RUXIENCE (PF-05280586 /RITUXIMAB) RISK MANAGEMENT PLAN

RMP version to be assessed as part of this application

RMP Version number:	2.1
Data lock points for this RMP:	Post marketing: 17 November 2024 Clinical: 23 July 2014
Date of final sign off:	09 June 2025

Rationale for submitting an updated RMP:

The Ruxience Risk management plan (RMP) update v. 2.0 (previously 1.2) has been prepared to align with the current Innovator's RMP (version 25.1 dated 08 Mar 2024). In response to the Request for Supplementary Information (RfSI) received on 22 May 2025, v. 2.0 has been updated to v. 2.1 to address Patient Alert Card (PAC) verbiage in Part V.2.

Summary of significant changes in this RMP:

RMP Part/Module	Major Change (s)
Part I. Product Overview	Updated to reflect the updated ATC code.
Part II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indication(s) and Target Populations	N/A for biosimilar products.
Module SII. Non-Clinical Part of the Safety Specification	No major changes.
Module SIII. Clinical Trial Exposure	No changes.
Module SIV. Populations Not Studied in Clinical Trials (and subsections)	No major changes.
Module SV. Post-Authorisation Experience	Updated to include cumulative post marketing exposure with the data lock point (DLP) of 17 November 2024.
Module SVI. Additional EU Requirements for the Safety Specification	No changes.
Module SVII. Identified and Potential Risks (and subsections)	Updated to align with RP RMP v. 25.1 dated 08 March 2024. The following important identified risks were removed: • Hepatitis B reactivation (All Indications) • Hypogammaglobulinaemia (Non-oncology indications) The following important potential risks were removed: • Relapses (GPA/MPA only) • Administration route error (NHL/CLL) The following missing information was removed: • Long-term use in GPA/MPA patients (GPA/MPA only)

RMP Part/Module	Major Change (s)
Module SVIII. Summary of the Safety Concerns	Updated to reflect the list of safety concerns listed in the RP RMP v. 25.1 dated 08 March 2024.
Part III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Routine Pharmacovigilance Activities Updated to remove reference to all the DCAs, including the one for PML, in line with removal of the guided questionnaires in the RP RMP v. 25.1 dated 08 March 2024. Additional Pharmacovigilance Activities No changes.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	None.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Updated to remove RMMs related to the removed safety concerns according to Modules SVII and SVIII and to remove reference to the educational material (EM) for HCPs and patients for the retained important identified risks. In response to the RfSI received on 22 May 2025, the wording "(non-oncology indications)" was removed from the tables' title in Table 22 and Table 23 to make clear it referred to the PAC. Additionally, the objective and the target audience of the PAC have been aligned with those of the reference product, MabThera, RMP version 25.1 dated 08 March 2024.
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN	Updated to reflect changes made to Modules SV, SVII, SVIII, Part III, and Part V.
PART VII ANNEXES	Annex 4 has been updated to remove all the DCAs. Annex 6 has been updated to remove reference to the EM for HCPs and patients. Annex 7 has been updated to remove literature references of the removed risks. Annex 8 has been updated to reflect changes made in Ruxience RMP version 2.1.

Other RMP versions under evaluation:

RMP Version Number:	Submitted on:	Procedure number:
NA	NA	NA

QPPV name[a]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

[a] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BAL	Burkitt leukaemia (mature B-cell acute leukaemia)
BL	Burkitt lymphoma
BLL	Burkitt-like lymphoma
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYC	Cyclophosphamide
DCA	Data capture aid
DLBCL	Diffuse large B-cell lymphoma
DLP	Data-lock point
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EM	Educational material
EMA	European medicines agency
EPAR	European public assessment report
EU	European Union
GPA	Granulomatosis with polyangiitis
HBV	Hepatitis B virus
HCP	Health care professional/provider
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IFX	Infliximab
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
INN	International non-proprietary name
IRR	Infusion related reaction
IV	Intravenous
JC	John Cunningham (virus)
KLH	Keyhole limpet haemocyanin
LLT	Low level term
LRTI	Lower respiratory tract infection
LTB-FL	Low tumour burden follicular lymphoma
MAH	Marketing authorisation holder
MedDRA	Medical dictionary for regulatory activities
MPA	Microscopic polyangiitis
MRI	Magnetic resonance imaging
MTX	Methotrexate
N/A	Not applicable

Abbreviation	Definition
NHL	Non-Hodgkin's lymphoma
NYHA	New York heart association
OI	Opportunistic infections
PAC	Patient alert card
PD	Pharmacodynamic
PJP	*Pneumocystis jiroveci* pneumonia
PK	Pharmacokinetics
PI	Product information
PL	Package leaflet
PM	Post marketing
PML	Progressive multifocal leukoencephalopathy
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic safety update report
PT	Preferred Term
PV	Pemphigus vulgaris
PVA	Pharmacovigilance activity
QPPV	Qualified Person Responsible for Pharmacovigilance
RA	Rheumatoid arthritis
RfSI	Request for supplementary information
RMM	Risk minimisation measure
RMP	Risk management plan
RP	Reference product
SAE	Serious adverse event
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SOC	MedDRA system organ class
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TK	Toxicokinetic
TNF	Tumour necrosis factor
ULN	Upper Limit of Normal
US	United States (of America)

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Rituximab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FA01)
Marketing Authorisation Holder or Applicant	Pfizer Europe MA EEIG (Belgium)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ruxience
Marketing authorisation procedure	Centralised
Brief description of the product	PF-05280586 (rituximab) has been developed as a biosimilar to MabThera (rituximab). Ruxience will also be used in this document to refer to the Pfizer rituximab product. Chemical class: 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. Summary of mode of action: Rituximab is believed to exert its therapeutic effect by promoting B-cell lysis. It binds to the transmembrane CD20 antigen on B-Lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis. The CD20 antigen is expressed on >95% of all B-cell Non-Hodgkin's lymphomas (NHLs). *In vitro* studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents. B-cells are thought to play a central role in the rheumatoid arthritis (RA) disease process through secretion of pro-inflammatory cytokines, antigen presentation, and auto-antibody production. Important information about its composition: Rituximab is produced by deoxyribonucleic acid (DNA) technology in Chinese hamster ovary cells.
Hyperlink to the Product Information:	Module 1.3.1.

Indication(s) in the EEA	Non-Hodgkin's lymphoma (NHL) Rituximab is indicated in the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. Rituximab maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. Rituximab monotherapy is indicated for the treatment of patients with stage III-IV follicular lymphoma, who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Rituximab is indicated for the treatment of patients with CD20 positive diffuse large B cell Non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy. Rituximab in combination with chemotherapy is indicated for the treatment of paediatric 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 leukaemia (CLL) Rituximab in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies, including rituximab, or patients refractory to previous rituximab plus chemotherapy. Rheumatoid arthritis (RA) Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. Granulomatosis with polyangiitis and microscopic polyangiitis (GPA/MPA) Rituximab, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA). Rituximab, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥2 to <18 years old) with severe, active GPA (Wegener's) and MPA. Pemphigus vulgaris Rituximab is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

Dosage in the EEA	Full posology details are listed in Section 4.2 of the Summary of Product Characteristics (SmPC). *Premedication and prophylactic medications* Premedication consisting of an anti-pyretic and an antihistaminic (eg, paracetamol and diphenhydramine), should always be given before each administration of rituximab. - In patients with NHL and CLL, premedication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy. - In paediatric patients with non-Hodgkin's lymphoma, premedication with paracetamol and H1 antihistamine (= diphenhydramine or equivalent) should be administered 30 to 60 minutes before the start of the infusion of rituximab. In addition, prednisone should be given as indicated in Table 1 (see Section 4.2 of SmPC). - Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L, it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with rituximab to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. - In patients with RA, GPA (Wegener's) or MPA in disease remission or pemphigus vulgaris, premedication with 100 mg intravenous (IV) methylprednisolone should be completed 30 minutes prior to rituximab infusions to decrease the incidence and severity of infusion-related reactions (IRRs). - In patients with GPA (Wegener's) or MPA, methylprednisolone given IV for 1 to 3 days at a dose of 1000 mg/day is recommended prior to the first infusion of rituximab (the last dose of methylprednisolone may be given on the same day as the first infusion of rituximab). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered as rapidly as possible based on clinical need) during and after the 4-week induction course of rituximab treatment. - In paediatric patients with GPA or MPA, prior to the first rituximab IV infusion, methylprednisolone should be given IV for three daily doses of 30 mg/kg/day (not to exceed 1 g/day) to treat severe vasculitis symptoms. Up to three additional daily doses of 30 mg/kg IV methylprednisolone can be given prior to the first rituximab infusion. - *Pneumocystis jirovecii* pneumonia prophylaxis is recommended for patients with GPA/MPA or PV during and following rituximab treatment, as appropriate according to local clinical practice guidelines. <u>Posology</u> <u>Non-Hodgkin's lymphoma</u> *Follicular Non-Hodgkin's lymphoma* - Combination therapy 375 mg/m^2 body surface area per cycle, for up to 8 cycles (rituximab should be administered on day 1 of each chemotherapy cycle, after IV administration of the glucocorticoid component of the chemotherapy, if applicable.)

Dosage in the EEA *(Cont'd)*	- Maintenance therapy 375 mg/m^2 body surface area, 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) in previously untreated follicular lymphoma, or 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) in relapsed or refractory cases. *Relapsed/refractory follicular lymphoma* - Monotherapy 375 mg/m^2 body surface area, administered as an IV infusion once weekly for four weeks. *Diffuse large B cell non-Hodgkin's lymphoma* Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after IV infusion of the glucocorticoid component of CHOP. In paediatric patients from ≥6 months to <18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, Ruxience should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy (see Tables 1 and 2 in Section 4.2 of SmPC). The recommended dosage of Ruxience is 375 mg/m^2 BSA, administered as an IV infusion. No Ruxience dose adjustments, other than by BSA, are required. The safety and efficacy of rituximab in paediatric patients ≥6 months to < 18 years of age has not been established in indications other than previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Only limited data are available for patients under 3 years of age. Ruxience should not be used in paediatric patients from birth to < 6 months of age with CD20 positive diffuse large B-cell lymphoma. <u>Chronic lymphocytic leukaemia</u> 375 mg/m^2 body surface area 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 rituximab infusion. <u>Rheumatoid arthritis</u> A course of rituximab consists of two 1000 mg IV infusions. The recommended dosage of rituximab is 1000 mg by IV infusion followed by a second 1000 mg IV infusion two weeks later. The need for further courses should be evaluated 24 weeks following the previous course. <u>Granulomatosis with polyangiitis and microscopic polyangiitis</u> - Induction of remission - 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks (four infusions in total).

Dosage in the EEA (*Cont'd*)	The recommended dosage of rituximab for induction of remission therapy in paediatric patients with severe, active GPA or MPA is 375 mg/m2 BSA, administered as an IV infusion once weekly for 4 weeks. The safety and efficacy of rituximab in paediatric patients (≥2 to <18 years of age) has not been established in indications other than severe, active GPA or MPA. Rituximab should not be used in paediatric patients less than 2 years of age with severe, active GPA or MPA as there is a possibility of an inadequate immune response towards childhood vaccinations against common, vaccine preventable childhood diseases (e.g. measles, mumps, rubella, and poliomyelitis) (see Section 5.1 of SmPC). - Maintenance treatment Following induction of remission with rituximab, maintenance treatment should be initiated no sooner than 16 weeks after the last rituximab infusion. Following induction of remission with other standard of care immunosuppressants, rituximab maintenance treatment should be initiated during the 4-week period that follows disease remission. Rituximab should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. Patients should receive rituximab for at least 24 months after achievement of remission (absence of clinical signs and symptoms). <u>*Pemphigus vulgaris*</u> The recommended dosage of rituximab for the treatment of pemphigus vulgaris 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 month 12 and 18, and then every 6 months thereafter based on clinical evaluation. - Treatment of relapse In the event of relapse, 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.
Pharmaceutical form(s) and strengths	<u>Proposed</u>: Ruxience 100 mg concentrate for solution for infusion: Each mL contains 10 mg of rituximab. Each vial contains 100 mg of rituximab. Ruxience 500 mg concentrate for solution for infusion: Each mL contains 10 mg of rituximab. Each vial contains 500 mg of rituximab.
Is/will the product be subject to additional monitoring in the EU?	Yes.

