(14;18) (q32;q21) involving the BCL-2 gene on chromosome 18 being translocated to chromosome 14 directly adjacent to the immunoglobulin heavy chain (IgH). This results in the overproduction of the BCL-2 protein, that prevents cells from undergoing apoptosis (Godon A et al. 2003). However, although overexpression of BCL2 protein is detected in 90% of cases using

immunohistochemistry, it is far from being specific for FL (Macintyre E et al. 2000, Skinnider BF et al. 1999).

- Natural history of the indicated condition in the untreated population:
  Mortality: There were an estimated 199,630 deaths worldwide, and 30,700 deaths in Europe (EU-28) from NHL in 2012 (Ferlay et al. 2013). In the US in 2014, there was expected to be an estimated 18,990 deaths from NHL (Howlader et al. 2014). For NHL patients diagnosed between 2004 and 2010 in the US, the 5-year relative survival for patients was 66.9% (Howlader et al. 2014). In Europe, the 5-year relative survival of NHL patients was 54.6% in the period 2000 – 2002 (Verdecchia et al. 2007). Survival rates of NHL patients differ between NHL subtypes. In Europe, the 5-year relative survival of FL patients in the period 2000 – 2002 was 72.8%, and 49.3% for DLBCL. In the US, the 5-year relative survival of FL patients diagnosed between 2004 and 2010 was 86.1% and 60.4% for DLBCL patients (Howlader et al. 2014).

  Outcome of the (untreated) target disease: Patients with FL are generally considered incurable, whereas between 30 and 60% of patients with DLBCL achieve long-term remission or cure.

  Adverse pregnancy outcomes: Lymphoma is the third most common malignancy occurring during pregnancy, with a reported frequency of 1 case per 6000 pregnancies in Western countries (Onishi et al. 2022). A population-based cohort study in the Healthcare Cost and Utilization Project – Nationwide Inpatient Sample from 2003 to 2011 in Canada reported that the overall incidence of pregnancy-associated NHL was 5.39 per 100,000 births. Maternal and fetal adverse outcomes were reported to be significantly higher in pregnant NHL women compared to control pregnant women (without NHL) that included pre-eclampsia (6.32% vs 3.90%), cesarean section (39.81% vs 30.83%), preterm birth (17.10% vs 7.27%), postpartum blood transfusion (15.69% vs 5.98%), and infectious morbidities (1.17% vs 0.43%). After adjusting for baseline characteristics, pregnant women with NHL were more likely to have preeclampsia, odds ratio (OR) 1.57 (95% confidence interval [CI] 1.06–2.32), cesarean section, OR 1.37 (95% CI 1.13–1.67), preterm births OR 2.50 (95% CI 1.94–3.22), postpartum blood transfusions, OR 2.73 (95% CI 2.10–3.55), and infectious morbidity, OR 2.81 (95% CI 1.16–6.79). Maternal (0.70% vs 0.01%) and fetal (1.17% vs 0.42%) mortality rates were significantly increased among pregnant women with NHL compared to pregnant women without NHL (El-Messidi et al. 2015). A retrospective study of clinically gathered data on 22 pregnant NHL women in Japan showed that the 5-year overall survival was 63%. Among the 28 patients (22 NHL and 6 HL), 26 gave birth, one experienced intrauterine fetal death (IUFD) at 30 weeks of gestation, and one experienced spontaneous abortion early in the first trimester. The incidence of spontaneous abortion, IUFD, and preterm birth was similar between the 13 patients who received chemotherapy during pregnancy and the 15 patients who did not (spontaneous abortion; 0% (0/13) vs. 7% (1/15), IUFD; 0% (0/13) vs. 7% (1/15), preterm birth; 54% (7/13) vs. 53% (8/15)) (Onishi et al. 2022). A study on 80 patients diagnosed with NHL during pregnancy in Belgium between 1986 and 2019, reported that 54

(68%) pregnant patients received chemotherapy, including rituximab. Four early pregnancies were terminated. Among 76 ongoing pregnancies, there was one stillbirth (1·3%). Overall, there was a high incidence of small for gestational age (39%), preterm delivery (52%), obstetric (41%) and neonatal complications (12·5%) (Maggen et al. 2021).

- Important co-morbidities:

  As a disease presenting in older adults, NHL is frequently associated with co-morbidities, which can often be a therapeutically limiting problem in older cancer patients.

  In a population-based study conducted in the Netherlands in 904 patients with newly diagnosed NHL, 40% had at least one comorbid condition at diagnosis. When analyzed by age group, 20% of patients younger than 60 years, 43% of patients aged 60–69 years, and 61% or more of patients over 70 years of age had at least one co-morbid condition at diagnosis (van Spronsen et al. 1999). The prevalence of comorbidity among patients with low-grade NHL was similar to that for intermediate/high-grade NHL.

  Some of the important comorbidities reported in the NHL population include CV disorders, hypertension, diabetes, chronic obstructive pulmonary disease, and secondary malignancies. Patients with severe cardiac or respiratory disease may be unable to tolerate rituximab-related infusion-related reactions (IRRs). Patients with renal, hepatic and/or cardiac disorders may be at increased risk of complications related to chemotherapy. Patients with pre-existing chronic or latent infections and/or patients who are already immunosuppressed as a result of co-morbid conditions or their treatment (such as patients requiring treatment with corticosteroids) may be at increased risk of infections associated with combined chemo-immunotherapy.

SI.5 CHRONIC LYMPHOCYTIC LEUKEMIA

- Incidence:

  The World Health Organization classification scheme considers B-cell chronic lymphocytic Leukemia (CLL) and small lymphocytic lymphoma (SLL) in an aggregate category (CLL/SLL), because of shared clinicopathological features. The incidence rate of CLL is approximately three times that of SLL (Dores et al. 2007). The HAEMACARE project estimates that the incidence rate of SLL/CLL was 4.92 per 100,000 in 2000 – 2002 (Sant et al. 2010). A total of 15,720 new cases of CLL were projected to occur in the US in 2014 (American Cancer Society. Cancer Facts & Figures 2014). Between 2007 and 2011, the US average annual age-adjusted incidence rate was 4.4 per 100,000 patient-years (age-adjusted to the 2000 US Standard Population); rates were higher in males than females (6.0 per 100,000 patient-years vs. 3.1 per 100,000 patient-years), and higher in white Americans than in African Americans (4.7 per 100,000 patient-years vs. 2.9 per 100,000 patient-years) (Howlader et al. 2014). The incidence of CLL per 100,000 population in the US was 0.0% under age 29; 0.1-1.9% between 30 and 49; 3.7 – 16.7% between 50 and 69; 20.0 – 36.9% above 70 years of age based on Surveillance Epidemiology

and End Results data, based on patients diagnosed between 2007 and 2011 (Howlader et al. 2014)

- Prevalence:

  The 1-, 5- and 10-year prevalence estimates of CLL within the EU with the additional inclusion of Norway, Iceland, and Lichtenstein in 2006 were 0.2 per 10,000, 0.9 per 10,000, and 2 per 10,000, respectively (Watson et al. 2008). The estimated prevalence of CLL in the EU in 2012 is 2.83 per 10,000. This latter estimate is based on applying a compound annual growth rate of 2.74% (i.e., the rate of increase observed from 2002 [2.16 per 10,000] to 2008 [2.54 per 10,000]) to the 2008 CLL prevalence estimate. The 2008 estimated CLL prevalence was calculated by applying the methods of Watson et al. (2008) to the most recent Leukemia International Agency for Research on Cancer (IARC) data (GLOBOCAN 2008) and data from the Scottish Cancer Registry. The 5-, 20- and 35-year prevalence estimates of CLL in the US were 58,140, 121,098, and 126,193 on 1 January 2011 (Howlader et al. 2014).

- Demographics:

  The incidence rate of CLL increases with age. Over the period 2005 to 2009, the median age at diagnosis of CLL was 72 years of age in the US; 0.2% between 20 and 34; 1.6% between 35 and 44; 9.0% between 45 and 54; 20.9% between 55 and 64; 26.5% between 65 and 74; 27.8% between 75 and 84; and 14.0% 85+ years of age (Howlader et al. 2014).

- Main existing treatment options:

  Available treatments generally induce remission, although nearly all patients relapse, and CLL remains an incurable disease, with the possible exception of the rare option of allogeneic stem cell transplantation, which due to its toxicity and intensity and the need for a donor is available only to a very small fraction of younger patients. None of the available treatment options is adequate for all CLL patients (Hallek et al. 2011).

  Current European Society for Medical Oncology (ESMO) guidelines for diagnosis, treatment, and follow-up of patients with CLL and SLL as well as National Comprehensive Cancer Network (NCCN) Guidelines list different treatment strategies for front-line therapy (Eichhorst et al. 2021, NCCN Guidelines v1 2020). In addition to chemotherapy/rituximab combination (FCR), continuous treatment with Bruton tyrosine kinase inhibitors such as ibrutinib until progression or time-limited therapy with chemotherapy/anti-CD20 antibodies (including rituximab) as well as the combination of venetoclax and obinutuzumab are recommended first-line therapies. Factors such as age/fitness of patients as well as mutational status (IGHV, TP53, del(17p)) are taken into consideration for choice of treatment.

- Risk factors for disease

  The aetiology of CLL is unclear; however, several risk factors associated with CLL have been identified. As well as age and gender (Gribben 2010, Catovsky et al. 1989), there is a familial risk with family members of patients with CLL having a two- to seven-fold higher risk of developing the disease (Shanshal et al. 2012). In

addition, exposure to certain agricultural chemicals may also increase the risk of developing CLL, and associations between CLL and several viruses (such as human T-cell lymphotrophic viruses I and II and Epstein-Barr virus) have been suggested, but no conclusive evidence of causal relationship exists (Lamanna et al. 2016).

Studies show that 4% of CLL patients over 40 years of age harbours a population of clonal B-cells with the phenotype of CLL or other B-cell malignancies. This asymptomatic condition is called monoclonal B-cell lymphocytosis (MBL) (Shanshal et al. 2012, Lamanna et al. 2016) and progression to Leukemia requiring CLL-directed therapy occurs in approximately 1% to 2% of MBL cases per year

- Natural history of the indicated condition in the untreated population:

  Mortality: In Europe (EU-28), there were approximately 41,459 deaths from Leukemia of all kinds in 2012 (Ferlay et al. 2013). It is estimated that 4,600 men and women will have died of CLL in 2012 in the US (American Cancer Society. *Cancer Facts & Figures 2014*). In the US, the age-adjusted death rate is 1.4 per 100,000 men and women per year. The age-adjusted death rate is higher for men (2.1 per 100,000 men) than for women (0.9 per 100,000 women (Howlader 2014).

  Outcome of the (untreated) target disease: Available treatments generally induce remission, although nearly all patients relapse, and CLL remains an incurable disease. In Europe, the 5-year relative survival of CLL and SLL patients in the period 2000−2002 was 69.1% (Marcos-Gragera et al. 2011).

  Adverse pregnancy outcomes: No epidemiological evidence was found describing the incidence of adverse pregnancy outcomes in CLL patients. The number of patients with CLL who become pregnant is extremely rare, since the median age for diagnosis is 72 years, only a few clinical cases have been reported. Managing CLL during pregnancy requires close cooperation between obstetricians and hematologists; due to the paucity of cases and the lack of specific guidelines (Murray et al. 2021).

- Important co-morbidities:

  CLL is a disease of older adults with a median age at diagnosis of 65-72 years. Comorbidity is a frequent and often therapeutically limiting problem in older cancer patients.

  In a study in unselected patients with CLL (Thurmes et al. 2008), nearly 90% had co-morbid conditions at the time of diagnosis and over 46% had at least one major comorbidity (cardiopulmonary or vascular disease, diabetes, or a second cancer other than non-melanomatous skin cancer). Other important reported comorbidities include cardiac disorders (e.g., cardiomyopathy, atrial fibrillation etc), respiratory disorders (e.g., chronic obstructive pulmonary disease), GI disorders (e.g., peptic ulcer, inflammatory bowel disease etc), and pulmonary embolism/deep vein thrombosis.

  Patients with severe CV or pulmonary diseases may be unable to tolerate rituximab-related IRRs. Patients with renal, hepatic and/or cardiac disorders may be at increased risk of complications related to chemotherapy. Patients with pre-existing

chronic or latent infections and/or patients who are already immunosuppressed as a result of co-morbid conditions or their treatment (such as patients requiring treatment with corticosteroids) may be at increased risk of infections associated with combined chemo-immunotherapy. In one retrospective study in patients with CLL, factors associated with risk of developing a major infection included a high serum creatinine concentration, as well as advanced disease stage, previous anti-neoplastic therapy, refractoriness to fludarabine-based therapy, high serum β2-microglobulin level, low serum albumin level and a low granulocyte count (Anaissie et al. 1998). In addition, patients with co-morbidities may be more likely to have an adverse outcome following a treatment-related complication. For example, in one study, the level of in-hospital mortality in CLL patients hospitalized for febrile neutropenia was found to be higher in patients with co-morbidities (21%) versus those without co-morbidities (9.5%) (Kuderer et al. 2006).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 TOXICITY

SII.1.1 Single- and repeat-dose toxicity studies

In single- and repeat-dose IV toxicity studies, rituximab was non-toxic to monkeys at the various doses and schedules studied. In the GLP single dose toxicology study, rituximab was administered intravenously at a dose of 10-, 30-, or 100 mg/kg to one male and one female per dose group. There were no treatment-related effects on mortality, body weight, food consumption or body temperature. There was a transient and mild decrease in platelet count, a decrease in lymphocyte ratio, and an increase in neutrophil ratio for both sexes in the 30 and 100 mg/kg dose groups. All hematologic changes were mild, dose independent and returned to baseline by Day 7 or 14; therefore, they were not considered to be biologically significant. In the repeat-dose GLP toxicology study, animals were administered rituximab intravenously at doses of 0 or 20 mg/kg once weekly for 4 or 8 weeks. Animals were euthanized 2 weeks after their last dose. There were no treatment-related effects on mortality, body weight, food consumption, hematology parameters, clinical chemistry, or urinalysis parameters. A possible treatment-related clinical observation included vomiting approximately 15-20 minutes after drug administration in three of the treated female animals (once in 1 female treated for 4 weeks; occasionally in 2 females treated for 8 weeks). The toxicological significance of these events is difficult to interpret given the low incidence and the absence of similar events in treated males. All other effects were consistent with the expected pharmacologic activity of rituximab; decreased B cells by flow cytometry in peripheral blood, lymph nodes, and femoral bone marrow; small spleens in four of the treated animals; histopathologic lymphoid atrophy in the spleen, mandibular lymph nodes, and submucosal lymphoid nodules of the colon; and decreased B cells by immunohistochemistry in the mandibular lymph nodes and spleen.

Relevance to human usage: Yes

Discussion:

A decline of peripheral B-cell counts in human beings is associated with its pharmacological action.

SII.1.2 Toxicology studies

The in vivo toxicology program conducted in cynomolgus monkeys identified pharmacological effects that are consistent with the anticipated findings for a B cell depleting therapy and included decreases in B cells in peripheral blood and tissues (spleen, lymph nodes, bone marrow, and submucosal lymphoid nodules of the colon), lymphoid atrophy, and alterations in hematology related to decreased B-cells.

Relevance to human usage: Yes

Discussion:
Potential increased susceptibility to infection or an inadequate response to vaccination due to B-cell immunocompromisation.

SII.1.3 Reproductive toxicity

Rituximab was administered weekly to pregnant female monkeys during the period of organogenesis at doses of 20, 50, or 100 mg/kg. There were no findings of toxicity to the dams or developing fetuses. The only effect noted was the dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the fetuses. B-cell depletion following exposure *in utero*, which appeared to be reversible in infants once drug had cleared or fallen to non-effective levels.

Relevance to human usage: Yes

Discussion:
No toxicity expected apart from B cell depletion. Potential risk is that maternal exposure to rituximab may lead to B-cell depletion in the human fetus/infant, either from in utero exposure, or from exposure to rituximab in breast milk in nursing infants.

SII.1.4 Embryofetal toxicity

Potential risk of embryofetal toxicity resulting from systemic exposure to Recombinant Human PH20 (hyaluronidase)(rHuPH20) (rituximab subcutaneous [SC]).