PART II. SAFETY SPECIFICATION

PF-05280586 (Ruxience) was developed as a biosimilar to the reference product (RP) MabThera (rituximab). MabThera is currently marketed by Roche Registration Limited. As such, this risk management plan (RMP) is based on the RMP developed by Roche (v. 25.1, dated 08 March 2024), with updates made as appropriate.

Module SI. Epidemiology of the Indication(s) and Target Population (s)

PF-05280586 (Ruxience) was developed as a biosimilar to the RP MabThera (rituximab). Module SI is not applicable for biosimilar products, where the epidemiology, indications and target population are identical to the RP.

Module SII. Non-Clinical Part of the Safety Specification

Table 1 provides a summary of key safety findings from the non-clinical studies with the IV formulation of MabThera, as presented in the MabThera RMP (v. 25.1, 08 March 2024), as well as from non-clinical single and repeat dose toxicity studies conducted by Pfizer.

PF-05280586 (rituximab) (Ruxience) has been shown by extensive analytical characterisation and in vivo studies to be similar to rituximab-EU or MabThera, therefore non-clinical in vivo data generated by the RP for rituximab can be extrapolated to PF-05280586. No significant safety findings were identified in the non-clinical programme for rituximab.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-Clinical Studies	Relevance to Human Usage
Toxicity including single and repeat dose toxicity:[a] In single- and repeat-dose IV toxicity studies, rituximab was non-toxic to monkeys at the various doses and schedules studied. The maximum single dose infused was 100 mg/kg and the highest repeat-dose infused was 20 mg/kg weekly for 4 or 8 weeks. No animal deaths were attributed to rituximab in any of these studies. Moreover, there were no significant toxicologic effects from rituximab in any of the animals studied. Changes in body weight and body temperature were not observed, nor were changes in haematologic or serum chemistry parameters. Other than effects consistent with the expected pharmacologic activity of rituximab (decreased B cells in peripheral blood and lymph nodes), there were no significant histopathologic findings.	Decline of peripheral B-cell counts in human beings, associated with its pharmacological action.
Developmental and reproductive:[a] 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 foetuses. The only effect noted was the dose-dependent pharmacologic depletion of B-cells in the lymphoid organs of the foetuses. B-cell depletion following exposure *in utero* appeared to be reversible in infants once drug had cleared or fallen to non-effective levels.	Potential risk is that maternal exposure to rituximab may lead to B-cell depletion in the human foetus/infant, either from accidental in utero exposure, or from exposure to rituximab in breast milk in nursing infants, which need be monitored in the clinical setting.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-Clinical Studies	Relevance to Human Usage
Genotoxicity NA	-
Carcinogenicity NA	-
Safety pharmacology[a] Decreased peripheral B-cells, decreased B-cells in tissues, lymphoid atrophy, and alterations in haematology related to decreased B-cells.	Potential increased susceptibility to infection or an inadequate response to vaccination due to reduced B-cell numbers.
Drug interactions[a] The elimination of rituximab is mediated by both the specific CD20 receptor-mediated pathway and the non-specific 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.	Although no specific drug interaction studies have been performed, based on PK data from Phase 2/3 studies, cyclophosphamide (CYC), MTX, and corticosteroids seemed to have little or no effect on the PK of rituximab.
Other non-clinical information or data for PF-05280586	
A single-dose toxicokinetic (TK) and tolerability study in sexually-mature cynomolgus monkeys, to compare the effects of PF-05280586 to those of MabThera. PF-05280586 administered at 2, 10, and 20 mg/kg IV was well tolerated and its toxicokinetics, tolerability, and antidrug antibodies (ADAs) response was similar to MabThera.	The study supports similarity of PF-05280586 with the RP. No new significant non-clinical safety findings were identified from this study.
A repeat-dose 4-week toxicity study, both in sexually-mature cynomolgus monkeys, to compare the effects of PF-05280586 to those of MabThera PF-05280586 administered at 20 mg/kg IV weekly on Days 1, 8, 15, 22, and 29 for a total of 5 doses, was well tolerated. No marked overall differences in the immune responses between PF-05280586 and MabThera were noted. B cell depletion was as expected and similar in the 2 treatment groups.	The study did not identify any new significant non-clinical safety findings.

Abbreviations: ADA = antidrug antibody; CYC = cyclophosphamide; IgG = Immunoglobulin G; IV = Intravenous; MTX = Methotrexate; PK = Pharmacokinetics; RMP = risk management plan; RP = reference product; TK = toxicokinetic.

a. Source: MabThera RMP v. 25.1 (08 March 2024), PART II: Module SII. Nonclincal Part of the Safety Specification.

Module SIII. Clinical Trial Exposure

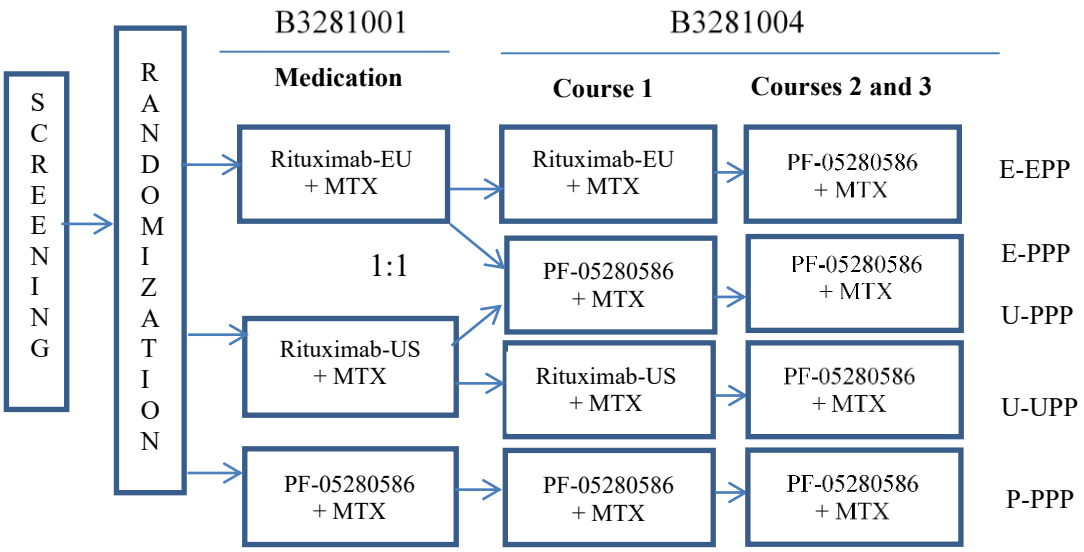
The clinical development program for PF-05280586 aimed at establishing that there were no clinically meaningful differences in the expected PK, safety, efficacy, and immunogenicity among PF-05280586, MabThera (ie, the commercially available rituximab RP in the EU, rituximab-EU), and Rituxan [ie, the commercially available rituximab RP in the United States (US)] (rituximab-US). The clinical development program includes:

- **Study B3281006**, a double blind, randomized, comparative clinical trial evaluating the efficacy, safety, PK and immunogenicity of PF-05280586 versus rituximab EU in patients with CD20 positive, LTB-FL in the first line treatment setting.

- **Study B3281001**, a 1:1:1 randomized, double-blind parallel group study that compared the PK, pharmacodynamic (PD), and safety (including immunogenicity) of a single course of treatment dosed on Day 1 and Day 15 of PF-05280586 to rituximab-EU or rituximab-US in patients with active RA on a background of MTX who had an inadequate response to 1 or more TNF antagonist therapies.

- **Study B3281004**, a randomized double blind extension study conducted in patients who had participated for at least 16 weeks in the prior B3281001 study and had not received intervening treatment (ie, in the period when the patient completed participation in Study B3281001 and sought enrolment in Study B3281004) with investigational agents or other biologics (including rituximab-EU and rituximab-US). The primary objective of Study B3281004 was to provide continued access to patients in Study B3281001, to three additional treatment courses 24 (+/-8) weeks apart. Patients who were assigned to licensed product in Study B3281001 were assigned in a blinded manner (1:1) to receive either the previously assigned licensed product or PF-05280586 for the first course of treatment (see Figure 1). In subsequent treatment courses, all subjects were assigned to receive PF-05280586.

Figure 1. Randomization of Patients to Treatment Arms in Rituximab Study B3281001 and Extension Study B3281004 in Rheumatoid Arthritis Patient[a]



Abbreviations: EU =European Union; MTX = methotrexate; US =United States.

a. Source: Clinical study report for study B3281004.

The following abbreviations were used to label the treatment sequence: P = PF 05280586; E = EU reference product (rituximab-EU); U = US reference product (rituximab-US). For example, the abbreviation E-EPP would indicate patients from the cohort randomized to rituximab-EU in the parent trial (B3281001) and then randomized to receive the EU reference product during Course 1 of B3281004 and then received PF 05280586 investigational product during Courses 2 and 3; U-UPP would indicate patients who were randomized to rituximab-US cohort in B3281001, were randomized to receive the US reference product during Course 1 of B3281004 and then received PF-05280586 investigational product during Courses 2 and 3; P-PPP denotes patients randomized to PF-05280586 in B3281001 were then treated with the PF 05280586 investigational product during Courses 1, 2 and 3 of B3281004.

Through 18 May 2018, a total of 391 subjects have been exposed to PF-05280586 in clinical trials. In Study B3281001, 73 subjects were randomized to the PF-05280586 group and treated, and subsequently 58 of the 73 subjects continued treatment with PF-05280586 in the extension Study B3281004 for one or more courses. In Study B3281004, a total of 122 subjects were switched to PF-05280586 during either Course 1 or 2 of the trial after initially receiving commercially available rituximab (Module 5.3.5.4 B3281004 Tables 14.4.1.1.1 and 14.4.1.1.2). In Study B3281006, 196 subjects were treated with PF-05280586.

In Studies B3281001 and B3281006, a total of 344 subjects received the following study treatments: rituximab-EU (271 subjects) (B3281006 and B3281001) and rituximab-US (73) (B3281001). Exposure data for PF-05280586 from these trials are presented in detail below. Due to the different patient populations and complexities of study design for Study B3281004, where some subjects previously treated with commercially available rituximab were switched to PF-05280586 (B3281004), the studies cannot be pooled and are presented individually below.

Table 2. Duration of Exposure by Indication and Treatment (Protocol B3281001)

Duration of Exposure	Persons (number of subjects)	Person Time (months)[a]
Indication: Rheumatoid arthritis (RA) (Rituximab 1000 mg on study Days 1 and 15+ methotrexate (MTX) 10-25 mg/week (7.5 mg/week in the event of prior poor tolerance)[b]		
PF-05280586 + MTX		
≤5 days	2	0.07
>5 days to ≤12 days	0	0.00
>12 days to ≤19 days	69	34.23
>19 days to ≤28 days	2	1.41
Total	**73**	**35.71**
Rituximab-EU + MTX		
≤5 days	1	0.03
>5 days to ≤12 days	0	0.00
> 12 days to ≤19 days	73	36.04
>19 days to ≤28 days	0	0.00
Total	**74**	**36.07**
Rituximab-US + MTX		
≤5 days	2	0.07
>5 days to ≤12 days	0	0.00
>12 days to ≤19 days	69	34.07
>19 days to ≤28 days	2	1.64
Total	**73**	**35.78**

Abbreviations: EU = European Union; IV = intravenous; MTX = methotrexate; RA = rheumatoid arthritis; US = United States.

a. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44].

b. Subjects in Study B3281001 were dosed on days 1 and 15 (+/- 1 day) with 1000 mg IV infusion (ie, 1000 mg on day 1 and 1000 mg on day 15).

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Table 3. Duration of Exposure by Indication and Treatment (Protocol B3281004)[a]

Duration of Exposure	Persons (number of subjects)	Person Time (months)[b]
Indication: Rheumatoid arthritis (RA)[c]		
P-PPP		
≤4 weeks	4	1.48
>4 weeks to ≤16 weeks	0	0.00
>16 weeks to ≤28 weeks	3	16.16
>28 weeks to ≤40 weeks	3	23.29
>40 weeks to ≤52 weeks	21	234.33
>52 weeks to ≤64 weeks	23	299.34
>64 weeks to ≤76 weeks	4	63.44
Total	**58**	**638.04**
E-EPP		
≤4 weeks	2	0.56
>4 weeks to ≤16 weeks	0	0.00
>16 weeks to ≤28 weeks	0	0.00
>28 weeks to ≤40 weeks	1	9.17
>40 weeks to ≤52 weeks	21	239.36

Table 3. Duration of Exposure by Indication and Treatment (Protocol B3281004)[a]

Duration of Exposure	Persons (number of subjects)	Person Time (months)[b]
>52 weeks to ≤64 weeks	8	102.76
>64 weeks to ≤76 weeks	0	0.00
Total	**32**	**351.84**
E-PPP		
≤4 weeks	2	0.95
>4 weeks to ≤16 weeks	0	0.00
>16 weeks to ≤28 weeks	0	0.00
>28 weeks to ≤40 weeks	2	17.21
>40 weeks to ≤52 weeks	8	88.67
>52 weeks to ≤64 weeks	17	220.11
>64 weeks to ≤76 weeks	4	62.02
Total	**33**	**388.96**
U-UPP		
≤4 weeks	1	0.49
>4 weeks to ≤16 weeks	0	0.00
>16 weeks to ≤28 weeks	1	5.98
>28 weeks to ≤40 weeks	3	24.18
>40 weeks to ≤52 weeks	11	122.73
>52 weeks to ≤64 weeks	13	166.16
>64 weeks to ≤76 weeks	1	15.18
Total	**30**	**334.72**
U-PPP		
≤4 weeks	1	0.49
>4 weeks to ≤16 weeks	0	0.00
>16 weeks to ≤28 weeks	0	0.00
>28 weeks to ≤40 weeks	2	16.29
>40 weeks to ≤52 weeks	11	128.78
>52 weeks to ≤64 weeks	14	180.12
>64 weeks to ≤76 weeks	2	30.91
Total	**30**	**356.60**

Abbreviations: E = EU reference product (rituximab-EU); EU = European Union; IV = intravenous; P = PF-05280586; RA = rheumatoid arthritis; U = US reference product (rituximab-US); US = United States.

a. Extension study of Study B3281001.

b. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44].

c. Subjects in Study B3281004 were dosed on days 1 and 15 (+/- 3 days) of each treatment course with 1000 mg IV infusion.

Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 28DEC2017 (14:07)

Table 4. Duration of Exposure by Indication and Treatment (Protocol B3281006)

Duration of Exposure	Persons (number of subjects)	Person Time (months)[a]
Indication: CD20+ low tumour burden follicular lymphoma (LTB FL) Rituximab 375 mg/m^2 body surface area[b]		
PF-05280586		
≤5 days	2	0.07
>5 days to ≤12 days	-	-
>12 days to ≤19 days	-	-
>19 days to ≤26 days	192	139.32

Table 4. Duration of Exposure by Indication and Treatment (Protocol B3281006)

Duration of Exposure	Persons (number of subjects)	Person Time (months)[a]
>26 days to ≤33 days	2	1.87
Total	196	141.26
Rituximab-EU		
≤5 days	-	-
>5 days to ≤12 days	1	0.33
>12 days to ≤19 days	-	-
>19 days to ≤26 days	195	141.46
>26 days to ≤33 days	1	0.95
Total	197	142.74

Abbreviations: EU = European Union; LTB, FL =low tumour burden, follicular lymphoma
a. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44].
b. Subjects in Study B3281006 were dosed on days 1, 8, 15, and 22 (+/- 1 day) with 375 mg/m^2 of either PF-05280586 or Rituximab-EU.
Date of Reporting Dataset Creation: 04DEC2017 Date of Table Generation: 08FEB2018 (10:29)

Table 5. Exposure by Age Group and Treatment Arm, by Indication

Age Group (years)	Persons (number of subjects)	Person Time (months)[a]
Indication: Rheumatoid arthritis (RA) (B3281001)		
Total Population: PF-05280586+ MTX		
18-44	14	5.98
45-64	47	23.72
≥65	12	6.01
Total	**73**	**35.71**
Total Population: Rituximab-EU + MTX		
18-44	12	5.42
45-64	47	23.29
≥65	15	7.36
Total	**74**	**36.07**
Total Population: Rituximab-US + MTX		
18-44	14	7.13
45-64	44	21.29
≥65	15	7.36
Total	**73**	**35.78**
Date of SDTM Dataset Creation: 23JUL2014 Date of Table Generation: 26DEC2017 (13:55)		
Indication: Rheumatoid arthritis (RA) (B3281004)[b]		
Total Population: P-PPP		
18-44	13	138.63
45-64	29	324.34
≥65	16	175.07
Total	**58**	**638.04**
Total Population: E-EPP		
18-44	5	47.77
45-64	20	217.21
≥65	7	86.86
Total	**32**	**351.84**

Table 5. Exposure by Age Group and Treatment Arm, by Indication

Age Group (years)	Persons (number of subjects)	Person Time (months)[a]
Total Population: E-PPP		
18-44	4	43.63
45-64	22	263.83
≥65	7	81.50
Total	**33**	**388.96**
Total Population: U-UPP		
18-44	7	78.25
45-64	17	182.49
≥65	6	73.98
Total	**30**	**334.72**
Total Population: U-PPP		
18-44	4	53.02
45-64	19	215.05
≥65	7	88.53
Total	**30**	**356.60**
Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 26DEC2017 (16:28)		
Indication: CD20+ low tumour burden, follicular lymphoma (LTB, FL) (protocol B3281006)		
Total Population: PF-05280586		
18-44	27	18.99
45-64	102	74.47
≥65	67	47.80
Total	196	141.26
Total Population: Rituximab-EU		
18-44	29	20.99
45-64	100	72.34
≥65	68	49.41
Total	197	142.74

Abbreviations: E = EU reference product (rituximab-EU); EU = European Union; IV = intravenous; MTX = methotrexate; P = PF-05280586; RA = rheumatoid arthritis; U = US reference product (rituximab-US); US = United States.

a. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44].

b. Extension study of Study B3281001.

Date of Reporting Dataset Creation: 04DEC2017 Date of Table Generation: 08FEB2018 (20:43)

Table 6. Exposure by Gender (by Indication)

	Persons (number of subjects)	Person Time (months)[a]
Indication: Rheumatoid arthritis (RA) (B3281001)		
Total Population: PF-05280586 + MTX		
Male	19	9.36
Female	54	26.35
Total	**73**	**35.71**
Total Population: Rituximab-EU + MTX		
Male	17	8.38
Female	57	27.69
Total	**74**	**36.07**

Table 6. Exposure by Gender (by Indication)

	Persons (number of subjects)	Person Time (months)[a]
Total Population: Rituximab-US + MTX		
Male	14	6.44
Female	59	29.34
Total	**73**	**35.78**
Date of SDTM Dataset Creation: 23JUL2014 Date of Table Generation: 27DEC2017 (00:50)		
Indication: Rheumatoid arthritis (RA) (B3281004)b		
Total Population: P-PPP		
Male	8	89.06
Female	50	548.98
Total	**58**	**638.04**
Total Population: E-EPP		
Male	3	32.59
Female	29	319.25
Total	**32**	**351.84**
Total Population: E-PPP		
Male	10	127.43
Female	23	261.53
Total	**33**	**388.96**
Total Population: U-UPP		
Male	10	112.02
Female	20	222.70
Total	**30**	**334.72**
Total Population: U-PPP		
Male	5	56.50
Female	25	300.10
Total	**30**	**356.60**
Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 27DEC2017 (12:55)		
Indication: CD20+ low tumour burden, follicular lymphoma (LTB, FL) (protocol B3281006)		
Total Population: PF-05280586		
Male	86	61.99
Female	110	79.27
Total	**196**	**141.26**
Total Population: Rituximab-EU		
Male	92	66.92
Female	105	75.82
Total	**197**	**142.74**

Abbreviations: E = EU reference product (rituximab-EU); EU = European Union; IV = intravenous; LTB, FL =low tumour burden, follicular lymphoma; MTX = methotrexate; P = PF-05280586; RA = rheumatoid arthritis; U = US reference product (rituximab-US); US = United States.

a. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44

b. Extension study of Study B3281001.

Date of Reporting Dataset Creation: 04DEC2017 Date of Table Generation: 08FEB2018 (10:30)

Table 7. Exposure by Ethnic Origin (by Indication)

	Persons (number of subjects)	Person Time (months)[a]
Indication: Rheumatoid arthritis (RA) (B3281001)		
Total Population: PF-05280586 + MTX		
Black	5	2.66
White	58	28.02
Asian	1	0.49
Other	9	4.53
Total	**73**	**35.71**
Total Population: Rituximab-EU + MTX		
Black	6	2.96
White	57	27.69
Asian	0	0.00
Other	11	5.42
Total	**74**	**36.07**
Total Population: Rituximab-US + MTX		
Black	2	0.99
White	56	26.74
Asian	3	1.48
Other	12	6.57
Total	**73**	**35.78**
Date of SDTM Dataset Creation: 23JUL2014 Date of Table Generation: 27DEC2017 (00:48)		
Indication: Rheumatoid arthritis (RA) (B3281004)[b]		
Total Population: P-PPP		
Black	1	9.95
White	43	466.29
Asian	3	23.26
Other	11	138.53
Total	**58**	**638.04**
Total Population: E-EPP		
Black	3	34.76
White	22	240.90
Asian	0	0.00
Other	7	76.18
Total	**32**	**351.84**
Total Population: E-PPP		
Black	3	22.60
White	26	307.75
Asian	0	0.00
Other	4	58.61
Total	**33**	**388.96**
Total Population: U-UPP		
Black	3	19.25
White	25	288.76
Asian	0	0.00
Other	2	26.71
Total	**30**	**334.72**
Total Population: U-PPP		
Black	2	25.49
White	21	238.21

Table 7. Exposure by Ethnic Origin (by Indication)

	Persons (number of subjects)	Person Time (months)[a]
Asian	0	0.00
Other	7	92.90
Total	**30**	**356.60**
Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 27DEC2017 (01:10)		
Indication: CD20+ low tumour burden, follicular lymphoma (LTB, FL) (B3281006)		
Total Population: PF-05280586		
Black	1	0.92
White	158	113.50
Asian	30	21.75
Other	7	5.09
Total	**196**	**141.26**
Total Population: Rituximab-EU		
Black	-	-
White	146	105.72
Asian	44	32.03
Other	7	4.99
Total	**197**	**142.74**

Abbreviations: E = EU reference product (rituximab-EU); EU = European Union; IV = intravenous; LTB, FL =low tumour burden, follicular lymphoma; MTX = methotrexate; P = PF-05280586; RA = rheumatoid arthritis; U = US reference product (rituximab-US); US = United States.

a. Months since first dose is defined as time from first dose to last dose [ie, (last dose date - first dose date + 1)/30.44].

b. Extension study of Study B3281001.

Date of Reporting Dataset Creation: 04DEC2017 Date of Table Generation: 08FEB2018 (10:31)

Module SIV. Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

PF-05280586 is a biosimilar to MabThera, and information in this module is largely based on information from the MabThera RMP (v. 25.1, 08 March 2024). Accordingly, the Ruxience (rituximab) EU Summary of Product Characteristics (EU-SmPC) is aligned to the MabThera EU-SmPC (16 May2024). Subjects were excluded from the studies according to the general criteria listed in the table below.