Relevance to human usage: No

Discussion:
Potential risk of embryofetal toxicity based on a very conservative interpretation of pharmacokinetic (PK) and toxicology data in animal studies at very high systemic exposure levels (reductions in fetal weight and increased number of resorptions) but did not show overt dysmorphogenic (i.e., teratogenic) potential. These findings are consistent with current knowledge of the natural activity of hyaluronidase. Studies in knock-out mice have demonstrated the importance of hyaluronan in normal heart development.

No data in humans have been collected and potential seriousness and outcomes are unforeseeable at this point in time.

SII.2 GENERAL SAFETY PHARMACOLOGY

SII.2.1 Mechanisms for drug interactions

The elimination of rituximab is mediated by both the specific CD20 receptor−mediated pathway and the non-specific immunoglobulin G (IgG) clearance pathways. These data suggest that rituximab would not be expected to have many of the common mechanisms of drug−drug interactions with small molecules, including changes in protein binding, P450 activity, and transporters.

Relevance to human usage: No

Discussion:

Although no specific drug interaction studies have been performed, based on PK data from Phase II/III studies, cyclophosphamide, methotrexate, and corticosteroids seemed to have little or no effect on the pharmacokinetics of rituximab.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE.

Overview of Estimated Total Exposure Data

Table 3 Clinical Trial Exposure

Indication	Number of patients exposed to Rituximab in Company Pivotal Trials
Rheumatoid Arthritis	3,595[1]
Granulomatosis with Polyangiitis and Microscopic Polyangiitis	181[2]
Non-Hodgkin's Lymphoma *(intravenous and subcutaneous)*	3,474[3]
Chronic Lymphocytic Leukemia *(intravenous and subcutaneous)*	914[4]
Pemphigus vulgaris	38[5]

IV = Intravenous; SC = Subcutaneous

[1]Data cutoff: September 2012.

[2]Total Number includes RAVE, ML22514 and WA25615 study

[3]Total Number includes studies BP22333, BO22334, MO18264, U4391G, MO28107 MO28457 and BO25380 data cut off dates vary and details are provided under respective sections below.

[4]Total Number includes studies BO17072, ML17102, BO25341, data cut off dates vary and details are provided under respective sections below

[5]In study ML22196, patient disposition in Rituximab + Prednisone arm: N=46 - PV=38, pemphigus foliaceus (PF)=8

Exposure - Clinical Trials in Rheumatoid Arthritis

The latest and last cutoff date for the pooled safety analysis (All Exposure population[1]) that was used to generate the clinical data for RA presented in this Risk Management Plan (RMP) is November 2012. The individual trials have all been completed and no further updates from RA clinical trials will be generated.

A total of 3595 patients (refer to Table 3) had received up to 20 courses of rituximab over an 11-year observation period (providing 14,816 patient-years). Of these patients, 1,246 had follow-up >5 years (equating to 8,970 patient-years) and 1246 patients had

[1] The All Exposure population refers to all patients from the pooled clinical database including eleven Phase II and III Global clinical trials in RA.

received at least five courses of rituximab. The RA clinical trial exposure by duration and clinical trial exposure by infusion and course are presented in Table 4 and Table 5 , respectively.

Table 4 Clinical Trial Exposure by Duration (Rheumatoid Arthritis)

Treatment Course	Duration of Observation	Number (Cumulative Percentage)
All Courses	Sample	N = 3595[1]
	Duration ≤ 6 months	85 (2.4)
	6 months < Duration ≤ 12 months	144 (6.4)
	12 months < Duration ≤ 18 months	254 (13.4)
	18 months < Duration ≤ 24 months	369 (23.7)
	24 months < Duration ≤ 36 months	760 (44.8)
	36 months < Duration ≤ 48 months	381 (55.4)
	48 months < Duration ≤ 60 months	356 (65.3)
	60 months < Duration ≤ 72 months	475(78.6)
	72 months < Duration ≤ 84 months	263 (85.9)
	84 months < Duration ≤ 96 months	53 (87.3)
	96 months < Duration ≤ 108 months	180 (92.4)
	Duration > 108 months	275 (100.0)
	Total patient years of observation	14,816

Duration of observation = day of first exposure to rituximab to date of last contact. Date of last contact is the last available date of efficacy, complete medication start date, laboratory, adverse event assessments, early withdrawal visit, date of last contact or date of death. Note: includes placebo patients from point of first exposure to rituximab.

[1]Data cutoff: September 2012.

Table 5 Clinical Trial Exposure by Infusion and Course (Rheumatoid Arthritis)

Treatment Course	Number of Infusions	All Exposure (%) N=3595[1]
First Course	1 infusion 2 infusions	3595 (100.0%) 3523 (98.0%)
Second Course	1 infusion 2 infusions	2753 (76.6%) 2688 (74.8%)
Third Course	1 infusion 2 infusions	1745 (48.5%) 1720 (47.8%)
Fourth Course	1 infusion 2 infusions	1477 (41.1%) 1456 (40.5%)

Treatment Course	Number of Infusions	All Exposure (%) N=3595[1]
Fifth Course	1 infusion 2 infusions	1215 (33.8%) 1183 (32.9%)
Sixth Course	1 infusion 2 infusions	925 (25.7%) 908 (25.3%)
Seventh Course	1 infusion 2 infusions	732 (20.4%) 713 (19.8%)
Eighth Course	1 infusion 2 infusions	535 (14.9%) 527 (14.7%)
Ninth Course	1 infusion 2 infusions	355 (9.9%) 351 (9.8%)
Tenth Course	1 infusion 2 infusions	166 (4.6%) 161(4.5%)
Eleventh Course	1 infusion 2 infusions	52 (1.4%) 52 (1.4%)
Twelfth Course	1 infusion 2 infusions	37 (1.0%) 37 (1.0%)
Thirteenth Course	1 infusion 2 infusions	28 (0.8%) 28 (0.8%)
Fourteenth Course	1 infusion 2 infusions	28 (0.8%) 15 (0.4%)
Fifteenth Course	1 infusion 2 infusions	9 (0.3%) 9 (0.3%)
Sixteenth Course	1 infusion 2 infusions	5 (0.1%) 5 (0.1%)
Seventeenth Course	1 infusion 2 infusions	1 (0.0%) 1 (0.0%)
Eighteenth Course	1 infusion 2 infusions	1 (0.0%) 1 (0.0%)
Nineteenth Course	1 infusion 2 infusions	1 (0.0%) 1 (0.0%)
Twentieth Course	1 infusion 2 infusions	1 (0.0%) 1 (0.0%)
Total Cumulative Dose (mg) Mean		6403.6
Median		4000.0
Min-Max		40 - 40000

One infusion is part of or a whole infusion. Percentages are based on the number of patients in the all exposure population (ST8BGIa8 (19 November 2012). Summary of the Number of Patients Exposed to Rituximab at Any Dose (All Exposure Population)

Exposure – Clinical Trials in Granulomatosis with Polyangiitis and Microscopic Polyangiitis

RAVE Study

Data in this RMP are taken from the summary of clinical safety and Clinical Study Report (CSR) for the pivotal RAVE study. RAVE consisted of a 6-month remission induction phase followed by a 12-month remission maintenance phase (Months 6 to 18).

A total of 99 patients received at least one dose of rituximab during the 6-month remission induction phase. The majority of patients in both groups completed the first 6-month study period (93 of 99 [94%] and 91 of 98 [93%] in the rituximab and cyclophosphamide [CYC] groups, respectively). Safety information was summarized from randomization until the 6-month visit or the point of study discontinuation, whichever occurred earlier, to yield a total duration of follow-up of 47.6 patient-years in the rituximab group and 47.0 patient-years in the CYC group. A small proportion of patients crossed over to the opposite treatment or received different treatment according to best medical judgment or as a result of a deviation from study drug administration during the first 6-month study period. The follow-up time for those patients who stayed on their initial treatment was 41.9 (rituximab only) and 40.5 (CYC only) patient-years, respectively.

During the maintenance phase of the study, patients in RAVE were followed up to a common closeout (CCO) date, corresponding to the last patient's 18-month visit. During the maintenance phase, treatment changes were common; 123 patients completed 18 months on their randomized treatment (61 of 99 [62%] on rituximab and 62 of 98 [63%] on CYC).

In total, up to the 18-month visit, there were 140 patient-years of exposure with rituximab in the RAVE study.

Table 6 Clinical Trial Exposure by Duration (Granulomatosis with Polyangiitis/Microscopic Polyangiitis)

Duration of Observation	Number
Sample	99
Treated with rituximab	99
Duration $\leq$ 6 months	82*
6 months $<$ Duration $\leq$ 12 months	74*
12 months $<$ Duration $\leq$ 18 months	61*
Common closeout	16*

Source: RAVE Summary of Clinical Safety - patient disposition until common closeout of study.
*Completed as randomized.

Study ML22514

The following data are taken from the Summary of Clinical Safety and Clinical Overview. Study ML22514 was a therapeutic, prospective, Phase III, multi-center, comparative, randomized, open-label study comparing azathioprine versus rituximab, both in combination with low-dose corticosteroids, for the maintenance of remission in patients with ANCA-associated vasculitis. In this study eligible patients were randomized 1:1 to either rituximab or azathioprine; randomization was stratified by newly diagnosed or relapsing disease. Patients randomized to the rituximab arm received 500 mg IV rituximab at Day 1, Day 15, and Months 6, 12, and 18. Patients randomized to the azathioprine arm received an oral dose of 2 mg/kg/day for 12 months, followed by a dose of 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after 22 months). Following the enrollment visit (Day 1) and a Day 15 visit (patients on rituximab only), patients were monitored every 3 months through Month 24, with a follow-up visit at Month 28. After the completion of maintenance treatment (Month 18 for rituximab and Month 22 for azathioprine), patients in the rituximab arm were followed for 10 months while those in the azathioprine arm were followed for 6 months.

One hundred fifteen patients (57 rituximab; 58 azathioprine) received study treatment during the study, more patients in the rituximab arm (83%) completed treatment compared with the azathioprine arm (54%). However, the proportion that completed the Week 28 visit was comparable between the arms (95% vs. 90%, respectively).

Table 7 Clinical Trial Exposure by Duration of Exposure

Duration of Exposure (at least)	Number of Patients (%)	Person Time (Months)
>=1 month	56 (98.2%)	989.9
>=3 months	56 (98.2%)	989.9
>= 6 months	54 (94.7%)	978.4

Table 8 Clinical Trial Exposure by Age (Study ML22514)

Age Group (years)	Number of Patients			Person Time (Months)		
	Female	Male	Total	Female	Male	Total
< 25 Years	1	0	1	18.0	0	18.0
25-35 Years	2	4	6	36.6	73.3	109.9
35-45 Years	3	4	7	42.0	72.5	114.5

Age Group (years)	Number of Patients			Person Time (Months)		
	Female	Male	Total	Female	Male	Total
45-65 Years	10	21	31	167.7	362.4	530.1
>=65 Years	4	8	12	72.5	145.0	217.5

WA25615 study

Study WA25615 was a Phase IIa, international, multicenter, open-label, single-arm uncontrolled study. The overall design consisted of a 28-day screening period, an initial 6-month Remission Induction Phase, followed by a minimum additional 12-month Follow-Up Phase. After Month 18, patients were followed at study visits every 3 months until the common closeout (CCO) date which occurred on 10 May 2018, 18 months after enrollment of the last patient.

The first patient was enrolled on 23 May 2013 and last patient was enrolled on 16 November 2016.

All 25 patients completed all 4 rituximab infusions and the 6-month Remission Induction Phase. A total of 24 out of 25 patients completed at least 18 months of the Follow-Up Phase; 1 patient withdrew on Day 476 before the 18-month visit due to an administrative/other reason and was transferred back to local hospital care. Eight patients discontinued from the study between month 18 and the CCO, primarily due to administrative/other reasons: physician or family decision and/or transfer to adult care services for their GPA or MPA. There were no withdrawals from the study due to AEs. Ten patients completed follow-up until the CCO (maximum up to 4.5 years [54 months]). At the time of CCO, 6 patients had entered Extended Follow-Up for continued 3 monthly monitoring visits as their peripheral B cells remained depleted following their last rituximab dose.

Table 9 Clinical Trial Exposure by Duration

Duration of Observation[2]	Number
Treated with rituximab	25
Duration ≤ 6 months	0
6 months < Duration ≤ 12 months	0
12 months < Duration ≤ 18 months	2
18 < Duration ≤ 24 months	9
24 < Duration ≤ 36 months	8
36 < Duration ≤ 48 months	3
48 < Duration ≤ 60 months	3

Exposure – Clinical Trials in Pemphigus Vulgaris

Study ML22196

The following data are taken from the summary of clinical safety and clinical overview for Study ML22196.

Ninety patients (74 PV patients and 16 pemphigus foliaceus [PF] patients) were randomized in a 1:1 ratio to 2 treatment arms: 46 patients to the rituximab + prednisone arm and 44 patients to the prednisone arm. More patients in the rituximab + prednisone arm (44 [95.7%]) completed the month 24 visit than in the prednisone arm (31 patients [70.5%]).

A protocol amendment was performed while the study was ongoing to include a post-treatment follow-up visit at month 36. Because this protocol amendment was implemented in June 2015, while the study was ongoing, there were patients who had already completed the month 24 visit. Therefore, the patients who had a follow-up visit that occurred after month 36 had their month 36 evaluations retrospectively documented. The majority of patients in each treatment arm completed a post-treatment follow-up visit either at month 36 or after month 36 (44 patients [95.7%] in the rituximab + prednisone; 40 patients [90.9%] in the prednisone arm). Of these patients, 35 patients (76.1%) in the rituximab + prednisone arm and 29 patients (65.9%) in the prednisone arm were evaluated at month 36.

Thirty-eight PV patients were randomized to the rituximab + prednisone arm and 36 PV patients to the prednisone arm. In the rituximab + prednisone arm, 38 PV patients (100.0%) completed the month 24 visit compared with 30 PV patients (83.3%) in the prednisone arm. In the rituximab + prednisone arm, 36 PV patients (94.7%) completed the month 36 or post- month 36 visit compared with 32 PV patients (88.8%) in the prednisone arm.

[2] Total Patient years of observation 61.1

Table 10 Clinical Trial Exposure by Duration of Exposure

Duration of Exposure (at least)	Number of Patients (%)	Person Time (Months)
>=1 month	46 (100%)	912.6
>=3 months	46 (100%)	912.6
>= 6 months	46 (100%)	912.6

Table 11 Clinical Trial Exposure by Age (Study ML22196)

Age Group (years)	Number of Patients			Person Time (Months)		
	F	M	Total (n=46[1])	F	M	Total
< 25 Years	0	1	1	0	18.2	18.2
25-35 Years	4	1	5	86.6	51.8	138.4
35-45 Years	4	3	7	69.3	51.9	121.2
45-65 Years	11	7	18	251.4	125.1	376.5
>=65 Years	12	3	15	203.2	55.1	258.3

[1]Exposure refers to exposure to Rituximab in PV and PF population who received treatment in Rituximab+Prednisone arm (N=46).

Exposure – Clinical Trials in Non-Hodgkin's Lymphoma (Including rituximab IV and rituximab SC in combination with chemotherapy and as maintenance treatment)

Majority of data on rituximab monotherapy come from early trials conducted in patients with follicular lymphoma. Data from these trials were submitted with the initial Marketing Authorization Application (MAA) for MabThera via the Centrally Authorised Procedure (CAP) which was approved on 2 June 1998. The submission included a total of 322 rituximab -treated patients with NHL, from seven trials. At the time, three of the six monotherapy trials were still ongoing. Final data from these three studies were submitted in the Type II variation that received a favorable decision on 15 July 2002. This resulted in an update to the Summary of Product Characteristics (SmPC). No significant new data on rituximab monotherapy have become available since then, with the exception of rituximab given as patients for maintenance therapy following induction chemotherapy (with or without rituximab), e.g the PRIMA study (MO18264).

The development program for the SC formulation of rituximab in NHL was led by two pivotal trials; a Phase Ib dose-finding and dose-confirmation study in follicular lymphoma maintenance (Study BP22333), and a Phase III, two-stage, randomized study (Study BO22334/SABRINA), using the selected SC dose of 1400 mg in patients with previously untreated follicular lymphoma.

Pooled exposure data from studies BP22333 (data cut-off 17 September 2013), BO22334 (data cut-off 31October 2017), MO18264 (data cut-off 31 December 2016), U4391G (data cut-off 15 August 2011), MO28107/MabEase, a randomized Phase III trial in DLBCL (data cut-off 31 December 2015) and MO28457, evaluating patients preference with SC versus IV MabThera/Rituxan (data cut-off 19 January 2015) are presented in the tables below.

Table 12 Non-Hodgkin's Lymphoma Clinical Trial Exposure by Duration of Safety Follow-up and Gender

expo_dur_rmp_update_S_NHL_DUR Non-Hodgkins Lymphoma Clinical Trial Exposure by Duration of Safety Follow-Up and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BP22333 {17SEP2013/17SEP2013}, BO22334 {26JAN2018/31OCT2017}, MO18264 {26JUN2017/31DEC2016}, U4391G {15AUG2011/15AUG2011}, MO28107 {08MAR2016/31DEC2015}, MO28457 {23MAR2015/19JAN2015}
Safety Analysis Population: (N=3615)

Duration of Safety Follow-Up	Female					Male					Total				
	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
Up to 6 months	151	70.0	0.46	0.30	0.00-2.35	151	63.0	0.42	0.27	0.00-2.24	302	133.0	0.44	0.27	0.00-2.35
> 6 to 12 month	278	223.2	0.80	0.46	0.00-2.50	262	172.4	0.66	0.43	0.00-1.92	540	395.6	0.73	0.44	0.00-2.50
>12 to 24 month	354	184.2	0.52	0.42	0.00-2.52	365	185.9	0.51	0.41	0.00-2.51	719	370.1	0.51	0.41	0.00-2.52
>24 to 36 month	194	265.7	1.37	1.99	0.00-2.61	202	233.9	1.16	0.43	0.00-2.52	396	499.6	1.26	0.45	0.00-2.61
>36 to 48 month	68	131.5	1.93	2.28	0.00-2.51	69	121.4	1.76	2.25	0.18-2.47	137	252.9	1.85	2.26	0.00-2.51
>48 to 60 month	47	70.4	1.50	2.21	0.29-2.48	49	60.2	1.23	0.86	0.00-2.71	96	130.6	1.36	1.13	0.00-2.71
>60 months	433	477.8	1.10	0.42	0.00-2.57	467	554.9	1.19	0.44	0.00-2.65	900	1032.7	1.15	0.43	0.00-2.65
Missing	239	88.6	0.37	0.29	0.00-1.94	282	93.0	0.33	0.29	0.00-2.15	521	181.6	0.35	0.29	0.00-2.15
Total	1764	1511.2	0.86	0.42	0.00-2.61	1847	1484.8	0.80	0.41	0.00-2.71	3611	2996.0	0.83	0.42	0.00-2.71

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.
For U4391G (RATE) no Safety Follow-Up visits are available.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_NHL_DUR.out
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Table 13 Non-Hodgkin's Lymphoma Clinical Trial Exposure by Number of Administrations and Gender

expo_dur_rmp_update_S_NHL_INF Non-Hodgkins Lymphoma Clinical Trial Exposure by Number of Administrations and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BP22333 {17SEP2013/17SEP2013}, BO22334 {26JAN2018/31OCT2017}, MO18264 {26JUN2017/31DEC2016}, U4391G {15AUG2011/15AUG2011}, MO28107 {08MAR2016/31DEC2015}, MO28457 {23MAR2015/19JAN2015}
Safety Analysis Population: (N=3615)

Number of Administrations	Female					Male					Total				
	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
1	57	0.2	0.00	0.00	0.00-0.01	66	0.2	0.00	0.00	0.00-0.01	123	0.4	0.00	0.00	0.00-0.01
2	37	4.0	0.11	0.06	0.00-0.24	41	4.1	0.10	0.06	0.00-0.25	78	8.2	0.10	0.06	0.00-0.25
3	33	6.2	0.19	0.12	0.08-0.47	36	7.3	0.20	0.12	0.08-0.58	69	13.5	0.20	0.12	0.08-0.58
4	46	10.3	0.22	0.18	0.11-0.70	56	12.9	0.23	0.18	0.12-0.79	102	23.2	0.23	0.18	0.11-0.79
5	34	12.3	0.36	0.24	0.18-0.93	39	14.9	0.38	0.24	0.23-0.93	73	27.2	0.37	0.24	0.18-0.93
6	158	57.4	0.36	0.29	0.28-1.28	161	55.9	0.35	0.29	0.21-1.38	319	113.3	0.36	0.29	0.21-1.38
7	51	50.1	0.98	1.37	0.22-1.49	47	42.7	0.91	1.02	0.24-1.48	98	92.7	0.95	1.36	0.22-1.49
8	839	357.1	0.43	0.41	0.27-1.16	911	382.4	0.42	0.41	0.26-1.10	1750	739.5	0.42	0.41	0.26-1.16
9	19	14.9	0.79	0.59	0.41-1.55	23	13.0	0.57	0.54	0.41-1.23	42	28.0	0.67	0.56	0.41-1.55
10	22	25.3	1.15	1.38	0.41-1.55	27	26.2	0.97	0.74	0.48-1.44	49	51.5	1.05	0.79	0.41-1.55
11	63	90.0	1.43	1.54	0.87-1.65	39	54.1	1.39	1.54	0.86-1.73	102	144.1	1.41	1.54	0.86-1.73
12	9	9.5	1.05	1.06	1.01-1.10	12	12.6	1.05	1.05	1.02-1.10	21	22.1	1.05	1.05	1.01-1.10
13	6	7.2	1.20	1.20	1.17-1.24	3	3.6	1.18	1.20	1.15-1.20	9	10.8	1.19	1.20	1.15-1.24
14	12	16.3	1.36	1.35	1.29-1.49	6	8.3	1.38	1.35	1.31-1.57	18	24.6	1.37	1.35	1.29-1.57
15	2	3.1	1.55	1.55	1.52-1.57	9	14.2	1.57	1.57	1.42-1.83	11	17.2	1.57	1.57	1.42-1.83
16	5	9.1	1.81	1.70	1.63-2.32	8	14.2	1.78	1.72	1.63-2.28	13	23.3	1.79	1.71	1.63-2.32
17	9	17.0	1.89	1.81	1.78-2.30	7	13.2	1.89	1.85	1.82-1.97	16	30.2	1.89	1.84	1.78-2.30
18	9	18.2	2.02	1.94	1.92-2.48	8	16.4	2.05	2.01	1.92-2.36	17	34.6	2.03	1.97	1.92-2.48
19	8	17.9	2.23	2.22	2.11-2.36	17	38.0	2.24	2.20	2.09-2.44	25	55.9	2.24	2.22	2.09-2.44
20	338	780.8	2.31	2.29	2.14-2.61	324	748.1	2.31	2.28	2.18-2.71	662	1528.9	2.31	2.29	2.14-2.71
21	1	2.5	2.50	2.50	2.50-2.50						1	2.5	2.50	2.50	2.50-2.50
Missing	6	2.1	0.34	0.41	0.00-0.42	7	2.6	0.37	0.42	0.00-0.47	13	4.7	0.36	0.41	0.00-0.47

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.
Administrations on the same visit on a different date are counted separately.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_NHL_INF.out
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Table 14 Non-Hodgkin's Lymphoma Clinical Trial Exposure by Age Group and Gender

expo_dur_rmp_update_S_NHL_AGE Non-Hodgkins Lymphoma Clinical Trial Exposure by Age Group (years) and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BP22333 {17SEP2013/17SEP2013}, BO22334 {26JAN2018/31OCT2017}, MO18264 {26JUN2017/31DEC2016}, U4391G {15AUG2011/15AUG2011}, MO28107 {08MAR2016/31DEC2015}, MO28457 {23MAR2015/19JAN2015}
Safety Analysis Population: (N=3615)

	Female					Male					Total				
Age Group (years)	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
< 40	123	118.5	0.96	0.43	0.00-2.41	176	142.4	0.81	0.41	0.00-2.59	299	260.9	0.87	0.42	0.00-2.59
40-50	227	239.1	1.05	0.48	0.00-2.52	279	255.2	0.91	0.42	0.00-2.52	506	494.2	0.98	0.43	0.00-2.52
51-60	454	437.9	0.96	0.43	0.00-2.57	473	458.1	0.97	0.43	0.00-2.52	927	896.0	0.97	0.43	0.00-2.57
> 60	877	688.2	0.78	0.41	0.00-2.61	831	600.9	0.72	0.41	0.00-2.71	1708	1289.1	0.75	0.41	0.00-2.71
Missing	83	27.5	0.33	0.41	0.00-0.62	88	28.2	0.32	0.40	0.00-0.57	171	55.8	0.33	0.41	0.00-0.62

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_NHL_AGE.out
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The target population for the approved oncology indications is the adult population as hematological malignancies are primarily found in this age group, however the Marketing Authorization Holder (MAH) is investigating the use of rituximab in younger age groups as part of a pediatric investigation plan (PIP).

Table 15 Non-Hodgkin's Lymphoma Clinical Trial Exposure by Race and Gender

expo_dur_rmp_update_S_NHL_RAC Non-Hodgkins Lymphoma Clinical Trial Exposure by Race and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BP22333 {17SEP2013/17SEP2013}, BO22334 {26JAN2018/31OCT2017}, MO18264 {26JUN2017/31DEC2016}, U4391G {15AUG2011/15AUG2011}, MO28107 {08MAR2016/31DEC2015}, MO28457 {23MAR2015/19JAN2015}
Safety Analysis Population: (N=3615)

	Female					Male					Total				
Race	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
ASIAN	104	58.2	0.56	0.41	0.00-2.50	108	56.0	0.52	0.42	0.00-2.45	212	114.2	0.54	0.42	0.00-2.50
BLACK	13	4.2	0.32	0.30	0.12-0.50	16	7.6	0.47	0.38	0.12-2.52	29	11.8	0.41	0.33	0.12-2.52
OTHER	70	57.5	0.82	0.42	0.00-2.51	54	49.7	0.92	0.44	0.00-2.33	124	107.2	0.86	0.43	0.00-2.51
WHITE	970	726.4	0.75	0.42	0.00-2.61	987	628.5	0.64	0.41	0.00-2.51	1957	1354.8	0.69	0.41	0.00-2.61
Missing	607	664.9	1.10	0.44	0.00-2.57	682	743.0	1.09	0.43	0.00-2.71	1289	1407.9	1.09	0.43	0.00-2.71

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.
For MO18264 (PRIMA) no Race information was captured within the study.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_NHL_RAC.out
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BO25380[3] (Intergroup B-NHL-2010)

Study BO25380 was a multicenter, open-label, randomized phase III study evaluating the benefit of adding 6 infusions of rituximab to the standard LMB chemotherapy regimen in untreated pediatric and adolescent patients aged 6 months to less than 18 years presenting with advanced stage mature B-cell non-Hodgkin lymphoma (B-NHL), specifically BL/ B-AL, Burkitt-like lymphoma (BLL) and diffuse large B-cell lymphoma (DLBCL) — and stage III plus lactate dehydrogenase (LDH) > upper limit of normal (ULN) × 2, stage IV. Patients with PMLBL were not included in this part of the study.

A total of 484 patients were enrolled into this study, of which 328 patients were randomized to either receive standard LMB-96 chemotherapy plus 6 infusions of rituximab (N=164, R-Chemo ITT set) or standard LMB-96 chemotherapy only (N=164, Chemo ITT set), respectively. Of these, 160 patients (97.6%) in the Chemo ITT set and 162 patients (98.8%) in the R-Chemo set were treated according to protocol treatment. A total of 309 patients from the randomized portion and single arm portion of the study received rituximab and were included in the rituximab safety set.

Exposure - Clinical Trials in Chronic Lymphocytic Leukemia (Including Rituximab IV and Rituximab SC)

Rituximab in combination with FC in CLL patients was studied in two large, Phase III trials using IV formulation: Study ML17102/CLL8 in previously untreated CLL and study BO17072/REACH in relapsed/refractory CLL.

Study BO25341/SAWYER using SC formulation of rituximab in CLL was based on a Phase Ib dose selection and C_{trough} non-inferiority study in combination with FC. The study investigated a non-inferior C_{trough} rituximab exposure when treated with a fixed dose of rituximab SC (1600 mg) as compared with the established rituximab IV CLL dose (500 mg/m^2).

Pooled exposure data from studies BO17072 (data cut-off 06JUN2012), ML17102 (data cut-off 31Oct2011), BO25341 (data cut-off 17 Nov2017), are presented in the tables below.

[3] Clinical data cut off 31 December 2017

Table 16 Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Duration of Safety Follow-up and Gender

expo_dur_rmp_update_S_CLL_DUR Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Duration of Safety Follow-Up and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BO17072 {16JUL2012/06JUN2012}, ML17102 {08JUN2012/31OCT2011}, BO25341 {15FEB2018/17NOV2017}
Safety Analysis Population: (N=914)

Duration of Safety Follow-Up	Female					Male					Total				
	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
Up to 6 months	14	3.7	0.26	0.28	0.00-0.46	28	6.5	0.23	0.18	0.00-0.54	42	10.2	0.24	0.22	0.00-0.54
> 6 to 12 month	10	3.5	0.35	0.34	0.24-0.53	21	7.0	0.33	0.39	0.00-0.46	31	10.5	0.34	0.39	0.00-0.53
>12 to 24 month	13	4.1	0.32	0.39	0.08-0.50	35	12.0	0.34	0.40	0.08-0.53	48	16.1	0.34	0.39	0.08-0.53
>24 to 36 month	19	6.8	0.36	0.39	0.13-0.61	39	14.1	0.36	0.39	0.01-0.56	58	20.8	0.36	0.39	0.01-0.61
>36 to 48 month	57	24.2	0.42	0.47	0.15-0.66	131	55.1	0.42	0.46	0.00-0.64	188	79.3	0.42	0.46	0.00-0.66
>48 to 60 month	45	17.7	0.39	0.39	0.00-0.64	111	44.2	0.40	0.41	0.00-0.64	156	62.0	0.40	0.40	0.00-0.64
>60 months	100	36.9	0.37	0.39	0.00-0.62	269	100.7	0.37	0.39	0.00-0.62	369	137.6	0.37	0.39	0.00-0.62
Missing	13	2.1	0.16	0.16	0.01-0.41	9	1.4	0.16	0.08	0.08-0.31	22	3.6	0.16	0.16	0.01-0.41
Total	271	99.1	0.37	0.39	0.00-0.66	643	240.8	0.37	0.39	0.00-0.64	914	339.9	0.37	0.39	0.00-0.66

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_CLL_DUR.out
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Table 17 Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Number of Administrations and Gender

expo_dur_rmp_update_S_CLL_AGE Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Age Group (years) and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BO17072 {16JUL2012/06JUN2012}, ML17102 {08JUN2012/31OCT2011}, BO25341 {15FEB2018/17NOV2017}
Safety Analysis Population: (N=914)

Age Group (years)	Female					Male					Total				
	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
< 40	5	1.9	0.38	0.41	0.16-0.53	9	4.0	0.44	0.43	0.39-0.48	14	5.9	0.42	0.43	0.16-0.53
40-50	27	10.5	0.39	0.39	0.16-0.64	78	29.9	0.38	0.40	0.00-0.62	105	40.4	0.38	0.39	0.00-0.64
51-60	83	30.9	0.37	0.39	0.00-0.62	183	71.8	0.39	0.41	0.00-0.60	266	102.7	0.39	0.40	0.00-0.62
> 60	156	55.8	0.36	0.39	0.00-0.66	373	135.2	0.36	0.39	0.00-0.64	529	191.0	0.36	0.39	0.00-0.66

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_CLL_AGE.out
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Table 18 Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Age Group and Gender

expo_dur_rmp_update_S_CLL_AGE Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Age Group (years) and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BO17072 {16JUL2012/06JUN2012}, ML17102 {08JUN2012/31OCT2011}, BO25341 {15FEB2018/17NOV2017}
Safety Analysis Population: (N=914)

	Female					Male					Total				
Age Group (years)	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
< 40	5	1.9	0.38	0.41	0.16-0.53	9	4.0	0.44	0.43	0.39-0.48	14	5.9	0.42	0.43	0.16-0.53
40-50	27	10.5	0.39	0.39	0.16-0.64	78	29.9	0.38	0.40	0.00-0.62	105	40.4	0.38	0.39	0.00-0.64
51-60	83	30.9	0.37	0.39	0.00-0.62	183	71.8	0.39	0.41	0.00-0.60	266	102.7	0.39	0.40	0.00-0.62
> 60	156	55.8	0.36	0.39	0.00-0.66	373	135.2	0.36	0.39	0.00-0.64	529	191.0	0.36	0.39	0.00-0.66

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_CLL_AGE.out
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M=Male, F=Female

Table 19 Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Race and Gender

expo_dur_rmp_update_S_CLL_RAC Chronic Lymphocytic Leukaemia Clinical Trial Exposure by Race and Gender

Protocol(s) {Snapshot Date/Cutoff Date}: BO17072 {16JUL2012/06JUN2012}, ML17102 {08JUN2012/31OCT2011}, BO25341 {15FEB2018/17NOV2017}
Safety Analysis Population: (N=914)

	Female					Male					Total				
Race	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY	No Pats	Total PY	Mean PY	Median PY	Range PY
ASIAN	1	0.4	0.35	0.35	0.35-0.35	1	0.4	0.40	0.40	0.40-0.40	2	0.8	0.38	0.38	0.35-0.40
OTHER	4	1.3	0.32	0.32	0.16-0.49	9	4.1	0.45	0.46	0.20-0.64	13	5.4	0.41	0.46	0.16-0.64
WHITE	158	59.3	0.38	0.40	0.01-0.66	334	128.6	0.39	0.41	0.00-0.64	492	187.9	0.38	0.41	0.00-0.66
Missing	108	38.2	0.35	0.39	0.00-0.62	299	107.7	0.36	0.39	0.00-0.58	407	145.9	0.36	0.39	0.00-0.62

PY = Person Years of Exposure, calculated as (Last treatment intake - First treatment intake + 1) / 365.25

Only Rituximab patients with non-missing exposure time are contributing to summary statistics.