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme[a]

Criterion	Reason for Being an Exclusion Criterion	Is it considered as missing information? (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients.	Despite hypersensitivity being a rare occurrence, the risk of anaphylactic and other hypersensitivity reactions cannot be excluded. Patients with hypersensitivity to rituximab are not to be treated.	No.	The criterion is considered a contraindication for use in autoimmune and oncology indications.
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 (eg, tuberculosis, 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, eg, hypogammaglobulinaemia.	No.	The criterion is considered to remain a contraindication for use in autoimmune and oncology indications.
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 (eg, 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, eg,	No.	The criterion is considered to remain a contraindication for use in autoimmune and oncology indications.

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme[a]

Criterion	Reason for Being an Exclusion Criterion	Is it considered as missing information? (Yes/No)	Rationale
	hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.		
Severe heart failure [New York Heart Association (NYHA) Class IV] or severe, uncontrolled cardiac disease[b]	Angina pectoris or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.	No.	The criterion is considered to remain as contraindications for use in autoimmune indications.
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).	Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following rituximab therapy.	No.	Section 4.6 *Fertility, pregnancy and lactation* (Contraception in males and females) of the EU SmPC warns as follows: "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 Ruxience."
Pregnant or breastfeeding women.	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 rituximab during pregnancy. For these reasons, rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Breast feeding: Whether rituximab is excreted in human milk is not known.	No.	Section 4.6 *Fertility, pregnancy and lactation (Pregnancy* and *Breast-feeding,* respectively*)* of the EU SmPC warns as follows: "Ruxience should not be administered to pregnant women unless the possible benefit outweighs the potential risk." "... breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment."

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme[a]

Criterion	Reason for Being an Exclusion Criterion	Is it considered as missing information? (Yes/No)	Rationale
	However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breast-feed while treated with rituximab and for 12 months following rituximab treatment.		
Administration of live vaccines within 4 weeks prior to commencing treatment	In a non-randomised study, patients with relapsed low-grade 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 KLH neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titre). For CLL patients, similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.	No.	Section 4.4 *Warnings and Precautions for Use* of the EU SmPC (*Immunisation)* warns as follows: "The safety of immunisation with live viral vaccines, following rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with Ruxience may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced."
Patients under 18 years of age [with the exception for MabThera studies WA25615 (PePRS) and BO25380 Intergroup B-NHL-2010 trial]	The safety and efficacy of rituximab in paediatric 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 (Paediatric population*, *Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)* "safety and efficacy of rituximab in paediatric patients (≥2 to <18 years of age) has not been established in indications other than severe, active GPA or MPA"

Abbreviations: CLL = chronic lymphocytic leukaemia; EU = European Union; IgG = immunoglobulin G; KLH = keyhole limpet haemocyanin; NHL = Non-Hodgkin's lymphoma; NYHA = New York Heart Association; RMP = risk management plan; SmPC = summary of product characteristics.

a. This table is based on information provided in the MabThera RMP (v. 25.1, 08 March 2024), Module SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme (Table 20).

b. Applicable only for non-oncology indication(s).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 9. Limitations of Adverse Drug Reaction Detection[a]

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	The limitations from clinical trials to detect rare AEs have been compensated for by the extensive (>20 years) rituximab RP post-marketing exposure.	Following over 20 years of post-authorisation exposure in standard medical practice to rituximab RP, the implication of this limitation is considered to be very low.
Due to prolonged exposure	As above.	As above.
Due to cumulative effects	As above.	As above.
Which have a long latency	As above.	As above.

Abbreviations: AE = adverse event; RP = reference product.

a. This table is based on information provided in the MabThera RMP (v. 25.1, 08 March 2024), Module SIV.2 Limitations of ADR Detection Common to Clinical Trial Development Programs.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

PF-05280586 is being developed as a biosimilar to MabThera. As such, the clinical development programme was designed to include only clinical studies that were required to demonstrate biosimilarity. Therefore, the following section provides information concerning populations typically under-represented in clinical trial development programmes that are available for MabThera based on the available RMP (version 25.1, 08 March 2024). Where applicable, some exclusion of particular populations or patients with specific comorbidities is reflected in the EU-SmPC.

Table 10. Exposure of special populations included or not in clinical trial development programmes[a]

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program. In PF-05280586 Study B3281004, there was one 32-year-old female subject who received prior treatment with rituximab-US therapy for the treatment of rheumatoid arthritis (RA) in the parent Study B3281001, who became pregnant (an ultrasound on an unreported date showed a gestational sac measuring 0.52 cm, consistent with 5 weeks and 2 days of gestation, but no embryo) 154 days after the most recent dose of PF-05280586. Serious adverse event (SAE) of blighted ovum was reported with onset date of 13 January 2014 (Study Day 371). PF-05280586 was permanently discontinued in response to the event and the subject was discontinued from the study due to pregnancy. In the opinion of the investigator, there was not a reasonable possibility that blighted ovum was related to PF-05280586, concomitant drugs, or a clinical trial procedure. The study sponsor concurred with this assessment.

Table 10. Exposure of special populations included or not in clinical trial development programmes[a]

Type of special population	Exposure
Patients with relevant co-morbidities:	
- 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 haematological disorders, since rituximab does not undergo hepatobiliary excretion and is not hepatotoxic.
- 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 haematological disorders, since rituximab is not renally excreted and is not nephrotoxic.
- 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 for malignant haematological disorders, some of which are known to be cardiotoxic (notably anthracyclines).
- Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Please refer to Module SII, Table 7, Exposure by Ethnic Origin (by Indication).
Subpopulations carrying relevant genetic polymorphisms	N/A
Other:	
Paediatric patients	Not included in the clinical development program[b]

Abbreviations: N/A = not applicable; NYHA = New York Heart Association; RA = rheumatoid arthritis; SAE = Serious Adverse Event; ULN = Upper Limit of Normal; US = United States.

a. This table is based on information provided in the MabThera RMP (v. 25.1, 08 March 2024), SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes (Table 21).

b. Except in MabThera paediatric studies WA25615 in GPA and MPA and Intergroup B-NHL-2010

Module SV. Post-Authorisation Experience

SV.1 Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

The cumulative estimates of patient exposure from IBD until 17 November 2024 is provided below.

The average usage of Ruxience per patient across indications was estimated using MIDAS database. The total patients' data was available from 01 January 2020 to 30 September 2024. For cumulative exposure, the country specific total patients were divided by the available days (1,735 days) and multiplied by the required days (1,783 days) to extrapolate till 17 November 2024.

SV.1.2. Cumulative Exposure from Marketing Experience

Cumulative estimated exposures by indication, age group, gender, formulation, and region extrapolated from MIDAS data through 17 November 2024[b], are summarized in Table 11.

Table 11. Cumulative Estimated Exposure for Rituximab-Pfizer – Factored Patient Distribution[a]

Indications	Age (years)		Sex		Formulation	Region		
	17-65	>65	Male	Female	(IV)	US	EU	Japan
1L DLBCL	57,087	57,611	62,587	52,112	114,699	63,634	16,498	34,567
2L+ DLBCL	27,234	45,565	35,743	37,057	72,799	55,254	8,380	9,165
1L FL	20,164	31,948	26,711	25,401	52,112	33,781	7,332	10,998
2L+ FL	29,067	83,798	53,683	59,182	112,866	94,535	12,308	6,023
Other NHL	22,259	38,757	35,614	25,401	61,016	39,804	2,095	19,116
CLL	9,951	43,208	35,614	17,545	53,159	45,827	3,928	3,404

a. The total indication, age group, sex, and formulation percentages provided by IQVIA were not equal to 100 for Rx splits. Therefore, the total split shares are not equal to their respective cumulative and interval patient exposure total.

[b] The IPSOS data have been used to calculate the demographic data. Since, IPSOS data are a commercial data source and not a medical data source, they may not represent the best data source for patient exposure, and it is still being investigated.

Cumulative estimated exposures by region are shown in Table 12

Table 12. Ruxience Patient Exposure by Regions

Region	Patients' exposure (Cumulative through 17 November 2024)
NORTH AMERICA	328,951
~~– US~~	~~299,329~~
~~– Canada~~	~~29,622~~
EUROPE	120,249
~~– Austria~~	~~1,166~~
~~– Czech Republic~~	~~648~~
~~– Denmark~~	~~13,216~~
~~– France~~	~~29,328~~
~~– Finland~~	~~4,972~~
~~– Germany~~	~~11,505~~
~~– Hungary~~	~~5,193~~
~~– Ireland~~	~~3,785~~
~~– Italy~~	~~9,093~~
~~– Netherlands~~	~~15,051~~
~~– Poland~~	~~4,303~~
~~– Portugal~~	~~2,992~~
~~– Romania~~	~~257~~
~~– Spain~~	~~10923~~
~~– United Kingdom~~	~~2,434~~
~~Turkey~~	~~2,818~~
~~Saudi Arabia~~	~~2~~
~~Brazil~~	~~15~~
~~JAPAN~~	~~14,616~~
TOTAL PATIENTS	**466,651**

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No potential for drug misuse for illegal purpose is expected for rituximab. To date, no reports of misuse of rituximab for illegal purposes have been received for the RP (MabThera) nor for rituximab based on the post marketing experience.

Module SVII. Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The safety concerns identified in the PF-05280586 initial RMP submission are based on the safety experience of the RP (MabThera) as presented in the RMP (v. 19.2, 26 February 2019), for intravenous formulation only, and are listed in Table 13 below. The safety concerns related to the subcutaneous formulation have not been included, because they are not applicable to this marketing authorization application, which seeks approval for the IV formulation only. No additional safety concerns were identified during the clinical trials conducted using PF-05280586. Please refer to Module part II.SVII.3 for details.

Table 13. Summary of Safety Concerns in the Initial RMP Submission[a]

Summary of Safety Concerns	
Important identified risks	• Infusion related reactions (All Indications) • Infections, including serious infections (All Indications) • Progressive multifocal leukoencephalopathy (All Indications) • Hepatitis B reactivation (All Indications) • Hypogammaglobulinaemia (Non-oncology indications)
Important potential risks	• Malignant events (Non-oncology indications) • Impact on cardiovascular disease (Non-oncology indications) • Relapses (GPA/MPA only) • Off-label use in paediatric patients (All Indications) • Administration route error (NHL/CLL)
Missing information	• Use in pregnancy and lactation (All Indications) • Long-term use in GPA/MPA patients (GPA/MPA only)

Abbreviations: CLL = Chronic Lymphocytic Leukaemia; GPA = Granulomatosis with Polyangiitis; MPA = Microscopic Polyangiitis; NHL = Non-Hodgkin's Lymphoma; RMP = risk management plan.
a. Based on MabThera RMP (v. 19.2, 26 February 2019), PART II: Module SVIII -Summary of The Safety Concerns (IV only).

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

PF-05280586 was developed as a biosimilar to the RP MabThera (rituximab) and the safety concerns were based on the RMP of the RP (v. 19.2, 26 February 2019).

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

PF-05280586 was developed as a biosimilar to the RP MabThera (rituximab) and the safety concerns were based on the RMP of the RP (RMP v. 19.2, 26 February 2019). No additional safety concerns were identified from PF-05280586 clinical trial data. Further details on the safety concerns are provided in Module part II.SVII.3 below.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

This RMP is being updated to align the safety concerns to those of the RP according to the latest EU RMP version available (MabThera EU RMP v. 25.1, dated 08 March 2024).

Based on the PRAC assessment (EMEA/H/C/000165/II/0201/G), the RP MAH has reassessed both the important identified risks 'Hepatitis B reactivation (All indications)' and 'Hypogammaglobulinemia (non-oncology indications)' as well characterized, not requiring additional activities/measures, and therefore they removed them from their RMP, in line with Good Pharmacovigilance Practice (GVP) Module V rev. 2. Additionally, in the final PRAC assessment report (AR) EMEA/H/C/PSUSA/00002652/202211, received for their 12th Periodic Safety Update Report (PSUR), the Pharmacovigilance Risk Assessment Committee (PRAC) requested to re-evaluate the need for the educational materials (EMs), which were

removed from their RMP and consequently the respective associated important potential risk(s) including 'Administration route error (NHL/CLL, SC)'.