Program : $PROD/cdt3490c/expo_dur_rmp_update.sas / Output : $PROD/cdt3490c/reports/expo_dur_rmp_update_S_CLL_RAC.out
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PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	If No, Rationale
Hypersensitivity	Hypersensitivity is a rare occurrence. Patients with hypersensitivity to rituximab are not treated.	No	As per the EU SmPC, MabThera is contraindicated in patients with hypersensitivity to the active substance or to murine proteins, or to any of the excipients.
Active, severe infections	Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to patients with an active, severe infection (e.g., TB, sepsis and opportunistic infections). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (e.g., hypogammaglobulinemia).	No	As per the EU SmPC, MabThera is contraindicated in patients with active, severe infections.
Patients in a severely immunocompromised state	Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (e.g., hypogammaglobulinemia). It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.	No	As per the EU SmPC, MabThera is contraindicated in patients in a severely immunocompromised state

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	If No, Rationale
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease*	Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.	No	As per the EU SmPC, MabThera is contraindicated (in non-oncology indications) in patients with Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease
Fertile men or women of childbearing potential not using adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile). Pregnant or breastfeeding women.	Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with MabThera. Pregnancy: IgG immunoglobulins are known to cross the placental barrier. There are no adequate and well-controlled data from studies in pregnant women; however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Breast-feeding: Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is	No	Since EU RMP Version 22.0 submitted on 03 July 2020 (CHMP positive opinion received on 03 September 2020), the safety concern ‘Use in pregnancy and lactation (all indications)’ is no longer presented as missing information and does not require active risk management in line with GVP Module V (Rev 2). Use in pregnancy and lactation will continue to be presented and evaluated in the PBRER as part of routine pharmacovigilance activities.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	If No, Rationale
	not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.		
Administration of live vaccines to be completed at least 4 weeks prior to commencing treatment	In a non-randomized study, patients with relapsed low-grade non-Hodgkin's lymphoma (NHL) who received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titer). For chronic lymphocytic Leukemia (CLL) patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.	No	As per the EU SmPC Special warnings and precautions for use, the safety of immunization with live viral vaccines, following MabThera therapy has not been studied. Vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted. Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced.
Patients under 18 years of age (with the exception for Study WA25615 (PePRS) and BO25380 Intergroup B-NHL-2010 trial	The safety and efficacy of MabThera IV in pediatric patients has not been established in indications other than GPA and MPA (for patients ≥ 2 to < 18 years of age), and B-NHL (aged ≥ 6 months to < 18 years old).	No	As per the EU SmPC, Section 4.2 Posology and method of administration, safety and efficacy of MabThera in pediatric patients (≥2 to < 18 years of age) has not been established in diseases other than GPA or MPA or B-NHL (aged ≥ 6 months to < 18 years old)

CHMP = Committee for Medicinal Products for Human Use; CLL = Chronic Lymphocytic Leukemia; EU = European Union; GPA=Granulomatosis with Polyangiitis, MPA = Microscopic Polyangiitis; NHL = Non-Hodgkin's lymphoma; SmPC = Summary of Product Characteristics.

*it is applicable only for non-oncology indication(s).

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAM

Use in Pregnancy and Lactation

The safety of using rituximab while pregnant or breastfeeding is not fully known, as pregnant and lactating women are excluded from clinical trials. Additionally, all patients in clinical trials (male and female) are required to use effective contraception during trial participation, and females of childbearing potential must have a negative urine pregnancy test within two weeks prior to randomization or rescue therapy.

Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk and due to the long retention time of rituximab in B-cell depleted patients, women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with rituximab. Moreover, breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment.

Table 21 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with renal impairment (with significantly elevated serum creatinine [e.g. > 1.5 x ULN or > 2.5 x ULN] or creatinine clearance [<60-70 mL/min])	Not included in the clinical development program *Note*: the restriction related specifically to the concomitant (potentially nephrotoxic) chemotherapy given for malignant hematological disorders, since rituximab is not renally excreted and is not nephrotoxic.
Patients with hepatic impairment (with poor hepatic function [e.g. bilirubin > 2 x ULN and/or alkaline phosphatase and/or transaminases > 2 x ULN])	Not included in the clinical development program *Note*: the restriction is mainly due to the concomitant chemotherapy (notably cyclophosphamide) given for malignant hematological disorders, since rituximab does not undergo hepatobiliary excretion

Type of special population	Exposure
	and is not hepatotoxic.
Patients with cardiac impairment (with poor function/severe impairment [variously defined]	Not included in the clinical development program *Note*: restriction is *partly* due to the concomitant chemotherapy given to for malignant hematological disorders, some of which are known to be cardiotoxic (notably anthracyclines).
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program
Other:	
Children	Not included in the clinical development program[4]

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

An approximation of rituximab patient exposure was calculated uniformly across the world and across indications. The report includes global brands (MabThera®/Rituxan®) as well as local trademarks/second brands.

The cumulative patient exposure estimates cover the period from international birth date (IBD) until 30 September 2023[5]. The following assumptions were used to stratify and estimate cumulative and interval exposures:

SV.1.2 Exposure Estimates by Indication

In the US, patient exposures for immunological disease types was based on dividing US sales volume (grams) of rituximab by a weighted average annual patient usage estimate for RA and vasculitis, which is estimated to be 3.2988 grams/patient/year[6]. The estimate is based on the following assumptions: RA retreatment interval=6.9 months; RA adherence (average of first and second course)=89%; RA average grams/course=1.96; GPA adherence=91%; GPA average grams/year=5.0g. Utilization of rituximab across AI conditions was evaluated using a US-based healthcare claims database where the distribution of rituximab use across AI conditions was estimated and the six-month average was used to inform the current exposure estimates. The rates were 60% RA,

4 except in pediatric study WA25615 in GPA and MPA and study Intergroup B-NHL-2010
5 Source: primary market research.
6 Source: Gesellschaft für Konsumforschung (GfK) Market Share Tracker Q4 2008.

4% lupus, 5% multiple sclerosis (MS), 4% myositis, 11% ANCA-AAV, 2% PV and 15% other AI. Within each condition the percentage of unique (new) out of total patients treated for that condition was estimated. For 2023, the percentages that are unique are: RA 28%, lupus 38%, 41% AAV, PV 40%, MS 27%, myositis 37%, and other immunology indications 37%.

The methodology for approximating patient exposures for immunological disease for ex-US and ex-Japan was based on dividing total volume of rituximab [ex-US and ex-Japan] by average number of vials used per course per treatment.

Compliance	100%
The average number of vials 500 mg used per course of treatment in a year	6
The average number of vials 100 mg used per course of treatment in a year	30

	Auto-immune	**Oncology**
MABTHERA VIALS 500 MG/50 ML	20%	80%
MABTHERA VIALS 100 MG/10 ML	20%	80%

Patient exposures for immunological disease types ex-US are further broken down into most frequently prescribed diseases including some of the off-label diseases. The estimated percentage splits are derived from market research (RA 78%; lupus 11%; vasculitis 5%; other AI diseases 6%[7]). The estimated patient exposures for immunological disease types are provided in both unique and non-unique estimates.

The unique patient exposure accounts for the chronic nature of the disease and estimates treated patients, whereas non-unique patient exposure estimate counts treatments received by an average patient. The unique patient exposure estimate is based on the assumption of new patients treated in a year derived from market research (56%). Unique patient exposure estimates are not available for hematological malignancy disease types.

Patient exposure for hematological diseases[8]for Rituxan (IV) was estimated by dividing the estimated number of vials shipped to distributors for treatment of hematological diseases by the average number of vials course of treatment. The average number of vials per course of treatment was based on market research results (MabThera® patient case market research 2017/2018; Rituxan® tracker market research 2017/2018). Hematological malignancies being considered for exposure estimates also include unapproved lymphoma and CLL indications. For EEA and ROW regions,

[7] Source: Gesellschaft für Konsumforschung (GfK) Market Share Tracker Q4 2008.
[8] Source: BioOncology Hematology Tracking + Chart Audit (2017 - 2018) + Claims (2020 - 2021).

stratification of exposures by indication in the hematological malignancies was estimated using patient chart audit market research conducted in France, Germany, Italy, Spain, and the UK, (5EU) in patients undergoing treatment for NHL or CLL (MabThera 5EU patient case market research Q3 2017).

Patient exposure for SC formulation in US: Patient exposure for Rituxan Hycela (SC) was estimated by the estimated number of vials shipped for treatment of hematological diseases by the average number of vials since launch. We have leveraged IV split of volume (avg over 4 quarters) of new (67%) and continuing (33%) patients and IV compliance assumptions (continuing patient accounts receive 4 doses for the 3-month period - 75% compliance; new accounts receive 1 dose for the 3-month period). This results in an average number of vials of 2.8 per vials shipped per patient.

Hematological malignancies being considered for exposure estimates also include unapproved NHL and CLL indications. For US, stratification of exposures by indication was estimated using patient chart audit market research in the USA undergoing treatment for NHL or CLL.

Exposure estimates for age and gender

Whilst the methodology for estimating patient exposures to MabThera is based on sales volumes and sales values, the stratification of the estimated number of exposed patients in gender and age is based on data from the Anti-Rheumatic Therapy in Sweden (ARTIS) registry.

In hematological malignancies however, an estimate of the use of MabThera in patients aged less than 18 years of age comes from a Japanese study where the percentage use is 0.1% in this age category. Estimation of the number of pediatric exposures ($<$ 18 years) calculated is based on the demographic data from a post-marketing usage surveillance conducted in Japan for the duration of 1 April 2004 to 31 March 2006 (n=1,137) where the percentage use was 0.1% in this category. All pediatric exposures were assumed to occur in NHL. The remainder of the age estimates is derived from the EU5 market research data.

Currently Roche does not have sufficient data to provide stratification of patient exposure by age and gender for AI indications globally. However, in Japan, following approval of the new AI indications (GPA/MPA and nephrotic syndrome [NS]), 231 pediatric patients ($\leq$ 16 years-old), 2 in GPA/MPA and 229 in NS were exposed to rituximab during the reporting interval, and 2,201pediatric patients (22 in GPA/MPA and 2,179 in NS) have been exposed to rituximab cumulatively (since the IBD until 30 September 2023).

Exposure estimate by dose (applicable to hematological malignancies only)

Stratification of exposures by dose in hematology (375 mg/m^2 vs. 500 mg/m^2) was also estimated from market research conducted in 5EU in patients undergoing treatment for NHL or CLL (500 mg/m^2 is the approved dose for second and subsequent infusions of MabThera in CLL).

Exposure estimate by formulation (applicable to hematological malignancies only)

Stratification of exposures by IV and SC formulation in hematology was estimated by dividing the estimated number of vials shipped to distributors for treatment of hematological diseases by the average number of vials per course of treatment, which in turn was based on input from market research conducted in EU5 in patients undergoing treatment for NHL or CLL (MabThera 5EU patient case market research Q3 2017).

Exposure estimate including Pediatric/Adult split for GPA/MPA and NHL indications

Following the approval of MabThera in pediatric use for GPA/MPA in the US in 2019 and 2020 in the EU, and NHL indication in the EU in 2020, a patient split between adult/children has been included in the patient-exposure estimation model. The patient split for these indications was collected based on insights and statistics provided by the respective affiliates. Based on these data, an estimated of 2% of total NHL patients corresponds to pediatric patients and 98% of them are adults. Similarly, in the case of GPA/MPA, 2% of total estimated AAV (GPA/MPA) patients are children and 98% are adults.

Cumulative Exposure from Marketing Experience

The estimated worldwide cumulative exposure to rituximab is presented in Annex 7, which also includes data received from Business Partners.

Since the IBD (26 November 1997) until 30 September 2023[9], approximately 7,861,869 Patient-market exposures[10] have been estimated for rituximab.

- Hematological malignancies: ~ 6,347,374
- AI Indications: ~ 1,514,495 (Unique patients = ~ 664,957)
  - RA: ~ 1,078,944 (Unique patients = ~470,482)
  - AAV ~ 111,538 (Unique patients = ~ 50,887)
  - PV: ~ 6,203 (Unique patients = ~ 2,465)

[9] The sales data are provided on a monthly basis; therefore, cumulative exposure is from the IBD to 30 September 2023.
[10] Note: Rounding errors may be introduced into the total figures presented.

- Other AI indications (AI excluding RA, PV & AAV): ~ 317,810 (Unique patients = ~141,123)

- Off-label use (including other oncology and AI indication): ~ 382,925

  (including 3,360 pediatric patients [age: 2 to 16 years] in AI indications; 86,686 adult patients [age: >16 years] in other oncology and AI indications, i.e. 65,115 and 21,571 adult patients, respectively; 292,879 patients of unknown age in Systemic Lupus Erythematosus (SLE) and other AI indications, i.e. 132,756 and 160,123 patients, respectively).

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have potential for misuse for illegal purposes are expected to share some general characteristics, such as psychoactive effects or, less commonly, anabolic effects or enhancement of hemoglobin levels. The lack of evidence of such side-effects that may lead to misuse for illegal purposes, in addition to the Warnings and Precautions section of the SmPC (which states that rituximab should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician), make it highly unlikely that there is a potential for misuse of rituximab for illegal purposes. To date, no reports of misuse of rituximab for illegal purposes have been received.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The safety concerns “Off-label use of the SC formulation (NHL/CLL, SC formulations)” and “Administration route error (NHL/CLL, SC formulations)” which were previously classified as important potential risks are no longer presented in the EU RMP.

All reports of AEs involving off-label use of the SC formulation were assessed periodically to determine the extent of off-label use. In addition, information concerning the route of administration, dose and dose-interval is obtained wherever possible for reported AEs concerning off-label use. Routine monitoring of Off-label use of SC

formulation is in place via routine signal detection activity. No safety concerns have been identified to date for Off-label use of SC formulation.

Over the last submitted seven PBRERs since 2016 (the Assessment on medication error due to accidental substitution of rituximab vials formulated for IV and SC route was started in 2016), the overall incidence of Administration route error has been low and with a small number of non-serious cases which has been comparable across PBRERs. No specific pattern of AEs has been observed. No new safety concern has been identified for the risk of Administration route error and thus the benefit-risk profile has remained unchanged over time.

Based on an extensive analysis of rituximab safety data gathered over the course of the last 20 years, the MAH is of the opinion that these risks are appropriately managed by healthcare professionals in clinical practice and there are no additional activities/measures needed to further characterize these risks.

The safety concerns of “Hepatitis B reactivation (All indications)” and “Hypogammaglobulinemia (non-oncology indications)” previously classified as important identified risks are no longer presented in the EU RMP as there are no additional activities/measures needed to further characterize these risks.

The use of rituximab has been associated with hepatitis B reactivation in Hepatitis B Surface Antigen (HBsAg)+ve as well as HBsAg-ve/Hepatitis B Core Antibody (HBcAb)+ve patients, particularly when administered in combination with immunosuppressive therapies such as steroids or chemotherapy, across all indications. Hepatitis B reactivation was an important identified risk for all approved indications (the risk was also updated to important identified for the AI indications in EU RMP v7.0, 2011), and the current EU SmPC provides a comprehensive description of this event, including clinical symptoms, potential mechanisms, diagnosis, risk factors, and preventability. Since 2013, the MAH recommends hepatitis B Virus (HBV) screening in all patients before the initiation of treatment with rituximab in all indications, and that patients with positive serology should consult with a liver disease specialist before start of treatment. Those patients should be monitored and managed following local standards to prevent hepatitis B reactivation.

Rituximab acts via binding to transmembrane antigen CD20, which is located on pre-B- and mature B-lymphocytes. Although antibody-producing plasma cells are not directly affected by rituximab, patients can develop prolonged B-cell depletion resulting in antibody deficiency. Hypogammaglobulinemia itself is asymptomatic but may predispose the patient to certain infections. Hypogammaglobinemia was added as an important identified risk for non-oncology indications only in EU RMP v8.0, 2012. The current EU SmPC contains Routine risk minimization activities recommending specific clinical measures to address the risk: Immunoglobulin levels are recommended to be

determined prior to initiating treatment with MabThera. Hypogammaglobulinemia can be treated with IV immunoglobulins.

Over the past 10 years, no new safety concern has been identified for the risks of hepatitis B reactivation and hypogammaglobulinemia; these risks remained unchanged in their evaluation (qualitatively and quantitatively) and thus the benefit-risk profile has remained unchanged over time. Healthcare professionals are informed via EU SmPC and aware of the risks of hepatitis B reactivation and hypogammaglobulinemia and have the appropriate measures in place as part of clinical practice.

The MAH continues routine PV activities including signal detection and will continue to present these important risks in the upcoming PBRERs.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 INFORMATION ON IMPORTANT IDENTIFIED RISKS

SVII.3.1.1.1 INFECTIONS, INCLUDING SERIOUS INFECTIONS (ALL INDICATIONS)

Medical Dictionary for Regulatory Activities (MedDRA): System Organ Class (SOC) Infections and Infestations

Potential mechanisms:

All Indications

Rituximab's anticipated mechanism of action induces B-cell depletion that can lead to a suppressed immune system. In addition, previous or concomitant immunotherapy, bone marrow infiltration, and/or corticosteroid therapy can be important contributing factors.

For NHL/CLL; underlying disease can also contribute to immunosuppression. It is possible that B-cell depletion ± associated hypogammaglobulinemia caused by rituximab could increase the risk of severe viral infections or viral reactivation and opportunistic infections, especially in patients with other predisposing conditions (e.g., T-cell deficiencies, bone marrow infiltration and/or immunotherapy, concomitant chemotherapy, previous immunosuppressive therapy).

Evidence source(s) and strength of evidence:

- MabThera® SmPC
- Drug Safety Report (DSR) No 1066792 on Infections (dated March 2016)
- DSR 1027733 on infections (dated, 29 October 2007), and references therein.
- DSR 1022732 on viral infections (dated August 2006) and references therein.

- DSR 1027731 (dated 29 October 2007), 1044830 (dated 30 June 2011). Genentech Issue Work up (dated 26 October 2007), and references therein.

RA

- Long-term safety of rituximab: pooled analysis of the RA global clinical trial program over 11 years (cutoff: September 2012) comprising of DANCER (WA17043/U2644g), IMAGE (WA17047/U3373g), MIRROR (WA17044, U2974g), REFLEX (WA17042/IDEC 102-20), SERENE (WA17045/U2973g), SIERRA (U3374g), SUNRISE (U3384g), WA16291, WA16855 (U2653g), WA17531 (IDEC 102-21).
- DSR 1042044 (dated 4 February 2011) on fatal infusion reactions in RA patients, and references therein.

GPA/MPA

- RAVE CSR and RAVE Summary of Clinical Safety.
- RaVeR (WA27893) Final CSR
- Study ML22514 (MAINRITSAN) CSR and Summary of Clinical safety
- DSR 1081144(cut-off date, 03 March 2017) Evaluation of the Safety Profile of Mabthera Maintenance Therapy in GPA (Wegener's) and MPA in the Post-Marketing Setting.

Pemphigus vulgaris

- Study ML22196 CSR and Summary of Clinical Safety
- DSR 1080390 (data cut-off date: 15 March 2017), a supplemental Safety Report for Rituximab in Pemphigus and Other AI Indications

NHL/CLL

- Data from pivotal studies (cutoff: July 2012) comprising M39021, M39022, M39045, E4494. E1496, PRIMA (MO18264), CLL8/ML17102, and BO17072/REACH
- Clinical Study Reports for Study ML17102/CLL 8 and BO17072/REACH and PRIMA (MO18264) studies.
- CSR 1088458 study Inter B NHL Ritux 2010 (11 March 2019)

Characterization of the risk:

Frequency with 95% Confidence Interval (CI):

RA

The overall rate of infection was 75.7 events per 100 patient years. This was numerically less than that observed in the pooled placebo population (90.39 events per 100 patient years) and was stable across multiple treatment courses (All Exposure data cutoff: September 2012).

The overall rate of serious infection in rituximab-treated patients was 3.76/100 patient-years (2.71/100 patient-years in patients observed for > 5 years). This is comparable with placebo populations (3.79; CI: 2.80; 5.13) and the rate remained stable over time and across multiple treatment courses (DSR 1066792, dated March 2016).

Bacterial infections were seen in 9% of patients, the biggest share of those being bacterial cellulitis at 3%. Species specific reporting was led by *Staphylococci* and *Streptococci* though both accounted for <1% each (DSR 1066792, dated March 2016).

Viral infections had the highest proportion of pathogen specific infections reported, at 19%. *Influenza* viruses accounted for 8% of those, followed by *Herpesviridae* family at 7% and viral gastroenteritis at 3%.

Fungal infections were reported in 9% of events; vulvovaginal mycotic infection and tinea pedis accounted for 3% each (DSR 1066792, dated March 2016).

In the All Exposure RA population, 22 potential opportunistic infections (of 12 different types) were identified in 21 (5.8%) patients (rituximab 0.05 events/100 patient-years; placebo, 0.09 events/100 patient-years).

GPA/MPA

In RAVE, the rate of serious infections (per patient-year) was similar between the two treatment groups (0.25 for rituximab, 0.28 for cyclophosphamide) at 6 months. The proportions of patients who experienced serious infections by 18 months were also similar between the rituximab (15 patients or 15.2%) and cyclophosphamide (15 patients or 15.3%) groups. The rates of serious infections (per patient-year) were also similar between the two groups at 18 months: 0.13 with 95% CI: 0.08; 0.20 for the rituximab group and 0.16 with 95% CI: 0.10; 0.24 for the cyclophosphamide group.

The frequency of serious adverse events (SAEs) was similar to that seen in other studies of vasculitis patients and appeared to largely reflect the influence of concurrent or previous immunosuppressive therapy, underlying disease, and corticosteroid therapy.

As pneumocystis infections are known to occur in GPA/MPA, patients in RAVE were required to receive pneumocystis prophylaxis. After the 6-month remission induction phase and the 12-month remission maintenance phase period of the RAVE study there had been a total of 2 non-serious opportunistic infections (*Mycobacterium avium complex and Esophageal candida*) reported in the rituximab group, and 2 opportunistic infections (1 serious and 1 non-serious) in the cyclophosphamide treatment group.

In Study WA27893 (RaVeR) in adults, fourteen patients had 24 serious infections, for an incidence rate of 7.11 per 100 patient years. The infection profile observed in this study was consistent with the known safety profile of rituximab in the patient population.

In Study ML22514 in adults, infections occurred at a comparable frequency between the arms (53% rituximab vs. 57% azathioprine). The incidence of serious infections was similar (12%) in both arms. The infection profile observed in this study was consistent with the known safety profile of rituximab in the patient population. Three patients reported opportunistic infections; two patients in the rituximab arm experienced one event each of severe esophageal candidiasis and moderate *pneumocystis jirovecii* pneumonia, and one patient in the azathioprine arm experienced moderate atypical mycobacterial pneumonia. No events of Progressive Multifocal Leukoencephalopathy (PML), or hepatitis B reactivation were reported in this study.

In the DSR 1081144, a total of 126 AEs (19.8%) including 102 SAEs were reported in the SOC Infections and infestations. The most frequently reported PTs in this SOC were infection, pneumonia, lower respiratory tract infection, sinusitis and pneumonia bacterial; the reported infections are consistent with the known safety profile of rituximab. No event of PML was reported in the DSR 108114.

In pediatric Study WA25615 (PePRS), during the overall study period, 105 infection AEs were reported in 23 patients (92%) of which the majority (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were upper respiratory tract infections (12 patients [48%]) all of which were non-serious.

Pemphigus vulgaris

In Study ML22196, fourteen patients (36.8%) in the rituximab + prednisone arm experienced 43 treatment-related infections and 15 patients (41.7%) in the prednisone alone arm experienced 28 treatment-related infections. The most frequent infection PTs (occurring in ≥5% in either treatment arm [rituximab + prednisone arm vs. prednisone), were: bronchitis (3 patients [7.9%] vs. 7 patients [19.4%]), urinary tract infection (2 patients [5.3%] vs. 3 patients [8.3%]), fungal infection (2 patients [5.3%] vs. 2 patients [5.6%]), skin bacterial infection (1 patient [2.6%] vs. 3 patients [8.3%]), herpes virus infection (3 patients [7.9%] vs. 0 patients), herpes zoster (2 patients [5.3%] vs. 1 patient [2.8%]), oral herpes (2 patients [5.3%] vs. 1 patient [2.8%]), and conjunctivitis (2 patients [5.3%] vs. 0 patients).

In Study WA29330 (PEMPHIX), no opportunistic infections occurred during the study.

NHL/CLL

Infections are very common in patients receiving rituximab (≥ 10% of patients), based on pooled clinical trial experience.

In order to provide a coherent view of the rates of infections associated with use of rituximab in various patient sub-populations, the clinical data below are presented sub-

divided by oncological indication and stage(s) when rituximab was administered (DSR 1066792, dated March 2016).

NHL Induction Only (BO16368, M39021, M39045)

Forty-nine (49) % of patients (384 out of a total 778 patients) who received rituximab in the induction phase reported at least 1 infectious adverse event (AE). In 47% of reported infectious events, the infectious agent was unspecified.

Bacterial infections were reported in 4.5% of patients. *E. coli* was the commonest bacterial pathogen (10 events), followed by *Staphylococcus* (7 events). No single type of infection, however, stood out and none accounted for more than 1% of events. The pattern was similar for serious infections with *E. coli* and *Staphylococci* leading the counts but no single event accounting for a majority share of events.

Viral infections were reported in 5.4% patients, with *Herpesviridae* accounting for 2.7% and hepatitis B accounting for 0.3%. A similar trend was noted for serious infections.

Fungal infections accounted for 2.3% patients with *Candida spp* accounting for 1% of these, followed by *Pneumocystis* at 0.7%. A similar trend was observed for serious fungal infections with *Candida* causing 2 out of the 3 reported fungal SAEs.

Opportunistic infections were reported in 0.6% cases (2 cases of *Candida* infection, 2 of *Herpesviridae* and 1 case of aspergillosis). No opportunistic bacterial infection was reported (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

Sixty (60) % of patients in studies where rituximab was given during both induction and maintenance phases for NHL reported at least 1 infectious event, 7.7% of which were reported as serious; in 56% of cases the causative agents were unspecified.

Bacterial infections were reported in 3.2% of patients, but no single species was responsible for a majority of infections. In 1.2% patients the bacterial infections were reported as serious, with *Clostridium difficile* reported in 0.2%.

Viral infections were reported in 5.7% of patients with *Herpesviridae* forming the largest group, being reported in 4.4% of patients. The majority of viral infections were non-serious with only 1.1% of the patients being reported as serious; *Herpesviridae* remained the commonest reported agent in this group.

Fungal infections were reported in 2.8% of patients, serious fungal infections reported in 1.8%. *Candida* was the commonest reported fungal infectious agent at 1.8% of all infections and 0.6% of serious infections.

Opportunistic infections were reported in only 0.33% of patients, including 1 case of *Pneumocystis jiroveci* pneumonia (PJP). No viral or bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18264)

Forty-four (44) % of patients who received rituximab for maintenance therapy reported at least 1 infectious AE.

Bacterial infections accounted for 4.4% patients with *E. coli* reported most commonly at 1% and *Staphylococci* at 0.8%. Two cases of serious infections were reported.

Viral infections accounted for 7.2% patients with *Herpes spp* being the most significant recognized infectious agent in this group at 4.6%. Six cases of serious viral infections were noted, including one case of PML.

Fungal infections were reported in 1.8% of patients, with *Candida spp* accounting for 0.8% of these cases. No serious fungal infections were reported.

Opportunistic infections were reported in only 2 cases which included 1 case of PML and 1 of mycobacterial infection. No fungal or bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

B-NHL pediatric (BO25380)

Infections were common during the overall treatment period of the study, occurring in 52.3% of subjects in the chemotherapy arm and 62.3% of subjects in the chemotherapy plus rituximab arm. The most common infections (≥10%) reported in the chemotherapy plus rituximab arm were sepsis (17.9%), device related infection (13.0%) and lung infection (13.0%).

CLL (BO17072, ML17102)

Thirty-three (33) % of patients administered rituximab in clinical trials reported at least 1 infectious AE; 18% of these were serious events. In 24% of these cases the causative agent was unspecified.

Bacterial infections were reported in 2.1% of patients. Cellulitis was reported most commonly (0.3%) but no specific organism was noted. For serious infections, bacteria were reported in 1.8% patients.

A total of 9.6% of patients reported viral infections while on rituximab during CLL clinical trials. *Herpesviridae* accounted for 5% among these and hepatitis B accounted for a further 1.1%. 3.8% of patients reported serious viral infections with *Herpesviridae* reported most commonly, followed by hepatitis B.

Fungal infections were reported in 3.6% patients with *Candida* reported in 1.6% and *P. jirovecii* reported in 0.7%. Serious fungal infections were reported in 1.3% patients, *P. jirovecii* accounting for 0.7%.

Opportunistic infections were reported in 2.9% cases. The leading pathogens in this group were PJP (5 cases) and *Aspergillus* (4 cases). No bacterial opportunistic infections were reported (DSR 1066792, dated March 2016).

Severity and nature of risk:

RA

In the All Exposure population, 72.6% (2611/3595) of patients experienced at least one infection. Infections observed in ≥5% of patients were upper respiratory tract infection (URTI, 26%), nasopharyngitis (18%), urinary tract infection (UTI, 17%), bronchitis (14%), diarrhea (11%), sinusitis (12%), influenza (8%), gastroenteritis (7%), and pneumonia (5%). The majority of infections were mild to moderate in severity. Severe infections (CTC Grade 3) were reported in 8% of cases, and were life threatening in < 1% and fatal in <1%.

The rate of all infections was highest during the first 12 months after administration of rituximab, decreased thereafter and remained stable across multiple treatment courses. Notably, the rate of serious infections was not higher during the first 12 month period after first exposure to rituximab than in the subsequent periods (DSR 1066792, dated March 2016). The rate and nature of all infectious events was similar over multiple treatment courses, with no evidence of an increased risk of infection with cumulative exposure to rituximab.

Seven serious opportunistic infections were reported in the All Exposure RA population, and 1 in the original placebo treatment-group.

GPA/MPA

Upper respiratory tract infections were the commonest reported infections (8.1%, 8/99), followed by nasopharyngitis (6.1%), sinusitis (5.1%), UTI (5.1%), and pneumonia (4%), (DSR 1066792, dated March 2016).

Serious infections comprised mainly respiratory tract infections. The majority of patients experienced mild-to-moderate (Grade 1 or 2) infections.

Data from two investigator-sponsored studies of refractory/relapsing GPA/MPA, comparing the dose of 2x1000 mg vs. 4x375mg/m² (Jones et al. 2009 and Smith et al. 2012), are similar to the data from the RAVE study regarding the infection rate. The most frequently reported serious infections were RTIs, as reported in RAVE.

Patients in RAVE were required to receive pneumocystis prophylaxis. After 18 months there had been a total of 2 non-serious opportunistic infections (*Mycobacterium avium complex* and esophageal *Candida*) reported in the rituximab group.