In summary the following safety concerns are being removed from current Ruxience RMP update:

Important identified risks:	• Hepatitis B reactivation(All Indications); • Hypogammaglobulinemia (GPA/MPA).
Important potential risks:	• Relapses (GPA/MPA only);[c] • Administration route error (NHL/CLL).
Missing information:	• Long-term use in GPA/MPA patients (GPA/MPA only)[c]

All these safety topics will continue to be managed via routine pharmacovigilance.

SVII.3 Details of Important Identified, Important Potential Risks, and Missing Information

Important identified risks, important potential risks, and missing information are based on information in the MabThera RMP (v. 25.1, 08 March 2024). This module includes data from both the above-mentioned RMP, PF-05280586 (Ruxience) clinical trial data, and PM data. PF-05280586 clinical trial data are presented to characterise the important risks, and are based on data from studies (B3281001, B3281004, and B3281006 – all completed at the DLP of the current RMP); data are presented for study treatment arms, PF-05280586, rituximab-EU (and rituximab-US) (as applicable). Search terms for the important risks are based on search strategies listed in the MabThera RMP and can be found in Annex 7.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

SVII.3.1.1.1. Important Identified Risk: Infections, Including Serious Infections (All Indications)

Potential mechanisms

Rituximab's anticipated 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 corticosteroid therapy can be important contributing factors.

[c] Please note that the important potential risk 'Relapses (GPA/MPA only)' and the Missing information 'Long-term use in GPA/MPA patients (GPA/MPA only)' were removed from the RP RMP in (a) prior version(s) not available to the MAH at the time of this RMP update; however, it is assumed that they were removed based on a similar rationale.

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

Evidence source and strength of evidence

PF-05280586 is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the PF-05280586 and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Characterisation of the risk

Frequency with 95% CI (as per MabThera RMP v. 25.1, 08 March 2024):

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 (data cut-off: 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.
The proportion of bacterial infections seen was 9%, 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.
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%.
The proportion of fungal infections was 9%; vulvovaginal mycotic infection and tinea pedis accounted for 3% each.
Twenty-two (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 the RAVE study, the rate of serious infections (per patient-year) was similar between the 2 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 2 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 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 Oesophageal candida)* reported in the rituximab group, and 2 opportunistic infections (1 serious and 1 non-serious) in the cyclophosphamide treatment group.

In the RP 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, 14 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 NHL/CLL pooled clinical trial experience.
In order to provide a coherent view of the rates of infections associated with use of rituximab in various patient subpopulations, the clinical data below are presented sub-divided by oncological indication and stage(s) when rituximab was administered.

<u>NHL Induction Only (BO16368, M39021, and M39045)</u>
Forty-nine (49) % of patients (384 out of a total 778 patients) who received rituximab in the induction phase reported at least 1 infectious AE. In 47% of reported infectious events, the infectious agent was unspecified.
Bacterial infections accounted for 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% of 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% of 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.

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% of 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.

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% of patients with *E. coli* reported most commonly at 1 % and *Staphylococci* at 0.8%. Two (2) cases of serious infections were reported.
Viral infections accounted for 7.2% of patients with *Herpes spp* being the most significant recognised infectious agent in this group at 4.6%. Six (6) 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.

B-NHL paediatric (BO25380)[d]
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

[d] Phase 3, Intergroup Trial for Children or Adolescents With B-Cell NHL or B-AL: Evaluation of Rituximab Efficacy and Safety in High Risk Patients. (Inter B NHL Ritux2010 study)

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 accounted for 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 %. Serious viral infections were reported in 3.8% of patients 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.

In PF-05280586 RA Study B3281001, 64 subjects experienced events reported in the Infections and infestations SOC. The overall frequency for these events was 30.1% for PF-05280586, 25.7% for rituximab-EU, and 31.5% for rituximab-US. The overall frequency of Infections, including serious infections by subject is presented in Annex 7.2.1.1 (Table 1).

In PF-05280586 RA Study B3281004, 81 subjects experienced events reported in the Infections and infestations SOC. The overall frequency for these events was 48.3%, 40.6%, 36.4%, 36.7%, and 56.7% in P-PPP, E-EPP, E-PPP, U-UPP, and U-PPP treatment arms, respectively. The overall frequency of Infections, including serious infections by subject is presented in Annex 7.2.1.1 (Table 2).

In PF-05280586 NHL Study B3281006, 115 subjects experienced events reported in the Infections and infestations SOC. The overall frequency for these events was 26.5% for PF-05280586 and 32.0% for –rituximab-EU. The overall frequency of Infections, including serious infections by subject is presented by treatment arm in Annex 7.2.1.1 (Table 3).

Severity and nature of risk

RA
In the MabThera All Exposure RA population, 72.6% (2611/3595) of patients experienced at least one infection. The majority of infections were mild to moderate in severity. Severe infections (CTC Grade 3) were reported in 8% of cases, were life threatening in <1%, and fatal in <1%.

GPA/MPA
In the RAVE study, the majority of patients experienced mild-to-moderate (Grade 1 or 2) infections.

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
There are no data from study ML22196.

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, 1 patient in the rituximab arm had an infection that led to treatment interruption (Grade 1 oral herpes).

NHL/CLL
Severity of AEs of Infections (≥Grade 3) reported in MabThera NHL/CLL studies is reported below.

NHL/CLL Studies	Severity
NHL Induction Only (BO16368, M39021, M39045) N=778	The percentage of patients reporting ≥Grade 3 infections stood at 12% (96/778). In 12 cases (1.5%) the infectious event was associated with fatality.
NHL Induction and Maintenance (E1496, E 4494, M39022) N=917	The percentage of patients reporting ≥Grade 3 infections stood at 18% (161/917). In 12 cases (1.3%) the infectious event had a fatal outcome.
NHL Maintenance Only (MO18265) N=501	The percentage of patients reporting >Grade 3 infections stood at 4.8% (24/501). Infection had a fatal outcome in 2 cases, including one case of PML
Pediatric B-NHL (BO25380)	Grade ≥3 infections were reported in 19.1% of subjects in the chemotherapy plus rituximab arm. Three (1.2%) of the events in the chemotherapy plus rituximab arm were fatal.
CLL (BO17072, ML17102) N=676	The percentage of patients reporting ≥Grade 3 infections was 18% (121/676). Infectious events led to fatality in 22 cases.

Severity of all causality AEs of Infections (including serious infections) reported more than once during PF-05280586 by Common Terminology Criteria for Adverse Events (CTCAE) grade is presented for PF-05280586 studies below. There were no subjects experiencing Grade 4/5 AEs in RA Study B3281001 (Table 14); 2 subjects who experienced Grade 4 AEs reported in RA Study B3281004 [PTs = Sinusitis (E-PPP), Arthritis bacterial (U-PPP), 1 each] (none reported in more than one subject) (Table 15) and no subjects experiencing Grade 4/5 AEs in RA Study B3281006.

Table 14. All Causality Infections (Including Serious Infections) AEs During Treatment by Grade presented by Treatment Arm (Protocol B3281001)[a]

SOC	PT	Maximum CTCAE Grade [n (%)][c]			
		Grade 1	Grade 2	Grade 3	Total
PF-05280586 + MTX (N= 73)					
Infections and infestations	**Any AEs[b]**	**7 (9.6)**	**10 (13.7)**	**5 (6.8)**	**22 (30.1)**
	Bronchitis	1 (1.4)	1 (1.4)	2 (2.7)	4 (5.5)
	Gastro-enteritis	1 (1.4)	1 (1.4)	-	2 (2.7)
	Influenza	1 (1.4)	1 (1.4)	-	2 (2.7)
	Nasopharyngitis	2 (2.7)	1 (1.4)	-	3 (4.1)
	Sinusitis	1 (1.4)	1 (1.4)	-	2 (2.7)
	Upper respiratory tract infection	2 (2.7)	2 (2.7)	-	4 (5.5)
	Urinary tract infection	2 (2.7)	-	-	2 (2.7)
Rituximab-EU + MTX (N=74)					
Infections and infestations	**Any AEs[b]**	**9 (12.2)**	**9 (12.2)**	**1 (1.4)**	**19 (25.7)**
	Bronchitis	-	2 (2.7)	-	2 (2.7)
	Gastro-enteritis	1 (1.4)	1 (1.4)	-	2 (2.7)
	Sinusitis	6 (8.1)	-	-	6 (8.1)
	Tooth abscess	-	2 (2.7)	-	2 (2.7)
	Upper respiratory tract infection	2 (2.7)	3 (4.1)	-	5 (6.8)
Rituximab-US + MTX (N=73)					
Infections and infestations	**Any AEs[b]**	**12 (16.4)**	**7 (9.6)**	**4 (5.5)**	**23 (31.5)**
	Bronchitis	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.1)
	Influenza	1 (1.4)	1 (1.4)	-	2 (2.7)
	Naso-pharyngitis	3 (4.1)	-	-	3 (4.1)
	Sinusitis	-	2 (2.7)	1 (1.4)	3 (4.1)
	Upper respiratory tract infection	6 (8.2)	1 (1.4)	-	7 (9.6)

Abbreviations: AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; MedDRA = medical dictionary for regulatory activities; MTX = methotrexate, PT = Preferred term; SOC = System organ class; US =United States.

a. Includes all data collected since the first infusion of study drug.
b. Subjects are counted only once in each row.
c. CTCAE V4.03 applied.

MedDRA (v. 17.0) coding dictionary applied.
Date of SDTM Dataset Creation: 23JUL2014 Date of Table Generation: 28DEC2017 (22:17)

Table 15. All Causality Infections (Including serious infections) AEs During Treatment by Grade presented by Treatment Arm (Protocol B3281004)[a]

SOC	PT	Maximum CTCAE Grade [n (%)]				
		Grade 1	Grade 2	Grade 3	Grade 4	Total
P-PPP (N=58)						
	Any AEs[b]	**12 (20.7)**	**9 (15.5)**	**7 (12.1)**	-	**28 (48.3)**
Infections and infestations	Bronchitis	4 (6.9)	1 (1.7)	-	-	5 (8.6)
	Conjunctivitis	2 (3.4)	-	-	-	2 (3.4)
	Gastrointestinal viral infection	3 (5.2)	-	-	-	3 (5.2)
	Nasopharyngitis	2 (3.4)	-	-	-	2 (3.4)
	Pneumonia	-	1 (1.7)	1 (1.7)	-	2 (3.4)
	Sinusitis	2 (3.4)	3 (5.2)	-	-	5 (8.6)

Table 15. All Causality Infections (Including serious infections) AEs During Treatment by Grade presented by Treatment Arm (Protocol B3281004)[a]

SOC	PT	Maximum CTCAE Grade [n (%)]				
		Grade 1	Grade 2	Grade 3	Grade 4	Total
	Upper respiratory tract infection	1 (1.7)	1 (1.7)	-	-	2 (3.4)
	Urinary tract infection	4 (6.9)	1 (1.7)	1 (1.7)	-	6 (10.3)
E-EPP (N=32)						
	Any AEs[b]	**8 (25.0)**	**5 (15.6)**	**-**	**-**	**13 (40.6)**
Infections and infestations	Bronchitis	2 (6.3)	-	-	-	2 (6.3)
	Sinusitis	2 (6.3)	-	-	-	2 (6.3)
	Upper respiratory tract infection	1 (3.1)	3 (9.4)	-	-	4 (12.5)
E-PPP(N=33)						
	Any AEs[b]	**5 (12.5)**	**4 (12.1)**	**2 (6.1)**	**1(3.0)**	**12 (36.4)**
Infections and infestations	Bronchitis	1 (3.0)	-	1 (3.0)	-	2 (6.1)
	Pneumonia	-	-	2 (6.1)	-	2 (6.1)
	Sinusitis	-	2 (6.1)	-	1 (3.0)	3 (9.1)
	Urinary tract infection	2 (6.1)	-	1 (3.0)	-	3 (9.1)
U-UPP (N=30)						
	Any AEs[b]	**6 (20.0)**	**5 (16.7)**	**-**	**-**	**11 (36.7)**
Infections and infestations	Bronchitis	3 (10.0)	-	-	-	3 (10.0)
	Nasopharyngitis	2 (6.7)	1 (3.3)	-	-	3 (10.0)
	Oral candidiasis	1 (3.3)	1 (3.3)	-	-	2 (6.7)
	Oral herpes	2 (6.7)	-	-	-	2 (6.7)
	Sinusitis	1 (3.3)	1 (3.3)	-	-	2 (6.7)
	Upper respiratory tract infection	3 (10.0)	1 (3.3)	-	-	4 (13.3)
U-PPP (N=30)						
	Any AEs[b]	**8 (26.7)**	**6 (20.0)**	**2 (6.7)**	**1 (3.3)**	**17 (56.7)**
Infections and infestations	Bronchitis	1 (3.3)	1 (3.3)	-	-	2 (6.7)
	Gastroenteritis	1 (3.3)	-	1 (3.3)	-	2 (6.7)
	Nasopharyngitis	1 (3.3)	1 (3.3)	-	-	2 (6.7)
	Sinusitis	-	2 (6.7)	-	-	2 (6.7)
	Upper respiratory tract infection	2 (6.7)	1 (3.3)	-	-	3 (10.0)
	Urinary tract infection	1 (3.3)	1 (3.3)	-	-	2 (6.7)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = EU reference product (rituximab-EU); EU = European Union; MedDRA = medical dictionary for regulatory activities; P = PF-05280586; PT = Preferred term; SOC = System organ class; U = US reference product (rituximab-US); US = United States.

a. Includes all data collected since the first infusion of study drug.

b. Subjects are counted only once in each row.

MedDRA (v. 19.0) coding dictionary applied.

CTCAE V4.03 applied.

Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 29DEC2017 (12:16)

Table 16. All Causality Infections (Including Serious Infections) AEs During Treatment by Grade presented by Treatment Arm (Protocol B3281006)[a]

SOC	PT	Maximum CTCAE Grade [n (%)]			
		Grade 1	Grade 2	Grade 3	Total
PF-05280586 (N=196)					
	Any AEs[b]	**23 (11.7)**	**24 (12.2)**	**5 (2.5)**	**52 (26.4)**
Infections and infestations	Bronchitis	1 (0.5)	2 (1.0)	-	3 (1.5)
	Gastroenteritis	2 (1.0)	-	-	2 (1.0)
	Influenza	1 (0.5)	3 (1.5)	-	4 (2.0)
	Nasopharyngitis	4 (2.0)	1 (0.5)	-	5 (2.5)
	Oral herpes	3 (1.5)	-	-	3 (1.5)
	Pharyngitis	1 (0.5)	2 (1.0)	1 (0.5)	4 (2.0)
	Respiratory tract infection	1 (0.5)	2 (1.0)	-	3 (1.5)
	Sinusitis	2 (1.0)	3 (1.5)	-	5 (2.5)
	Upper respiratory tract infection	3 (1.5)	6 (3.0)	-	9 (4.6)
	Urinary tract infection	2 (1.0)	3 (1.5)	-	5 (2.5)
Rituximab-EU (N=197)					
	Any AEs[b]	**20 (10.2)**	**40 (20.4)**	**3 (1.5)**	**63 (32.1)**
Infections and infestations	Bronchitis	1 (0.5)	6 (3.1)	-	7 (3.6)
	Conjunctivitis	2 (1.0)	1 (0.5)	-	3 (1.5)
	Cystitis	-	3 (1.5)	-	3 (1.5)
	Gastroenteritis	1 (0.5)	2 (1.0)	-	3 (1.5)
	Herpes zoster	-	3 (1.5)	-	3 (1.5)
	Influenza	4 (2.0)	2 (1.0)	-	6 (3.1)
	Nasopharyngitis	3 (1.5)	6 (3.1)	-	9 (4.6)
	Oral herpes	2 (1.0)	-	-	2 (1.0)
	Pharyngitis	3 (1.5)	1 (0.5)	-	4 (2.0)
	Rhinitis	3 (1.5)	-	-	3 (1.5)
	Sinusitis	1 (0.5)	1 (0.5)	-	2 (1.0)
	Skin infection	-	2 (1.0)	-	2 (1.0)
	Upper respiratory tract infection	2 (1.0)	3 (1.5)	-	5 (2.6)
	Urinary tract infection	1 (0.5)	4 (2.0)	-	5 (2.6)
	Viral pharyngitis	-	2 (1.0)		2 (1.0)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SOC = System organ class.

a. Includes all data collected since the first infusion of study drug.

b. Subjects are counted only once in each row.

MedDRA (v. 21.0) coding dictionary applied.

CTCAE V4.03 applied.

Date of SDTM Dataset Creation: 18MAY2018 Date of Table Generation: 31OCT2018 (12:01)

Seriousness/Outcomes

RA

In the MabThera All exposure RA population (3595 subjects), 415 subjects (11.5%) 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).

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.
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* septicaemia, 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 Hepatitis B Virus (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.

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.

GPA/MPA
In the MabThera RAVE study, the proportions of rituximab patients experiencing a serious or severe (Grade ≥3) infectious AEs was 11/99 subjects, 11.1% at 6 months. 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.

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

The proportion of rituximab patients experiencing serious infections in the MabThera NHL/CLL studies is displayed below.

NHL/CLL Studies	**Number (n [%]) of Subjects with SAEs [Fatal]**
NHL Induction Only (BO16368, M39021, M39045) N=778	86 (11.0) [12 (1.5)]
NHL Induction and Maintenance (E1496, E 4494, M39022) N=917	71 (7.7) [12 (1.3)]
NHL Maintenance Only (MO18265) N=501	26 (5.2) [2 (0.4)]
CLL (BO17072, ML17102) N=676	125 (18.0) [22 (3.3)]

For each PF-05280586 study protocols, treatment emergent adverse events (TEAEs) of infection, including serious infections, reported in more than one subjects are displayed in Table 17, Table 18, and Table 19 below by seriousness and outcome.

In RA Study B3281001, there were 3 subjects experiencing SAEs, with the following PTs reported: Pyelonephritis (1) in the PF-05280586 + MTX treatment arm, and Arthritis bacterial, Bacterial sepsis, and Septic shock (1 each) in the rituximab-US treatment arm.

There were no SAEs reported in more than 1 subject. Information for AEs occurring in more than 1 subject is presented in Table 17 below.

Table 17. All Causality Infection (Including Serious Infections) AEs by Treatment Arm by Seriousness and Outcome (Protocol B3281001)[a]

SOC	**Preferred Term**	**Number (n [%]) of Subjects with AEs**		
		Total [SAE, if any]	**Resolved**	**Not Resolved**
PF-05280586 + MTX (N = 73)				
Infections and infestations	**Any AEs[b]**	**22 (30.1) [1 (1.4)]**	**20 (27.4)**	**2 (2.7)**
	Bronchitis	4 (5.5)	4 (5.5)	-
	Gastroenteritis	2 (2.7)	2 (2.7)	-
	Influenza	2 (2.7)	2 (2.7)	-
	Nasopharyngitis	3 (4.1)	3 (4.1)	-
	Sinusitis	2 (2.7)	2 (2.7)	-
	Urinary tract infection	2 (2.7)	1 (1.4)	1 (1.4)

Table 17. All Causality Infection (Including Serious Infections) AEs by Treatment Arm by Seriousness and Outcome (Protocol B3281001)[a]

SOC	Preferred Term	Number (n [%]) of Subjects with AEs		
		Total [SAE, if any]	Resolved	Not Resolved
Rituximab-EU + MTX (N = 74)				
Infections and infestations	**Any AEs[b]**	**19 (25.7)**	**14 (18.9)**	**5 (6.8)**
	Bronchitis	2 (2.7)	2 (2.7)	-
	Gastroenteritis	2 (2.7)	2 (2.7)	-
	Sinusitis	6 (8.1)	4 (5.4)	2 (2.7)
	Tooth abscess	2 (2.7)	2 (2.7)	-
	Upper respiratory tract infection	5 (6.8)	4 (5.4)	1 (1.4)
Rituximab-US + MTX (N=73)				
Infections and infestations	**Any AEs[b]**	**23 (31.5) [2 (2.7)]**	**17 (23.3)**	**6 (8.2)**
	Bronchitis	3 (4.1)	1 (1.4)	2 (2.7)
	Influenza	2 (2.7)	2 (2.7)	-
	Nasopharyngitis	3 (4.1)	3 (4.1)	-
	Sinusitis	3 (4.1)	2 (2.7)	1 (1.4)
	Upper respiratory tract infection	7 (9.6)	6 (8.2)	1 (1.4)

Abbreviations: AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; PT = preferred term; SAE = serious adverse event; SOC = System organ class; US = United States.

a. Includes all data collected since the first infusion of study drug.

b. Subjects are counted only once in each row.

MedDRA (v. 17.0) coding dictionary applied.

Serious adverse events– according to the Investigator's assessment.

Date of SDTM Dataset Creation: 23JUL2014 Date of Table Generation: 29DEC2017 (11:57)

In RA Study B3281004, there were 8 subjects experiencing SAEs: Arthritis infective, Gastroenteritis viral, Pneumonia, Subcutaneous abscess and Urinary tract infection (1 each) in the P-PPP treatment arm (5 subjects in total); Bronchitis, Sinusitis, Wound infection staphylococcal (1 each) and Pneumonia (2) in the E-PPP treatment arm (2 subjects in total); and Arthritis bacterial (1) in the U-PPP treatment arm. Outcome information for AEs occurring in more than 1 subject is presented in Table 18 below.

Table 18. All Causality Infection (Including Serious Infections) AEs by Treatment Arm by Seriousness and Outcome (Protocol B3281004)[a]

SOC	Preferred Term	Number (n [%]) of Subjects with AEs		
		Total [SAE, if any]	Resolved	Not Resolved
P-PPP (N=58)				
Infections and infestations	**Any AEs[b]**	**28 (43.3) [5 (8.6)]**	**25 (43.1)**	**3 (5.2)**
	Bronchitis	5 (8.6)	5 (8.6)	-
	Conjunctivitis	2 (3.4)	2 (3.4)	-
	Gastrointestinal viral infection	3 (5.2)	3 (5.2)	-
	Nasopharyngitis	2 (3.4)	2 (3.4)	-
	Pneumonia	2 (3.4) [1 (1.7)]	2 (3.4)	-

Table 18. All Causality Infection (Including Serious Infections) AEs by Treatment Arm by Seriousness and Outcome (Protocol B3281004)[a]

SOC	Preferred Term	Number (n [%]) of Subjects with AEs		
		Total [SAE, if any]	Resolved	Not Resolved
	Sinusitis	5 (8.6)	5 (8.6)	-
	Upper respiratory tract infection	2 (3.4)	2 (3.4)	-
	Urinary tract infection	6 (10.3) [1 (1.7)]	5 (8.6)	1 (1.7)
E-EPP (N=32)				
Infections and infestations	**Any AEs[b]**	**13 (40.6)**	**12 (37.5)**	**1 (3.1)**
	Bronchitis	2 (6.3)	2 (6.3)	-
	Sinusitis	2 (6.3)	2 (6.3)	-
	Upper respiratory tract infection	4 (12.5)	4 (12.5)	-
E-PPP (N = 33)				
Infections and infestations	**Any AEs[b]**	**12 (36.4) [2 (6.1)]**	**12 (36.4)**	**-**
	Bronchitis	2 (6.1) [1 (3.0])	2 (6.1)	-
	Pneumonia	2 (6.1) [2 (6.1)]	2 (6.1)	-
	Sinusitis	3 (9.1) 1 (3.0)	3 (9.1)	-
	Urinary tract infection	3 (9.1)	3 (9.1)	-
U-UPP (N =30)				
Infections and infestations	**Any AEs[b]**	**11 (36.7)**	**8 (26.7)**	**3 (10.0)**
	Bronchitis	3 (10.0)	2 (6.7)	1 (3.3)
	Nasopharyngitis	3 (10.0)	3 (10.0)	-
	Oral candidiasis	2 (6.7)	1 (3.3)	1 (3.3)
	Oral herpes	2 (6.7)	2 (6.7)	-
	Sinusitis	2 (6.7)	2 (6.7)	-
	Upper respiratory tract infection	4 (13.3)	4 (13.3)	-
U-PPP (N =30)				
Infections and infestations	**Any AEs[b]**	**17 (56.7) [1 (3.3)]**	**15 (50.0)**	2 (6.7)
	Bronchitis	2 (6.7)	2 (6.7)	-
	Gastroenteritis	2 (6.7)	1 (3.3)	1 (3.3)
	Nasopharyngitis	2 (6.7)	2 (6.7)	-
	Sinusitis	2 (6.7)	2 (6.7)	-
	Upper respiratory tract infection	3 (10.0)	3 (10.0)	-
	Urinary tract infection	2 (6.7)	2 (6.7)	-

Abbreviations: AE = adverse event; E = EU reference product (rituximab-EU); EU = European Union; P = PF-05280586; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SAE = serious adverse event; SOC = System organ class; U = US reference product (rituximab-US); US = United States.

a. Includes all data collected since the first infusion of study drug.

b. Subjects are counted only once in each row.