In Study WA27893, from the 33 events of infections reported, 21 were Grade 3 to 5. The most commonly reported infection was pneumonia.

In Study ML22514 most infections reported were mild or moderate in intensity and were manageable. In the rituximab arm, the most commonly reported infections were bronchitis, nasopharyngitis, gastroenteritis and rhinitis.

In pediatric Study WA25615 (PePRS), during the overall study period, the majority of infection AEs (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were upper respiratory tract infections (12 patients [48%]) all of which were non-serious.

Pemphigus Vulgaris

A total of 217 AEs were reported in the SOC infections and infestations in the Company safety database [DSR 1080390]. The most frequently reported to the Company database (postmarketing) infectious PTs were nasopharyngitis, pneumonia, sepsis, infection and influenza. The nature of infectious AEs is in line with the known safety profile of the drug. Of all the AEs in the SOC, 51.6% (112/217) AEs were reported as serious. There were no reports of PML with rituximab for pemphigus indication [DSR 1080390].

In Study WA29330 (PEMPHIX), the majority of infections were Grade 1 or 2 (five patients in the rituximab arm experienced grade 3 or higher infections). One patient in the rituximab arm had an infection that led to treatment interruption (Grade 1 oral herpes).

NHL/CLL

Patients with NHL or CLL are already at risk of infection due to their underlying disease. This risk is increased by the myelosuppressive effects of chemotherapy and radiotherapy, and the immunosuppressive effects of corticosteroids and particular cytotoxic agents (e.g., fludarabine). Damage to mucosal barriers (e.g., due to mucositis or diarrhea) may also increase the risk of infection.

Serious viral infections including new infections, reactivation of latent infections and exacerbation of existing infections, some with a fatal outcome, have been reported in patients treated with rituximab. The majority of the patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

It is important to note that in many patients with hematological malignancies who develop infections, a pathogen is never identified because of the need to institute broad spectrum antibiotic/antiviral therapy without delay.

NHL Induction Only (BO16368, M39021, M39045)

In the study population of the above mentioned trials, 49% (384/778) of patients reported at least 1 infectious event; the pathogen was unspecified in 46% cases, and infections-not elsewhere classified (NEC) formed the largest group. Where classification was noted, bronchitis was commonest, being reported in 4.2%, followed by pneumonia (3.3%). Other infections reported in more than 1% of patients included naso-pharyngitis, sinusitis, URTI, LRTI, neutropenic infection, and UTI.

The percentage of patients reporting ≥ Grade 3 infections stood at 12% (96/778). Where information was available regarding the specific infection, pneumonia formed the largest group among severe infections with 1.6%, LRTI and *Herpesviridae* were reported in 0.6% each. In 12 cases (1.5%) the infectious event was associated with fatality (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

In the study population of the above mentioned studies, 60% (547/917) of the patients administered rituximab reported at least 1 infectious event. The pathogen was unspecified in 56% cases, and infections-NEC again formed the largest group. Where classification was noted, URTI was the commonest reported at 3.7%, followed by neutropenic infection at 3.2%. Other infections reported in > 1% of patients include bronchitis, LRTI, naso-pharyngitis, pharyngitis, pneumonia, RTIs, rhinitis, sepsis, sinusitis and UTI.

The percentage of patients reporting ≥ Grade 3 infections stood at 18% (161/917). Where classification was noted, neutropenic infection was reported most (3.2%), followed by sepsis (1.3%), and pneumonia (1.1%). In 12 cases (1.3%) the infectious event had a fatal outcome (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18265)

In the PRIMA study, 44% (220.501) of patients reported at least 1 infectious event while on rituximab maintenance therapy. The pathogen was unspecified in 43% cases, with infections-NEC constituting the largest fraction. Where classification of infection was noted, bronchitis was the commonest at 11%, followed by URTI at 5.8%. Other infections that were reported in $>$ 1% of patients included lung infection, naso-pharyngitis, neutropenic infection, pharyngitis, pneumonia, RTI, rhinitis, sinusitis, and UTI.

The percentage of patients reporting $>$ Grade 3 infections stood at 4.8% (24/501). No specific site/type of infection stood out. Infection had a fatal outcome in 2 cases, including one case of PML (DSR 1066792, dated March 2016).

Pediatric B-NHL (BO25380)

Infections were common during the overall treatment period of the study, occurring in 52.3% of subjects in the chemotherapy arm and 62.3% of subjects in the chemotherapy plus rituximab arm. The most common infections ($\geq$10%) reported in the chemotherapy plus rituximab arm were sepsis (17.9%), device related infection (13.0%) and lung infection (13.0%). Grade $>$3 infections were reported in 19.1% of subjects in the chemotherapy plus rituximab arm (primarily events of sepsis). Three (1.2%) of the events in the chemotherapy plus rituximab arm were fatal (all events of sepsis).

CLL (BO17072, ML17102)

Thirty-three (33) % of patients (226/676) in CLL clinical trials reported at least 1 infectious event. The pathogen was unspecified in 24% cases. Where infection classification was noted, bronchitis was the commonest reported at 3.6%, followed by pneumonia at 3.5% and URTI at 3.4%. Other infections which were reported in $>$ 1% of patients included naso-pharyngitis, RTI, sepsis and sinusitis.

The percentage of patients reporting $\geq$ Grade 3 infections was 18% (121/676). The commonest reported infection in this group was pneumonia (4.0%), followed by sepsis and bronchitis (1.5% each). Infectious events led to fatality in 22 cases (3.3%), (DSR 1066792, dated March 2016).

Opportunistic infections are infections occurring in a compromised host, which are caused by microorganisms that normally do not cause serious disease in healthy people. A range of organisms can cause opportunistic infections and these overlap with non-opportunistic infections (which occur in healthy individuals), neutropenic infections, and reactivation of latent viral infections. Opportunistic infections range in severity from mild to life-threatening or fatal. Commonly recognized serious opportunistic infections include viruses (*Cytomegalovirus* [*CMV], Varicella Zoster, Herpes Simplex and John*

Cunningham [JC] viruses), fungi (*Pneumocystis pneumoniae/jiroveci, Aspergillosis*, some *Candida* infections, cryptococcal and coccidioido-mycosis), bacteria [*Mycobacterium avium complex and Mycobacterium tuberculosis*] and protozoa [*Cryptosporidium* and *Toxoplasma*]).

Seriousness/Outcomes:

Serious infections for oncology and GPA/MPA trials were defined as those infections which resulted in death, a life-threatening event, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly/birth defect. For RA trials, serious infections were defined as those which were reported as SAEs or required treatment with an IV anti-infective.

RA

In the All Exposure population (all data, irrespective of treatment course) 415/3595 (11.5%) patients experienced a total of 532 serious infections following treatment with rituximab, with an overall rate of 3.76 per 100 patient-years (95% CI: 3.46;4.09), 2.71/100 patient-years in patients observed for > 5 years. This is comparable with placebo populations (3.79; CI: 2.80; 5.13) and also with rates reported previously in rituximab-treated patients at 9.5 years observation (3.94/100 patient-years and 3.26/100 patient-years, respectively), (DSR 1066792, dated March 2016).

The rate of serious infections was stable across time periods and also between multiple courses of rituximab treatment. There was no evidence of an increased risk of serious infection with cumulative exposure to rituximab.

Table 22, displays the rates of serious infections by treatment course over the first 7 courses, and Table 23 displays a summary of the serious infections reported in at least 5 patients.

Table 22 Summary of Rate of All Serious Infections per 100 Patient Years (All Exposure RA Population)1

Incidence rates	All Exposure Population (N =3595)	First Course (N = 3595)	Second Course (N = 2752)	Third Course (N = 1744)	Fourth Course (N = 1471)	Fifth Course (N = 1202)	Sixth Course (N = 906)	Seventh Course (N = 709)
Total Patient-years	14816	3957	3586	1947	1596	1216	834	615
Number of Serious Infections	532	160	129	67	61	58	26	15
Serious Infections Per 100 Patient-years	3.76	4.0	3.6	3.4	3.8	4.8	3.1	2.4
95% CI for Rate Per 100 Patient-years	3.5:4.1	3.5:4.7	3.0:4.3	2.7:4.4	3.0:4.9	3.7:6.2	2.1:4.6	1.5:4.0

[1]Data cutoff: September 2012.

Table includes all events reported as serious and/or treated with IV Antibiotics.

Table 23 Summary of Serious Infections Reported in ≥ 5 Patients (All Exposure Rheumatoid Arthritis Population)

Body System/ Adverse Event	All Exposure Population N = 3595 No. (%)
ALL BODY SYSTEMS	
Total Pts with at Least one AE	415 (12)
Total Number of AEs	532
INFECTIONS AND INFESTATIONS	
Total Pts With at Least one AE	381 (11)
PNEUMONIA	76 (2)
CELLULITIS	39 (1)
URINARY TRACT INFECTION	35 (<1)
GASTROENTERITIS	23 (<1)
BRONCHITIS	17 (<1)
DIVERTICULITIS	13 (<1)
LOWER RESPIRATORY TRACT INFECTION	13 (<1)
BRONCHOPNEUMONIA	12 (<1)
APPENDICITIS	11 (<1)
PYELONEPHRITIS	11 (<1)
SEPSIS	11 (<1)
PYELONEPHRITIS ACUTE	9 (<1)
UROSEPSIS	9 (<1)
ARTHRITIS BACTERIAL	8 (<1)
RESPIRATORY TRACT INFECTION	7 (<1)
CLOSTRIDIUM DIFFICILE COLITIS	6 (<1)
INFECTION	6 (<1)
POSTOPERATIVE WOUND INFECTION	5 (<1)
SINUSITIS	5 (<1)
GASTROINTESTINAL DISORDERS	
Total Pts With at Least one AE	15 (<1)
DIARRHOEA	8 (<1)

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
** Reported as serious and/or treated with IV Antibiotics.
Includes placebo data from patients treated with Rituximab who then received placebo as retreatment
Imputed start dates were used to identify whether the adverse event was treatment emergent.
Terms were identified by using the Infections AEGT and the identifying tick box on the adverse event page for studies
U3374G, U3384G, U3924G, WA17044, WA17045 and WA17047
AE11 20NOV2012:13:09:42
Source: stae11sifc_a

With the exception of the 15 deaths, the majority of infections (non-serious and serious infections) followed a typical course and were successfully treated with standard antibiotics.

The most frequently reported serious infections in the All-Exposure population were lower respiratory tract infection (LRTI; 3%, 114 patients), predominantly pneumonias (2.7%, 96 patients). Of the 11.5% patients who reported serious infections, 8% reported no specific pathogen, 2% reported bacteria and $<1\%$ reported viruses and fungi each (DSR 1066792, dated March 2016).

In the All Exposure RA population, 7 serious opportunistic infections were reported. These included 2 cases of atypical pneumonia (no organisms isolated) and 1 case each of *Candida* septicemia, pharyngeal abscess (organism unspecified), *Scedosporium* lung infection, PJP (leading to withdrawal) and PML (with fatal outcome). One event of PJP occurred in the placebo population. Among other infections, 1 case of de novo HBV infection occurred in the All Exposure population, as well as 2 cases of pulmonary tuberculosis (TB), both treated with a course of standard anti-TB medication. There were no reported cases of extrapulmonary TB, atypical *Mycobacterial* infection or multidrug-resistant TB (DSR 1066792, dated March 2016).

Fifteen serious infections ($<1\%$) in the All Exposure population resulted in death. Seven fatal cases were from respiratory infections, 6 from septic events (including septic shock) and 1 patient each died from *C.difficile* colitis and PML. No apparent relationship between time of event onset and time since the first rituximab dose was identified (range of 145 to 2886 days). Four of the fifteen serious infection events with fatal outcome were assessed as related to the study treatment (2 events of septic shock, and 1 each of sepsis and PML); while other events were assessed as not related to the study treatment (DSR 1066792, dated March 2016).

GPA/MPA

In the RAVE study the proportions of rituximab patients experiencing a serious or severe (Grade ≥ 3) infectious AE groups at 6 months was 11.1% (11/99 patients) for serious infections and 10.1% (10/99 patients) for severe infectious events. No infection events were reported as fatal in rituximab treated patients. By 18 months the incidence of serious infections was 15.2%. The incidence of serious infections reported in rituximab-treated patients were consistent with those observed with the control arm (cyclophosphamide) treatment, where the incidence of serious infections was 15.3%. Similarly, the incidence of severe infections was comparable at 13.1% for the rituximab and 13.3% for the cyclophosphamide group at 18 months.

Given the small number of serious and/or severe infectious events reported, no single organism (bacterial, viral or fungal) stood out from the data (DSR 1066792, dated March 2016).

The 2 opportunistic infections that were reported in the RAVE study were non-serious.

In Study WA27893, fourteen patients had 24 serious infections with the most reported terms being gastroenteritis, influenza, pneumonia and staphylococcal bacteremia. One patient died due staphylococcal bacteremia and septic shock.

In Study ML22514, the incidence of serious infections was similar between the two treatment arms (12.3% rituximab vs 12.1% azathioprine) and the most commonly reported serious infection in the rituximab arm was bronchitis. A total of three

opportunistic infections were reported in study ML22514 (all serious); two patients in the rituximab arm experienced one event each of severe oesophageal candidiasis and moderate *pneumocystis jirovecii* pneumonia, and one patient in the azathioprine arm experienced moderate atypical mycobacterial pneumonia. One patient in the azathioprine arm died due to infection versus none in the rituximab arm.

In the DSR 1081144 (data cut-off date: 03-Mar-2017) the following serious infections were reported in the Roche global safety database; pneumonia (n=18), infection (not otherwise specified, n=13), lower respiratory tract infection (n=7), pneumonia bacterial (n=6) and sinusitis (2).

In pediatric Study WA25615 (PePRS), during the Overall Study Period, 105 infection AEs were reported in 23 patients (92%) of which the majority (96 out of 105 AEs [91%]) were reported to be non-serious. Similar to the Remission Induction Phase, the most frequently reported infections during the overall study period were upper respiratory tract infections (12 patients [48%]) all of which were non-serious.

Pemphigus vulgaris

In Study ML22196, 3 patients (7.9%) from the rituximab + prednisone arm experienced 5 serious infections. In the prednisone arm, 1 patient (2.8%) experienced 1 serious infection. The PTs for serious infections (rituximab + prednisone arm vs. prednisone) were *pneumocystis jirovecii* pneumonia (1 patient in each treatment arm), infective thrombosis (1 patient vs. 0 patients), intervertebral discitis (1 patient vs. 0 patients), lung infection (1 patient vs. 0 patients), and staphylococcal sepsis (1 patient vs. 0 patients).

In Study WA29330 (PEMPHIX), in the rituximab arm 42 patients (62.7%) experienced 74 infections. In the rituximab arm, infections reported in ≥5% of patients were upper respiratory tract infection (7 patients, 10.4%), nasopharyngitis and oral candidiasis (6 patients each, 9.0%) and urinary tract infection (5 patients, 7.5%).

NHL/CLL

Serious Infections are a major cause of morbidity and mortality in patients with hematological malignancies and are a frequent complication of treatment. Infections are often severe, requiring rapid diagnosis and aggressive antibiotic treatment, and infection is often the ultimate cause of death in patients with refractory, progressive hematological malignancies such as CLL or NHL.

Opportunistic infections are a major cause of morbidity and mortality in immunosuppressed patients, including cancer patients receiving chemotherapy, organ transplant recipients, and patients with human immunodeficiency virus (HIV) infection.

NHL Induction Only (BO16368, M39021, M39045)

Serious infections were reported in 11% of patients (86/778). In 7.7% of cases no infectious agent was specified. Fatal infections accounted for 1.5% of cases (12/778). Two patients died due to bacterial infections and 1 died from *Candida* sepsis. No fatal viral infections were noted.

Serious bacterial infections were reported in 2.6% cases. *Staphylococci spp* accounted for 1% and *E. coli* for another 0.4% of these.

Serious viral infections were reported in 1% cases with *Herpesviridae* accounting for half of these (0.5%)

Serious fungal infections were reported in only 3 cases, accounting for 0.4%; these were also the only serious opportunistic infections reported. No specific pathogen stood out (DSR 1066792, dated March 2016).

NHL Induction and Maintenance (E1496, E 4494, M39022)

Serious infections were reported in 7.7% (71/917) of patients. In 6.5% patients, the pathogen was unspecified. Infections were fatal in 1.3% of cases. One patient died due to pulmonary mycosis. No causative agent was specified in the other fatal cases.