MedDRA (v. 19.0) coding dictionary applied.

Serious adverse events – according to the Investigator's assessment.

Date of SDTM Dataset Creation: 17JUN2016 Date of Table Generation: 29DEC2017 (12:02)

In NHL Study B3281006, there were 4 subjects experiencing SAEs in the PF-05280586 treatment arm (PTs: Appendicitis, *Clostridium difficile* infection, Diverticulitis, Peritonitis, and Urinary tract infection, 1 each), with the PT Urinary tract infection only reported in more than 1 subject (5 subjects in total, of whom, 1 experienced a serious AE). There were 3 subjects experiencing SAEs in the rituximab-EU treatment arm (PTs: *Escherichia* sepsis, Hepatitis B, Kidney infection, and Viral sinusitis, 1 each). Outcome information for events reported in more than 1 subject is provided in Table 19 below.

Table 19. All Causality Infection (Including Serious Infections) AEs by Treatment Arm by Seriousness and Outcome (Protocol B3281006)[a]

MedDRA SOC	PT	Number (n [%]) of Subjects with AEs		
		Total [SAE, if any]	Resolved	Not Resolved
PF-05280586 (N=196)				
Infections and infestations	**Any AEs[b]**	**52 (26.5) [4 (2.0)]**	**49 (25.0)**	**3 (1.5)**
	Bronchitis	3 (1.5)	3 (1.5)	-
	Gastroenteritis	2 (1.0)	2 (1.0)	-
	Influenza	4 (2.0)	4 (2.0)	-
	Nasopharyngitis	5 (2.6)	4 (2.0)	1 (0.5)
	Oral herpes	3 (1.5)	3 (1.5)	-
	Pharyngitis	4 (2.0)	4 (2.0)	-
	Respiratory tract infection	3 (1.5)	3 (1.5)	-
	Sinusitis	5 (2.6)	4 (2.0)	1 (0.5)
	Upper respiratory tract infection	9 (4.6)	9 (4.6)	-
	Urinary tract infection	5 (2.6) [1 (0.5)]	5 (2.6)	-
Rituximab-EU (N=197)				
Infections and infestations	**Any AEs[b]**	**63 (32.0) [3 (1.5)]**	**57 (28.9)**	**6 (3.0)**
	Bronchitis	7 (3.6)	7 (3.6)	-
	Conjunctivitis	3 (1.5)	2 (1.0)	1 (0.5)
	Cystitis	3 (1.5)	2 (1.0)	1 (0.5)
	Gastroenteritis	3 (1.5)	3 (1.5)	-
	Herpes zoster	3 (1.5)	3 (1.5)	-
	Influenza	6 (3.0)	6 (3.0)	-
	Nasopharyngitis	9 (4.6)	9 (4.6)	-
	Oral herpes	2 (1.0)	2 (1.0)	-
	Pharyngitis	4 (2.0)	4 (2.0)	-
	Rhinitis	3 (1.5)	3 (1.5)	
	Sinusitis	2 (1.0)	2 (1.0)	-
	Skin infection	2 (1.0)	2 (1.0)	-
	Upper respiratory tract infection	5 (2.5)	5 (2.5)	-
	Urinary tract infection	5 (2.5)	5 (2.5)	-
	Viral pharyngitis	2 (1.0)	2 (1.0)	-

Abbreviations: AE = adverse event; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = System organ class.

a. Includes all data collected since the first infusion of study drug.

b. Subjects are counted only once in each row.

MedDRA (v. 21.0) coding dictionary applied.

Serious adverse events – according to the Investigator's assessment.

Date of Reporting Dataset Creation: 18MAY2018 Date of Table Generation: 31OCT2018 (12:08)

Data from the safety database[e,f]

Post-marketing (PM)[g] cases: 4642 (19.8% of total PM cases), 6924 relevant events, of which 4797 SAEs.[h]

The most frequently reported (>2%) relevant PTs were (SAEs within parenthesis): COVID-19 1208 (589), Pneumonia 791 (791), Nasopharyngitis 441 (127), Infection 387 (236), Urinary tract infection 232 (117), Sinusitis 184 (83), COVID-19 pneumonia 164 (164), Influenza 144 (56).

Overall event seriousness and outcomes are summarised below.

	Total No. of PTs (N=489) (%)[a]
Serious Events	4797 (69.3)
Hospitalisations	2201 (31.8)
Outcome: Fatal	615 (8.9)
Outcome: Resolved / Resolving	2289 (33.1)
Outcome: Resolved with Sequelae	25 (0.4)
Outcome: Not Resolved	1581 (22.8)
Outcome: unknown	2438 (35.2)

a. Please note the sum of percentages may not be 100 due to rounding.
For the outcome count, the multiple LLTs that code to the same PT within a case are counted and presented individually, whereas multiple LLTs that code to the same PT within a case are counted once. Therefore, the total count of event outcomes may exceed from the total number of events.

Reversibility

Infections are a frequent complication of treatment and major cause of morbidity and mortality in patients with haematological 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 anti-infective 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 [eg, *Herpes*

[e] Pfizer safety database contains cases of AEs reported spontaneously, cases reported from RAs, cases published in the medical literature, and cases of serious adverse events (SAEs) reported from clinical studies and other solicited sources, including marketing programs sponsored by Pfizer.

[f] The safety database was searched for rituximab Pfizer cases received cumulatively through 17 November 2024 (MedDRA v. 27.1).

[g] Post-marketing cases contain all valid spontaneous and literature cases, all serious related non interventional studies (NISs) and compassionate use cases.

[h] Please note that multiple adverse events can be reported in a single case.

simplex virus (HSV), CMV].
Haematogenous bacterial and fungal infections require hospitalisation 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).

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 hospitalisation 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 hospitalisation and extended antibiotic therapy, the impact of infection on quality of life can be substantial.

Risk factors and risk groups

RA and GPA/MPA
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).[1] 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 relative risk were joints, bone, skin and soft tissues.[1] The hazard ratio 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[2]. Data about other DMARDs are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection[3]. Anti-TNF-α agents like infliximab (IFX) are associated with an increased risk for TB, HBV reactivation and opportunistic infections (OIs)[4].
Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents.

Pemphigus vulgaris
None.

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,[5] 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 β_2-microglobulin level, low serum albumin level, low granulocyte count, and high serum creatinine concentration.[6]

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 cytomegalovirus (CMV) and John Cunningham (JC) virus/PML, and this is probably related to the induction of profound CD4+ lymphopenia.

The risk of developing PJP among human immunodeficiency virus (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 haematological 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 SmPC includes information pertaining to minimising 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 (eg, tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (eg, 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 eg, hypogammaglobulinaemia. It is recommended that immunoglobulin levels are determined prior to initiating treatment with rituximab.
Pneumocystis jiroveci pneumonia (PJP) prophylaxis is recommended for patients with GPA or MPA during and following rituximab treatment, as appropriate.

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 (eg, 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 PJP 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 eg, 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 haematological 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 risk-benefit balance of the product

Serious infections, including fatalities, can occur during therapy with rituximab. Appropriate management and monitoring for infections, as described in the product SmPC, minimises the occurrence of infections and contributes to the maintenance of the favourable risk-benefit profile of rituximab.

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. Important Identified Risk: Progressive Multifocal Leukoencephalopathy (All Indications)

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 corticosteroid therapy might be important contributing factors of reactivation of latent JC virus.

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

Evidence source and strength of evidence

PF-05280586 is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).

Characterisation of the risk

Frequency with 95% CI (as per MabThera RMP v. 25.1, 08 March 2024):

RA
Confirmed PML is very rare (<1/10,000 patients) in patients receiving rituximab for the treatment of rheumatoid arthritis, based on all data from the RP clinical and post-marketing experience. The cumulative (cut-off 17 November 2023) reporting rate (RA exposure ~ 1,078,944) of 24 confirmed PML cases in patients treated with rituximab for RA is 2.2 per 100,000 patients. Thirteen (13) 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 111,538patients were exposed to rituximab in GPA/MPA, and 9 confirmed PML cases in GPA/MPA were reported.

No events of PML were reported in paediatric Study WA25615.

Pemphigus vulgaris
No events of PML were reported in Study ML22196.

NHL/CLL
The reporting rate of PML in oncology indications (confirmed and unconfirmed) is around 6.9/100,000 non-unique 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.

There were no subjects experiencing the AEs of Progressive multifocal leukoencephalopathy in PF-05280586 RA studies B3281001, B3281004 and NHL study B3281006.

Severity and nature of risk

There are no data from PF-05280586 or MabThera clinical trials.

Seriousness/Outcomes

There are no data from PF-05280586 or MabThera clinical trials.

Data from the safety database[e,f]

Post-marketing (PM)[g] cases: 86 (0.4% of total PM cases), 92 relevant events.[h]

The relevant PTs reported AEs (SAEs in parenthesis) were: Progressive multifocal leukoencephalopathy 62 (62), Demyelination 6 (6), Encephalopathy 5 (5), JC polyomavirus

test positive 5 (4), Leukoencephalopathy 5 (5), Encephalitis viral 3 (3), JC virus infection 3 (3), Human polyomavirus infection 2 (1), JC virus CSF test positive 1 (1).

Overall event seriousness and outcomes are summarised below.

	Total No. of PTs (N=92) (%)[a]
Serious	90 (97.8)
Hospitalisations	37 (40.2)
Outcome: Fatal	19 (20.7)
Outcome: Resolved / Resolving	13 (14.1)
Outcome: Resolved with Sequelae	-
Outcome: Not Resolved	25 (27.2)
Outcome: Unknown	35 (38.0)

a. Please note the sum of percentages may not be 100 due to rounding.

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 autoimmune diseases [including systemic lupus erythematosus (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 autoimmune diseases and immunosuppressive therapy. Fludarabine has been associated with an increased risk, possibly related to the induction a profound CD4+ lymphopenia.

Preventability

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

Impact on the risk-benefit balance of the product

Potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML) is anticipated in patients treated with rituximab. A warning in the SmPC, together with a patient alert card (PAC) are proposed to support rituximab use in patients with RA and GPA/MPA. This is intended to minimise the risk and contribute to maintenance of the favourable risk-benefit profile of rituximab.

Public health impact

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. Important Potential Risks

None.

SVII.3.2. Presentation of the Missing Information

None.

Module SVIII. Summary of the Safety Concerns

Table 20. 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

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

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2. Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities planned for rituximab. Routine pharmacovigilance activities are considered 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

As stated above, there are no additional pharmacovigilance activities (category 1-3 studies) planned for rituximab.

Routine pharmacovigilance activities are considered 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 AUTHORISATION EFFICACY STUDIES

There are no ongoing or planned post-authorisation efficacy studies for rituximab.

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

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 21. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation 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* PL Section 2 *What you need to know before you use Ruxience (Warnings and precautions* paragraph*)* PL Section 4 *Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk: EU SmPC Section 4.4 recommends not to administer rituximab to patients with an active, severe infection (eg, tuberculosis, sepsis and opportunistic infections) and to 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. Other routine risk minimisation measures beyond the Product Information: *Medicine's legal status:* Medicinal product subject to restricted medical prescription.
Progressive Multifocal Leukoencephalopathy (PML) (All Indications)	Routine risk communication: EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 4 *Possible side effects* Routine risk minimisation activities recommending specific clinical measures to address the risk EU SmPC Section 4.4 recommends as follows '*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. Consultation with a Neurologist should be considered as clinically indicated.* *If any doubt exists, further evaluation, 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 rituximab must be permanently discontinued'.* Other routine risk minimisation measures beyond the Product Information: *Medicine's legal status:* Medicinal product subject to restricted medical prescription.

Abbreviations: MRI = magnetic resonance imaging; EU = European Union; PL = package leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = summary of product characteristics.

V.2. Additional Risk Minimisation Measures

Additional risk minimisation activities are proposed for the risks of infections, including serious infections, and PML in non-oncology indications only (see Table 22, and Table 23). In line with the RP RMP (v. 25.1 dated 08 March 2024), proposal is to discontinue the educational material (EM) for Healthcare Professionals and Patients; therefore, any reference to EM was removed from these tables.

Table 22. Infections, including serious infections

Risk minimisation measures	Patient alert card (Non-oncology indications)
Objective(s)	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 minimisation activity	Rationale for the PAC is that, with timely diagnosis of infections, continued treatment with rituximab can be evaluated and reductions or discontinuation of concomitant immunosuppressive therapy considered.
Target audience and planned distribution path	Patients. The dissemination of the PAC to healthcare professionals can be achieved by distribution of the PAC to HCPs via local affiliate routes.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Reviewing reporting rates of Infections, including serious infections for each scheduled PSUR for rituximab.

Abbreviations: HCP = health care professional/provider; PAC = Patient Alert Card; PSUR = periodic safety update report.

Table 23. Progressive Multifocal Leukoencephalopathy

Risk minimisation measures	Patient alert card (Non-oncology indications)
Objective	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 minimisation activity	Rationale for the PAC is that, with timely diagnosis of PML, treatment with rituximab can be discontinued and reductions or discontinuation of concomitant immunosuppressive therapy considered.
Target audience and planned distribution path	Patients The dissemination of the PACs to healthcare professionals can be achieved by distribution of the PAC to HCPs via local affiliate routes.
Plans to evaluate the effectiveness of the interventions and criteria for success	Reviewing reporting rates of PML for each scheduled PSUR for rituximab

Abbreviations: HCP = health care professional/providers; PAC = Patient Alert Card; PML = progressive multifocal leukoencephalopathy; PSUR = periodic safety update report.

V.3. Summary of Risk Minimisation Measures

Table 24. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Infections, including serious infections (All Indications)	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 2 *Warnings and precautions* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional RMMs: Patient alert card (PAC) (Non-oncology indications). The text of the PAC is included in the PI Annexes.	*Routine PVAs beyond ADRs reporting and signal detection / Additional PVAs*: None.
PML (All Indications)	Routine risk minimisation measures: EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional RMMs: PAC (Non-oncology indications). The text of the PAC is included in the PI annexes.	*Routine PVAs beyond ADRs reporting and signal detection/Additional PVAs*: None.

Abbreviations: ADR = adverse drug reaction; PAC = patient alert card; PI = package insert; PL = package leaflet; PML = progressive multifocal leukoencephalopathy; PVA = pharmacovigilance activity; RMM = risk minimisation measure; SmPC = summary of product characteristics.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Ruxience

This is a summary of the risk management plan (RMP) for Ruxience. The RMP details important risks of Ruxience, how these risks can be minimised, and how more information will be obtained about Ruxience's risks and uncertainties (missing information).

Ruxience summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ruxience should be used.

This summary of the RMP for Ruxience should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Ruxience's RMP.

I. The Medicine and What It Is Used For

Ruxience indications in adults are: rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), *Pemphigus vulgaris*, Non-Hodgkin's Lymphoma (NHL), and chronic lymphocytic leukaemia (CLL).

Additionally, Ruxience is indicated for the treatment of paediatric patients:

- aged ≥6 months to <18 years old, *in combination with chemotherapy, in previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma, Burkitt lymphoma/Burkitt leukaemia (mature B-cell acute leukaemia) or Burkitt-like lymphoma.*

- aged ≥2 years to <18 years old, *in combination with glucocorticoids, for the induction of remission in severe, active GPA (Wegener's) and MPA.*

It contains rituximab as the active substance, and it is given by intravenous (IV) route of administration.

Further information about the evaluation of Ruxience benefits will be found in Ruxience European public assessment report (EPAR), including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ruxience.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise 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 authorised 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 (eg, with or without prescription) can help to minimise its risks.

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

In the case of Ruxience, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about AEs will be collected continuously and regularly analysed, 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 Ruxience is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Ruxience are risks that need special risk management activities to further investigate or minimise 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 rituximab. 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 (eg, on the long-term use of the medicine).

Table 25. 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

Table 26. Important Identified Risk: Infections, including serious infections (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the PF-05280586 and MabThera clinical trial data, and the MabThera RMP which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	**RA and GPA/MPA** 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).[1] 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 relative risk were joints, bone, skin and soft tissues.[1] The hazard ratio 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.[2] Data about other DMARDs are scarce, and the main cause of therapy withdrawal is related to toxicity rather than infection.[3] Anti-TNF-α agents like IFX are associated with an increased risk for TB, HBV reactivation and OIs.[4] Risk factors for infection in GPA/MPA patients include the concomitant use of high dose corticosteroids and/or other immunomodulatory agents. **Pemphigus vulgaris** None identified. **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 JF et al,[5] a higher infection rate in NHL patients was associated with granulocytopoenia 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 b_2-microglobulin level, low serum albumin level, low granulocyte count, and high serum creatinine concentration.[6] 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.

Table 26. Important Identified Risk: Infections, including serious infections (All Indications)

Risk factors and risk groups (*Cont'd*)	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 haematological 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.
Risk minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 2 *Warnings and precautions* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures Patient Alert Card (PAC) (Non-oncology indications). The text of the PAC is included in the PI Annexes.

Abbreviations: CD4 = cluster of differentiation 4; CLL = chronic lymphocytic leukaemia; CMV = cytomegalovirus; DMARD = disease-modifying anti-rheumatic drug; EU = European Union; GPA = granulomatosis with polyangiitis; HBV = hepatitis B virus; HCP = health care professional; HIV = human immunodeficiency virus; IFX = infliximab; MPA = microscopic polyangiitis; JC = John Cunningham (virus); MTX = methotrexate; NHL = Non-Hodgkin's lymphoma; OI =opportunistic infection; PAC = patient alert card; PI = package insert; PL = package leaflet; PJP = *Pneumocystis jiroveci* pneumonia; PI = package insert; PML = progressive multifocal leukoencephalopathy; RA = rheumatoid arthritis; RMP = risk management plan; RP = reference product; SmPC = summary of product characteristics; TB = tuberculosis; TNF = tumour necrosis factor.

Table 27. Important Identified Risk: Progressive multifocal leukoencephalopathy (All Indications)

Evidence for linking the risk to the medicine	Ruxience (rituximab) is a biosimilar medicinal product and the RP is MabThera. The evidence of the above-mentioned risk is derived from the MabThera RMP, which provides sufficient evidence from multiple sources (literature, clinical and/or post marketing).
Risk factors and risk groups	**RA** Progressive multifocal leukoencephalopathy (PML) has been reported in patients with autoimmune diseases (including SLE and RA) who have received immunosuppressive agents. **GPA/MPA** Cyclophosphamide (CYC) is a risk factor for development of PML in GPA/MPA patients. **Pemphigus vulgaris** No information available.

Table 27. Important Identified Risk: Progressive multifocal leukoencephalopathy (All Indications)

Risk factors and risk groups (*Cont'd*)	**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 minimisation measures	Routine risk minimisation measures EU SmPC Section 4.4 *Special warnings and precautions for use* EU SmPC Section 4.8 *Undesirable effects* PL Section 4 *Possible side effects* *Medicine's legal status:* Medicinal product subject to restricted medical prescription. Additional risk minimisation measures Patient Alert Card (PAC) (Non-oncology indications). The text of the PAC is included in the PI Annexes.

Abbreviations: CD4 = cluster of differentiation; CLL = chronic lymphocytic leukaemia; CYC = cyclophosphamide; EU = European Union; GPA = granulomatosis with polyangiitis; HCP = health care professional; MPA = microscopic polyangiitis; PML = progressive multifocal leukoencephalopathy; RA = rheumatoid arthritis; NHL = Non-Hodgkin's lymphoma; RMP = risk management plan; PAC = patient alert card; PI = package insert; PL = package leaflet; RP = reference product; SLE = systemic lupus erythematosus; SmPC = summary of product characteristics.

II.C. Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation, specific obligations, or required pharmacovigilance activities for Ruxience at the time of initial RMP submission.

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

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES

1 Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. Arthritis Rheum 2006; 54(8):2368-76.

2 McLean-Tooke A, Aldridge C, Waugh S, et al. Methotrexate, rheumatoid arthritis and infection risk: what is the evidence? Rheumatology (Oxford) 2009; 48(8):867-71.

3 Iaccarino L, Rampudda M, Canova M, et al. Mycophenolate mofetil: what is its place in the treatment of autoimmune rheumatic diseases? Autoimmun Rev 2007; 6(3):190-5.

4 Botsios C. Safety of tumor necrosis factor and interleukin-1 blocking agents in rheumatic diseases. Autoimmun Rev 2005; 4(3):162-70.

5 Bishop JF, Schimpff SC, Diggs CH, et al. Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med 1981; 95(5):549-55.

6 Anaissie EJ, Kontoyiannis DP, O'Brien S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 1998; 129(7):559-66.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Draft key messages of the additional risk minimisation measures

Prior to the launch of Ruxience in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at ensuring that patients seek medical attention early to facilitate timely diagnosis, and/or that the health care professional are aware of the need for timely and appropriate measures.

The MAH shall ensure that in each Member State where Ruxience is marketed, all healthcare professionals and patients/carers who are expected to prescribe/dispense/use Ruxience are provided with the following Patient information pack:

- Patient alert card
- Patient information leaflet.

Patient alert card

The Patient Alert Card contains important safety information related to non-oncology indications only, that a patient needs to be aware of before and during treatment with Ruxience. This alert card is helpful to the patient as it highlights the risk of infections and Progressive Multifocal Leukoencephalopathy (PML), including the symptoms. To mitigate the risks of PML in patients, a patient alert card will be given to every patient treated with Ruxience. The Physician or care giver will explain the content and importance of carrying this card to the patient before hospital discharge.

The Patient Alert Card for Ruxience in non-oncology indications will contain the following key elements:

- 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 PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur.

The Physician information and Patient information will be agreed with the National Competent Authorities prior to distribution and Patient Alert Card will be included with the patient information.

Contact details of the Ruxience prescriber: <name>; <telephone number>.

Before treatment with Ruxience inform your doctor if you have

- An infection even if it is a very minor one.
- Ever had problems with your immune system.
- Current or previous use of medicines including chemotherapy drugs which may affect your immune system.

During treatment with Ruxience inform your doctor

- straight away if you have signs of an infection (Signs include a fever or persistent cough, weight loss, pain without injuring yourself, feeling generally unwell tired or low energy and burning pain when passing urine).
- straight away if you notice signs of a serious brain infection, called “Progressive Multifocal Leukoencephalopathy (Signs include confusion, memory loss or problems thinking , loss of balance or a change in the way you walk or talk, decreased strength or weakness on one side of your body and blurred vision or loss of vision).