Serious bacterial infections were reported in 1.2% of patients (11 in number). No specific prominent bacterial pathogen stood out.

Serious viral infections were reported in 1.2% of patients (10/917) and in these studies too, *Herpesviridae* were the commonest reported pathogen, accounting for half the reported serious viral infections.

Serious fungal infections were reported in 1.0% of patients (9/917). *Candida spp* were the largest group, accounting for 0.6% of the reports. One case of PJP was reported.

Serious opportunistic infections were reported in 2 cases, 1 of PJP and the other with pulmonary mycosis (DSR 1066792, dated March 2016).

NHL Maintenance Only (MO18265)

Serious infections were reported in 5.2% (26/501) of patients who received maintenance rituximab in the MO18265 study. 0.4% (2/501) of patients had a fatal infectious event, which included 1 case of PML. No fatal bacterial or fungal infections were noted.

Serious bacterial infections were reported in 0.4% of cases. No specific pathogen stood out.

Serious viral infections were reported in 6 cases, which included 2 cases of hepatitis B.

No serious fungal infections were noted.

Two serious opportunistic infections were reported, 1 case of PML and 1 of mycobacterial infection (DSR 1066792, dated March 2016).

CLL (BO17072, ML17102)

Eighteen (18) % (125/676) of patients receiving rituximab for CLL in clinical studies reported a serious infection. In most cases the pathogen was not specified. 3.3% of patients had fatal infectious events. Sepsis and respiratory tract infections (RTIs) accounted for a major share of fatalities where the pathogen was not specified. Viral infections (including 2 cases of hepatitis B) were associated with 6 fatal events and aspergillosis was associated with 1 fatal event. No fatal bacterial infections were noted.

Serious bacterial infections were reported in 1.8% (12/676) cases. No specific pathogen stood out

Serious viral infections were reported in 3.8% (26/676) of cases with *Herpesviridae* accounting for almost half of these (12 cases) and hepatitis B accounting for another 6.

Serious fungal infections were reported in 1.3% (9/676) of patients and included 2 cases of PJP and 2 cases of aspergillosis.

Serious opportunistic infections were reported in 2.0% of patients and mainly comprised Pneumocystis and *Aspergillus*. Two serious CMV infections were also reported (DSR 1066792, dated March 2016).

Reversibility:

Infections are a frequent complication of treatment and major cause of morbidity and mortality in patients with hematological malignancies. Many infections occurring in immunocompromised patients can be cured, although opportunistic fungal and viral infections typically are associated with high morbidity and mortality, and may require long-term treatment to prevent relapse. The majority of infections occurring in patients receiving rituximab for RA and GPA/MPA are non-serious and are successfully cured with standard antiinfective agents (See further information in risks of *PML*). The extent of reversibility depends on the pathogen. Many infections caused by common respiratory and enteric viruses are likely to resolve completely without long-term sequelae, and require only supportive treatment. Others may require anti-viral therapy (e.g., HSV, CMV). Hematogenous bacterial and fungal infections require hospitalization and aggressive treatment, and are associated with substantial morbidity and mortality, although complete resolution can be expected in patients who survive. Some

opportunistic viral infections are irreversible. (See further information of risks of PML, Hepatitis B Reactivation).

Impact on quality of life:

Although the impact on patient quality of life depends on the specific pathogen, many infections in immunocompromised patients are life threatening or require prolonged hospitalization and anti-infective therapy. Serious viral infections like encephalitis can be associated with significant morbidity and mortality. Most opportunistic infections are associated with substantial morbidity and mortality. Some are irreversible and/or associated with serious long-term sequelae, disability and dependence. Depending on the seriousness of the infection, the increased chance of hospitalization and extended antibiotic therapy, the impact of infection on quality of life can be substantial.

Risk factors and risk groups:

RA, GPA/MPA, and PV

Patients with advanced RA are at a higher risk of infection than the general population largely because of altered immunological function or other factors such as decreased mobility, or therapies used to treat the underlying disease (steroids, immunomodulating agents) (Dixon et al. 2006). A retrospective cohort study found that the rate of infection in RA patients was higher than in patients without RA in each of the 11 infection categories examined; sites associated with the highest RR were joints, bone, skin and soft tissues (Dixon et al. 2006). The HR for the development of objectively confirmed infections in RA patients compared with non-RA patients, after adjustment for confounding variables, was 1.70. Within RA patients, increasing age, presence of extra-articular manifestations of RA, and co-morbidities, as well as use of corticosteroids, were strong predictors of infection risk. The predicting co-morbidities were chronic lung disease, chronic kidney disease, alcoholism, organic brain disease, and diabetes mellitus. Of the disease-modifying therapies examined, corticosteroids consistently increased infection risk. In large studies, infection rates are clearly increased with cyclophosphamide or azathioprine, whereas MTX appears to be associated with minimal, if any, increased infection risk (McLean-Tooke A et al. 2009). Data about other DMARDs are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection (Iaccarino L et al. 2007). Anti-TNF-α agents like IFX are associated with an increased risk for TB, HBV reactivation and opportunistic infections (OIs), (Botsios 2005).

Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents.

No risk factors have been identified for PV patients.

NHL/CLL

No risk factors or risk groups have been identified specifically for rituximab and the risk of infection is closely related to concomitant chemotherapy and the patient's underlying condition. In a retrospective analysis by (Bishop et al. 1981), a higher infection rate in NHL patients was associated with granulocytopenia and post splenectomy. The commonest sites of infection were lung, skin, and alimentary canal. Risk factors for infections identified in the literature in patients with CLL include advanced disease stage, previous antineoplastic therapy, refractoriness to fludarabine-based therapy, high serum β2-microglobulin level, low serum albumin level, low granulocyte count and high serum creatinine concentration (Anaissie et al. 1998).

The risk of serious viral infection/reactivation is mainly related to concomitant chemotherapy and the patient's underlying condition. Fludarabine in particular, has been associated with an increased risk of serious viral infections including CMV and JC virus/PML, and this is probably related to the induction of profound CD4+ lymphopenia.

The risk of developing PJP among HIV patients rises markedly when circulating CD4+ cell counts fall below 200/µL. A low CD4+ count is likely to be a major risk factor for opportunistic infections in other patients including those receiving immunosuppressive therapy (particularly glucocorticoids) for hematological malignancies such as NHL or CLL.

Patients with CLL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.

Preventability:

RA and GPA/MPA

The MabThera SmPC includes information pertaining to minimizing the risk of infections. Based on the mechanism of action of rituximab and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following rituximab therapy. Serious infections, including fatalities, can occur during therapy with rituximab. Rituximab should not be administered to patients with an active severe infection (e.g., TB, sepsis and opportunistic infections) or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection e.g. hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera. Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA or MPA during and following rituximab treatment, as appropriate.

Information to inform patients on the risks of PML and infections in RA and GPA/MPA has been developed as an additional risk minimization activity. This information is summarized in the Patient Alert Card (PAC).

NHL/CLL

The increased risk of infection associated specifically with administration of rituximab (if it occurs) cannot be prevented and no specific measures are recommended for rituximab itself. Rituximab should not be administered to patients with an active infection or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.

Primary prophylaxis for PCP with cotrimoxazole and for viral infection with agents such as acyclovir is not generally indicated for patients with NHL or CLL treated with rituximab. However, it may be indicated for the concomitant chemotherapy e.g., patients receiving fludarabine-based regimens (regardless of whether rituximab is given).

Patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab treatment, patients should be re-evaluated for any potential risk for infections. Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.

Indications for primary prophylaxis against opportunistic infections are not clear for patients with hematological malignancies, including patients with NHL or CLL treated with rituximab-containing regimens. Primary prophylaxis (with trimethoprim/sulphamethoxazole ± antivirals) is probably indicated for patients receiving fludarabine-based regimens (regardless of whether rituximab is given).

Impact on the benefit-risk balance of the product:

No new aspects of the important identified risk Infections, including Serious Infections, has become available to the MAH in any indications to date. The benefit-risk profile of rituximab in the approved indications remains unchanged and favorable.

Public health impact:

No public health impact in view of the population treated and the limitations placed upon administration of rituximab by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-Healthcare professionals is not anticipated.

SVII.3.1.1.2 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (ALL INDICATIONS)

Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 Terms (Roche "Risk PML" basket):

Potential mechanisms:

Rituximab's mechanism of action induces B-cell depletion that can lead to a depressed immune system. In addition, previous or concomitant immunotherapy, bone marrow infiltration, and/or corticotherapy might be important contributing factors of reactivation of latent John Cunningham (JC) virus.

Further for NHL/CLL, the underlying malignancy can also contribute to immunosuppression.

Evidence source(s) and strength of evidence:

- MabThera SmPC
- MabThera PBRER 1126778, reporting interval (18 November 2022 to 17 November 2023)
- DSR 1096921 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated January 2019 (cutoff 17 November 2019).
- DSR 1091848 PML annual update report (cut-off 17 September 2018)
- DSR 1081270 Progressive Multifocal Leukoencephalopathy (PML) – Review of reported cases in rituximab-treated patients and potential risk factors, dated 04 September 2017 (cut-off 28 June 2017)
- DSR 1074893 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2017 (cutoff 17 November 2016)
- DSR 1066994 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2016 (cutoff 17 November 2015; submitted with PBRER 1066862 on 20 January 2016), and references therein.
- Previous DSRs on PML (and references therein): 1024621 (dated 10 January 2007), abbreviated – 1030699 (dated 21 August 2008), 1038755 (dated 26 April 2010), and 1044761 (dated 11 July 2011).

- Six more cumulative updates: 1042104, 1047784, 1050172, 1053546, 1058316, and 1062808 (cutoff 18 November 2010, 17 November 2011, 17 May 2012, 17 November 2012, 17 November 2013, and 17 November 2014, respectively).
- Study WA27893 (RaVeR) Final CSR
- Study ML22514 CSR and Summary of Clinical Safety
- DSR 1081144 (cut-off date, 03 March 2017) Evaluation of the Safety Profile of Mabthera Maintenance Therapy in GPA (Wegener's) and MPA in the Post-Marketing Setting.
- Study ML22196 CSR and Summary of Clinical Safety
- DSR 1080390 (data cut-off date: 15 March 2017), a supplemental Safety Report for Rituximab in Pemphigus and Other AI Indications

Characterization of the risk:

Frequency with 95%:

RA

Confirmed PML is very rare (< 1/10,000 patients) in patients receiving rituximab for the treatment of RA, based on all data from clinical and post-marketing experience. The cumulative (cutoff 17 November 2023) reporting rate of 24 confirmed PML cases in patients treated with rituximab for RA is 2.2 per 100,000 patients (RA exposure ~ 1,078,944). Thirteen out of the 24 confirmed cases of PML resulted in fatal outcome.

GPA/MPA

Confirmed PML is very rare (< 1/10,000) in patients receiving rituximab for the treatment of GPA/ MPA. In the cumulative period until 17 November 2023, an estimation of 111,538 patients were exposed to rituximab in GPA/MPA, and 9 confirmed PML cases in GPA/MPA were reported.

No events of PML were reported in studies WA27893, ML22514, in DSR 1081144, and in pediatric Study WA25615.

Pemphigus vulgaris:

No events of PML were reported until 17 November 2023.

NHL/CLL

The reporting rate of PML in oncology indications (confirmed PML cases) is around 6.9/100,000 (442/6,347,374) patient exposures and remains very rare to rare, based on post-marketing experience and clinical trial data.

Pediatric B-NHL (BO25380)

No events of PML were reported at the time of the primary analysis.

Severity and nature of risk:

PML is a rare progressive subacute-demyelinating disorder of the central nervous system (CNS) usually leading to death or severe disability. The severity of the PML was not reported in the majority of cases.

The majority of patients with a diagnosis of PML after treatment with rituximab (across all indications), had not recovered at the time of reporting. Only in a few cases, the PML was “resolving” at the time of the last report.

Seriousness/ Outcomes:

A cumulative multiaxial search of PML events and PML confirmatory tests was carried out covering all the data for rituximab in the company safety database ARISg up to the cutoff date 17 November 2023.

RA

As of 17 November 2023, 24 cases of confirmed PML have been reported in patients treated for RA, of which 13 cases had a fatal outcome. Seventeen out of 24 confirmed cases reported in RA were reported in female patients, which is representative of the AI patient population. Of the 24 confirmed PML cases, 19 patients had significant known risk factors for PML. All 19 patients had received prior and/or concomitant immunosuppressant therapy including DMARDs and TNF inhibitors.

GPA/MPA

As of 17 November 2023, 9 cases of confirmed PML have been reported in patients with GPA/MPA. Considering the 9 confirmed PML cases in GPA/MPA and the cumulative exposure of 111,538 patients, the reporting rate is 8.0 per 100,000 patients and remains very rare. In 6 out of the total 9 cases, the patient had significant known risk factors for PML including concomitant immunosuppressive therapy predominantly cyclophosphamide, epirubicin, fluorouracil, methotrexate, azathioprine and prednisolone or had concomitant condition of polyarthralgia or underlying lymphoproliferative disease, systemic AI disease or primary immunodeficiency. In one case, prior to the start of rituximab, the patient had signs of PML which were reported as deficiencies in higher cognitive functions. In addition, this patient had a medical history of breast cancer and also had received significant prior and concomitant immunosuppressive therapy. In the remaining two literature cases, there was limited information reported for adequate assessment.

Pemphigus Vulgaris:

No information available

NHL/CLL

As of 17 November 2023, 293 cases of confirmed PML have been reported in patients treated for underlying NHL, of which 149 cases have thus far had a fatal outcome. Also, 149 cases of confirmed PML have been reported in patients treated for underlying CLL, of which 71 cases have thus far had a fatal outcome.

The majority of the patients who developed PML under rituximab therapy for NHL indications were receiving concomitant cytotoxic chemotherapy (predominantly CHOP). In a few cases, the information regarding concomitant chemotherapy was not reported. The patients also had pertinent alternative causes (past medical history like HIV, IRIS, Sjögren's syndrome, past drugs and concomitant drugs like chlorambucil, fludarabine, steroids) of underlying immunosuppression.

The majority of the patients who developed PML under rituximab therapy for CLL indications were receiving concomitant cytotoxic chemotherapy (predominantly fludarabine) or were immunosuppressed intentionally following stem cell transplant. In addition, the majority of the patients were receiving steroids. In a few cases, the information regarding concomitant chemotherapy was not reported. The patients also had pertinent alternative causes of underlying immunosuppression.

Reversibility:
There is currently no treatment available for PML, although disease progression has been slowed or halted in some patients by withdrawal of treatment.

Impact on quality of life:

PML causes gradual, progressive CNS demyelination, multifocal neurological deficit, and death, usually within 1 year. Hence, the impact on quality of life is very substantial.

Risk factors and risk groups:

RA

PML has been reported in patients with AI diseases including SLE and RA who have received immunosuppressive agents.

GPA/MPA

Cyclophosphamide is a risk factor for development of PML in GPA/MPA patients.

Pemphigus Vulgaris:

No information available

NHL/CLL

PML almost exclusively occurs in immunocompromised patients. It may occur in patients with deficits in the humoral and/or cellular immune response such as lymphoproliferative diseases, myeloproliferative diseases, carcinomatous diseases and acquired immunodeficiency due to AI diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia.

A close evaluation of rituximab associated cases of PML found that most cases occurred in individuals with a well-known concomitant risk of PML such as prior or concurrent exposure to a recognized immunosuppressant. In NHL/CLL, PML occurred at any time after rituximab treatment. Although after 12-24 months the frequency of PML was lower (DSR 1081270; dated 28 June 2017).

Preventability:

There are no approved treatments available to prevent, retard, stop, or reverse the disease once established in patients.

Impact on the benefit-risk balance of the product:

No new aspects of the important identified risk PML have become available to the MAH in any indications to date. The benefit-risk profile of rituximab in the approved indications remains unchanged and favourable.

Public health impact:

RA, GPA/MPA and PV

Limited public health impact in view of the population treated and the limitations placed upon administration of rituximab by virtue of the warnings and precautions and its formulation. Use outside of controlled environments by non-Healthcare professionals is not anticipated. The MAH continues to monitor for any such occurrences.

NHL/CLL

None. There is no reason to suppose that PML occurring in a patient receiving rituximab would have any public health implications since JC virus infection is ubiquitous and the disease is caused by reactivation of a latent form.

SVII.3.1.2 INFORMATION ON IMPORTANT POTENTIAL RISKS

None

SVII.3.2. Presentation of the Missing Information

None

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 24 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications)
Important potential risks	• None
Missing Information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding:

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities for MabThera.

Routine pharmacovigilance activities are considered by the MAH/Applicant to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities for MabThera.

Routine pharmacovigilance activities are considered by the MAH/Applicant to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or planned post-authorization efficacy studies for MabThera.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 25 Description of Routine Risk Minimization Measures by Safety Concern

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

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Table 26 Safety concern: Infections, including serious infections

Additional Risk minimization Measure	**Patient Alert Card (PAC)** (non-oncology indications)
Objectives	The objective is to provide patients with important safety information to ensure that patients seek medical attention early, to facilitate timely diagnosis of infections generally, and PML in particular.
Rationale for the additional risk minimization activity	The rationale is that with timely diagnosis of infections, continued treatment with MabThera can be evaluated and reductions or discontinuation of concomitant immunosuppressive therapy considered
Target audience and planned distribution path	Target audience: Patients. To be distributed directly to HCPs via national routes for provision to patients at each administration of MabThera. In addition, the PAC is distributed in-carton attached to the Patient Information Leaflet.
Plans for evaluating the effectiveness of the interventions and criteria for success	<u>How effectiveness of risk minimization measures for the safety concern will be measured:</u> Effectiveness will be assessed using both process and outcome indicators. <u>Process indicator:</u> The extent of distribution of the PAC by affiliates. The distribution of the PAC via the direct-to-HCP route can be considered as a process indicator, and is documented within each scheduled PSUR (PBRER) for rituximab, based on information received from the MAH's affiliates. Of note, the dissemination of the PAC attached to the patient information leaflet follows the distribution of the patient information leaflet, and therefore no longer fulfills the additional risk minimization features. <u>Outcome indicator:</u> Routine PV with relative reporting rate in relation to drug exposure. <u>Criteria for judging the success of the proposed risk minimization measures:</u> The occurrence of infections will be monitored through the MAH's routine pharmacovigilance system. <u>Planned dates for assessment:</u> Process (distribution) is measured once a year at the data lock point (DLP) -1 month. Outcome is measured at the DLP for each scheduled PSUR (PBRER) for rituximab.

Table 27 Safety concern: Progressive Multifocal Leukoencephalopathy

Additional Risk minimization Measure	**Patient Alert Card (PAC)** (non-oncology indications)
Objectives	The objective is to provide patients with important safety information to ensure that patients seek medical attention early, to facilitate timely diagnosis of PML.
Rationale for the additional risk minimization activity	The rationale is that with timely diagnosis of PML, treatment with MabThera can be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy considered.
Target audience and planned distribution path	Target audience: Patients. To be distributed directly to HCP via national routes for provision to patients at each administration of MabThera. In addition, the PAC is distributed in-carton attached to the Patient Information Leaflet.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness of risk minimization measures for the safety concern will be measured: Effectiveness will be assessed using only process indicator. Process Indicator: The distribution of the PAC via the direct-to-HCP route can be considered as a process indicator and is documented within each scheduled PSUR (PBRER) for rituximab, based on information received from our affiliates. Of note, the dissemination of the PAC attached to the patient information leaflet follows the distribution of the patient information leaflet; and therefore no longer fulfills the additional risk minimization process indicator features. Outcome indicator: Given the very low incidence of PML, and given that the purpose of the PAC is to raise awareness of PML among patients, to encourage early recognition and diagnosis, it is not possible to directly measure whether the PAC has an effect on patient outcome. Criteria for judging the success of the proposed risk minimization measures: Distribution of the PAC at affiliate level will be used as an indicator of success of the overall process. Planned dates for assessment: Process (distribution) is measured once a year. Outcome is measured at the DLP for each scheduled PSUR (PBRER) for rituximab (As agreed during the procedure EMEA/H/C/PSUSA/00002652/201911 [opinion date: 11/06/2020]).

Rationale for removal of the additional risk minimization measures

In the final PRAC AR EMEA/H/C/PSUSA/00002652/202211 which was received for the 12th PSUR in June 2023, the MAH was asked to address the following topic in a variation to be submitted within 6 months: “The need for continuation of the additional risk minimization measures in place for rituximab in the form of educational materials (EMs) to both HCPs and patients should be re-evaluated as the information included in the EM may be considered well-known by now, given that rituximab has been marketed in the EU since 1997”.

The MAH introduced EM as an additional risk minimization measure for HCPs and patients for the risks of PML and Infections, including serious infections in non-oncology indications in the EU RMP Version 7.0 endorsed by CHMP in 2012. For the two important potential risks: Off-label Use of the SC Formulation and Administration Route Error, EM for HCP has been in use since 2014.

Additionally, a PAC focused on risk of PML and infections, including serious infections in non-oncology indications was implemented in 2009 to provide patients with important safety information to ensure that patients seek medical attention early, to facilitate timely diagnosis of infections generally, and PML in particular.

Considering the well-established safety profile of MabThera and extensive post-marketing experience worldwide for more than 20 years, the risks associated with its use are well characterized and adequately described in the current labeling to allow informed benefit/risk treatment decisions for treating physicians and/or patients. In the recent PBRER review period (18 November 2022 to 17 November 2023) and based on the information presented across the previous PBRERs, the cumulative PML event reporting rates remained stable since 2011 for oncology indications and since 2013 in AI indications. No new safety concerns for the risks of PML and Infections, including serious infections have been identified, and the benefit risk assessment for RA, GPA/MPA, NHL, and CLL indications therefore remains unchanged. Comprehensive safety information on PML and serious infections is also provided in the EU SmPC and package leaflet in the form of routine risk minimization measures available to the HCPs and patients, respectively. Specifically, the MabThera SmPC warnings and precautions section states that patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. Over the past decades, extensive clinical experience and educational efforts regarding MabThera treatment have made the dissemination of safety information regarding PML to patients and HCPs a routine aspect of standard clinical practice. Physicians, particularly rheumatologists, are now well-informed about the risks of PML associated with the use of MabThera for non-oncology indications [CSR BA28478].

Similarly, over the last seven PBRERs the overall prevalence of Administration route error has been observed to be low and isolated to a small number of non-serious cases

which has been comparable across PBRERs and represents no specific pattern of AE reporting. No new safety concern was identified for the risk of Administration route error and thus the benefit-risk profile has remained unchanged over time.

All reports of AEs involving off-label use of the SC formulation were assessed periodically to determine the extent of off-label use. In addition, information concerning the route of administration, dose and dose-interval is obtained wherever possible for reported AEs concerning off-label use. Routine monitoring of Off-label use of SC formulation is in place via routine signal detection activity. No safety concerns have been identified till date for Off-label use of SC formulation.

Based on an extensive analysis of rituximab safety data gathered over the course of last 20 years, the MAH is of the opinion that the existing routine risk minimization activities and maintaining the PAC (as an additional risk minimization measure) are sufficient to address the risks of PML and Infections, including serious infections in non-oncology indications.

The MAH recommends the discontinuation of the following MabThera additional risk minimization measure: EM for HCPs and the EM for patients for the risk of PML and the risk of infections, including serious infections in non-oncology indications. The MAH continues to keep the PAC as additional risk minimization measure for the risk of PML and the risk of infections, including serious infections in non-oncology indications. The PAC aims to provide the patients with important safety information on PML and infections, especially new patients.

In addition, the MAH also recommends the discontinuation of the EMs for HCPs for the risk of Off-label use of the SC formulation and Administration route error for the SC formulation used in NHL/CLL indications.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 28 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infections, including serious infections **All Indications**	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:**

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

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Patient Alert Card (PAC) (non oncology indications)	

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR MABTHERA®

This is a summary of the RMP for MabThera®. The RMP details important risks of MabThera®, how these risks can be minimized, and how more information will be obtained about MabThera® risks and uncertainties (missing information).

MabThera® SmPC and its package leaflet give essential information to healthcare professionals and patients on how MabThera® should be used.

This summary of the RMP for MabThera® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of MabThera® RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

MabThera® is authorized for Rheumatoid Arthritis, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, Pemphigus Vulgaris, Non-Hodgkin's Lymphoma (SC and IV), Chronic Lymphocytic Leukemia (SC and IV) (see SmPC for the full indication). It contains Rituximab as the active substance and it is given by SC and IV route.

Further information about the evaluation of MabThera® benefits can be found in MabThera® EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of MabThera®, together with measures to minimize such risks and the proposed studies for learning more about MabThera® risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of MabThera®, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about AEs is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of MabThera® is not yet available, it is listed under 'missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of MabThera® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of MabThera®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications)
Important potential risks	• None
Missing information	• None

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Infections, including serious infections (All Indications)	
Evidence for linking the risk to the medicine	MabThera® SmPC DSR No 1066792 on Infections (dated March 2016) DSR 1027733 on infections (dated 29 October 2007), and references therein. DSR 1022732 on viral infections (dated August 2006) and references therein. DSR 1027731 (dated 29 October 2007), 1044830 (dated 30 June 2011). Genentech Issue Work up (dated 26 October 2007), and references therein. Genentech Issue Work up (dated 26 October 2007) and references therein. **RA** Long-term safety of rituximab: pooled analysis of the RA global clinical trial program over 11 years (cutoff: September 2012) comprising of DANCER (WA17043/U2644g), IMAGE (WA17047/U3373g), MIRROR (WA17044, U2974g), REFLEX (WA17042/IDEC 102-20), SERENE (WA17045/U2973g), SIERRA (U3374g), SUNRISE (U3384g), WA16291, WA16855 (U2653g), WA17531 (IDEC 102-21). DSR 1042044 (dated 4 February 2011) on fatal infusion reactions in RA patients, and references therein. **GPA/MPA** RAVE CSR and RAVE Summary of Clinical Safety. Study (WA27893 (RaVeR) Final CSR • Study ML22514 (MAINRITSAN) CSR and Summary of Clinical safety • DSR 1081144 (cut-off date, 03 March 2017) Evaluation of the Safety Profile of Mabthera Maintenance Therapy in GPA (Wegener's) and MPA in the Post-Marketing Setting **Pemphigus Vulgaris** • Study ML22196 CSR and Summary of Clinical Safety • DSR 1080390 (data cut-off date: 15 March 2017) a supplemental Safety Report for Rituximab in Pemphigus and Other AI Indications **NHL/CLL** Data from pivotal studies (cutoff: July 2012) comprising M39021, M39022, M39045, E4494. E1496, PRIMA (MO18264), CLL8/ML17102, and BO17072/REACH Clinical Study Reports for Study ML17102/CLL 8 and

Important Identified Risk: Infections, including serious infections (All Indications)	
	BO17072/REACH and PRIMA (MO18264) studies. • DSR1093782 review of safety data from the use of MabThera/Rituxan in pediatric patients with NHL, CLL and other oncology diseases (cut-off 31 December 2018) CSR 1088458 study Inter B NHL Ritux2010 (11 March 2019
Risk factors and risk groups	**RA, GPA/MPA, PV** Patients with advanced RA are at a higher risk of infection than the general population largely because of altered immunological function or other factors such as decreased mobility, or therapies used to treat the underlying disease (steroids, immunomodulating agents) (Dixon et al. 2006). A retrospective cohort study found that the rate of infection in RA patients was higher than in patients without RA in each of the 11 infection categories examined; sites associated with the highest RR were joints, bone, skin and soft tissues (Dixon et al. 2006). Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents. No risk factors have been identified for PV patients. **NHL/CLL** No risk factors or risk groups have been identified specifically for rituximab and the risk of infection is closely related to concomitant chemotherapy and the patient's underlying condition.
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use EU SmPC Section 4.8: Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:*

Important Identified Risk: Infections, including serious infections (All Indications)	
	Medicinal product subject to restricted medical prescription **Additional risk minimization measures:** Patient Alert Card (PAC) (non oncology indications)
Additional pharmacovigilance activities	None

Important identified risk: Progressive Multifocal Leukoencephalopathy (All Indications)	
Evidence for linking the risk to the medicine	• MabThera SmPC • DSR 1096921 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated January 2019 (cutoff 17 November 2019). • DSR 1081270 Progressive Multifocal Leukoencephalopathy (PML) – Review of reported cases in rituximab-treated patients and potential risk factors, dated 04 September 2017 (cut-off 28 June 2017) • DSR 1074893 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2017 (cutoff 17 November 2016)) • DSR 1066994 Progressive Multifocal Leukoencephalopathy (PML) Cumulative update report for Rituximab, dated 12 January 2016 (cutoff 17 November 2015; submitted with PBRER 1066862 on 20 January 2016), and references therein. • Previous DSRs on PML (and references therein): 1024621 (dated 10 January 2007), abbreviated – 1030699 (dated 21 August 2008), 1038755 (dated 26 April 2010), and 1044761 (dated 11 July 2011). • Six more cumulative updates: 1042104, 1047784, 1050172, 1053546, 1058316, and 1062808 (cutoff 18 November 2010, 17 November 2011, 17 May 2012, 17 November 2012, 17 November 2013, and 17 November 2014, respectively). • Study WA27893 (RaVeR) Final CSR • Study ML22514 CSR and Summary of Clinical Safety • DSR 1081144 Evaluation of the Safety Profile of Mabthera Maintenance Therapy in GPA (Wegener's) and MPA in the Post-Marketing Setting • Study ML22196 CSR and Summary of Clinical Safety • DSR 1080390, a supplemental Safety Report for Rituximab in Pemphigus and Other Autoimmune Indications
Risk factors and risk groups	**RA** PML has been reported in patients with autoimmune diseases (including SLE [Systemic Lupus Erythematosus] and RA) who have received immunosuppressive agents. **GPA/MPA** Cyclophosphamide is a risk factor for development of PML in GPA/MPA patients.

Important identified risk: Progressive Multifocal Leukoencephalopathy (All Indications)	
	Pemphigus vulgaris No information available **NHL/CLL** PML almost exclusively occurs in immunocompromised patients. It may occur in patients with deficits in the humoral and/or cellular immune response such as lymphoproliferative diseases, myeloproliferative diseases, carcinomatous diseases and acquired immunodeficiency due to autoimmune diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia
Risk minimization measures	**Routine risk communication:** EU SmPC section 4.4: Special warnings and precautions for use **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, includes MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of MabThera must be permanently discontinued. **Other risk minimization measures beyond the Product Information:** *Medicine's legal status:* Medicinal product subject to restricted medical prescription. **Additional risk minimization measures:** Patient Alert Card (PAC) (non oncology indications)
Additional pharmacovigilance activities	None

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

None.

II.C.2 Other studies in post-authorization development plan

None.

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6:

DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

For this particular RMP update, the text related to Patient Alert card (PAC) has been updated in line with integrated format EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.

1. ADDITIONAL RISK-MINIMIZATION ACTIVITIES FOR THE RISK OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AND THE RISK OF INFECTIONS, INCLUDING SERIOUS INFECTIONS IN NON-ONCOLOGY INDICATIONS

1.1 PATIENT ALERT CARD

The PAC for MabThera in non-oncology indications includes the following key elements and are described below in details:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and progressive multifocal leukoencephalopathy (PML), including the symptoms
- The need for patients to contact their health care professional if symptoms occur
- PAC must be agreed with the National Competent Authorities prior to distribution.

Details of the key elements of PAC for MabThera in non-oncology indications:

All patients treated with MabThera in non-oncology indications must always carry the PAC during each infusion that contains the information about the risks of the medicine, and instructions on when to contact their doctor if they experience symptoms. This card must be kept for 2 years after the patient's last dose of MabThera because the side effects can develop several months after treatment.

- There is a potential increased risk of infections with use of MabThera and the possible signs of infection may include:
  - Fever or cough all the time
  - Weight Loss
  - Pain without injury
  - Feeling generally unwell or listlessness
- Rarely MabThera can cause a serious brain infection, called PML which may result in signs such as:
  - Confusion, memory loss or problems thinking
  - Loss of balance or a change in the way the patient walks or talks

- Decreased strength or weakness on one side of the body
- Blurred vision or loss of vision

If a patient experiences any of the above signs, they should inform a doctor or nurse straight away and also tell them about their MabThera treatment.

For more details on when to seek attention from a healthcare professional and the Contact details of the MabThera prescriber and contact details for the patient's emergency contact, please refer to the PAC.