30 January 2020
EMA/CHMP/155201/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ruxience

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/004696/0000

Note

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

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List of abbreviations

ACF	animal-derived component-free
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AUC	area under the serum concentration-time curve
$AUC_{0\text{-}2wk}$	area under the concentration-time curve from zero to 2 weeks
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from zero to infinity
$AUC_{0\text{-}T}$	area under the concentration-time curve from zero to last measurable time point
CD	chemically-defined
CD19	B-lymphocyte antigen (Cluster of Differentiation 19)
CD20	B-lymphocyte antigen (Cluster of Differentiation 20)
CDC	complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CLL	chronic lymphocytic leukemia
C_{max}	maximum serum concentration
CMA	critical material attributes
CPP	critical process parameters
CQA	critical quality attribute
CR	complete response
CRP	C-reactive protein
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DAS28	Disease Activity Score in 28 joints
DAS28-CRP	Disease Activity Score in 28 joints - C-reactive protein
DMARDs	disease modifying antirheumatic drugs
DOR	duration of response
ECG	electrocardiogram
E	EU reference product
E-E, E-EP, E-EPP	subjects from the cohort randomized to rituximab-EU in the parent trial (B3281001) who were then randomized in Study B3281004 to receive the rituximab-EU reference product during Course 1, and PF-05280586 investigational product during Courses 2 and 3
EMA	European Medicines Agency
EOT	end of treatment/trial
ERA	Environmental Risk Assessment
EU	European Union
EULAR	European League Against Rheumatism
$Fc\gamma$	Fc gamma
FDA	Food and Drug Administration
FL	follicular lymphoma
FLIPI2	Follicular Lymphoma International Prognostic Index 2
GPA	granulomatosis with polyangiitis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HL	Hodgkin's lymphoma
ICH	International Council for Harmonisation
IGA-VAS	Investigator's Global Assessment of Arthritis-Visual Analog Scale
IgG	immunoglobulin G
IgG1k	immunoglobulin G1 kappa
IgM	immunoglobulin M
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous/intravenously

κ	kappa
LDAS	low disease activity score (according to DAS28)
LTB-FL	low tumor burden follicular lymphoma
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOAs	mechanisms of action
MPA	microscopic polyangiitis
MTX	methotrexate
NAb	neutralizing antibody
NHL	non-Hodgkin's lymphoma
NK	natural killer
ORR	overall response rate
non-CPP	non-critical process parameters
OS	overall survival
P	PF-05280586
PAIN-VAS	Patient's assessment of arthritis pain visual analog scale
PCD	primary completion date
PD	pharmacodynamic(s)
PF	Pfizer
PF-05280586	Rituximab Pfizer
PFS	progression free survival
PK	pharmacokinetic(s)
PMAR	population modeling analysis report
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
P-PPP	subjects from the cohort randomized to PF-05280586 in the parent trial (B3281001) who were then treated with PF-05280586 during Courses 1, 2, and 3 of B3281004
PR	partial response
PS	propensity score analysis
PT	preferred term
PV	Pemphigus vulgaris
PY	persons year
RA	rheumatoid arthritis
RF	rheumatoid factor
RP	reference product
SAE	serious adverse event
SCS	Summary of Clinical Safety
SD	standard deviation
SJC	swollen joint count (28 or 66 joints)
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha
T/PJC 68	tender/painful joint count 68
U	US reference product
U-U, U-UP, U-UPP	subjects from the cohort randomized to rituximab-US in the parent trial (B3281001) who were then randomized in Study B3281004 to receive the US reference product during Course 1, and PF-05280586 investigational product during Courses 2 and 3.
TTF	time-to-treatment failure
vs	versus
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 25 July 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Ruxience, through the centralised procedure falling within the Article 3(1) and point 1of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 10 November 2016.

The applicant initially applied for the following indications:

Non-Hodgkin's lymphoma (NHL)

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

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

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

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

Chronic lymphocytic leukaemia (CLL)

Ruxience 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.

See section 5.1 for further information.

Rheumatoid arthritis

Ruxience 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 antirheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Ruxience 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

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

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

MabThera, 100 and 500 mg, Concentrate for solution for infusion

- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: (02-06-1998)
  - Marketing authorisation granted by the European Union
  - Marketing authorisation number: EU/1/98/067/001-002

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant received Scientific Advice on 17 February 2011 (EMEA/H/SA/2076/1/2011/III), 20 October 2011 (EMEA/H/SA/2076/1/FU/1/2011/II), 21 November 2013 (EMEA/H/SA/2076/1/FU/2/2013/II), 26 June 2014 (EMEA/H/SA/2076/1/FU/3/2014/III) and 24 September 2015 (EMEA/H/SA/2076/1/FU/4/2015/III) for the development programme supporting the indication granted by CHMP. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

Quality: Reference Product Sourcing. Comparability exercise, analytical methods and approach proposed.

Non-clinical: Use of *in-vivo* animal study to demonstrate biosimilarity.

The main clinical aspects under consideration were:

- The design of the PK/PD trial in patients with mild to severe active rheumatoid arthritis including collection of the long-term safety data.
- The design of the efficacy and safety trials in patients with advance NHL and low tumour burden (LTB), CD20-positive, follicular lymphoma (FL) in the first-line treatment setting. Aspects under consideration were population selected, the primary endpoint, proposed margins, statistical assumptions, compare population PK profile, duration of the study and safety database.
- Extrapolation of the clinical results obtained in rheumatoid arthritis and in follicular lymphoma to support registration in the other indications approved for the Reference Medicinal Product.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	25 July 2018
The procedure started on	16 August 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	13 December 2018
GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product. The outcome of the inspections carried out was issued on	9 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ruxience on	30 January 2020
The CHMP adopted a report on similarity of Ruxience with Imbruvica, Gazyvaro, Kymriah, Yescarta and Polivy on	30 January 2020

2. Scientific discussion

2.1. Problem statement

About the product

PF-05280586 (rituximab, Ruxience) has been developed as a biosimilar product of MabThera (rituximab). It belongs to pharmacotherapeutic group of antineoplastic agents, monoclonal antibodies, with ATC code: L01X C02.

Mode of action

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95% of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector mediated cell lysis include complement dependent cytotoxicity (CDC) resulting from C1q binding, and antibody dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

The same indications were sought as for the reference product MabThera.

At the time of the CHMP opinion, the recommended indications were aligned with the indications of the originator MabThera, which had been extended as follows:

Ruxience is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

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

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

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

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

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patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

See section 5.1 for further information.

Rheumatoid arthritis

Ruxience 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.

Ruxience 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

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

Pemphigus vulgaris

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

2.2. Quality aspects

2.2.1. Introduction

Ruxience is a biosimilar medicinal product (reference product MabThera). It is presented as a sterile concentrate for solution for infusion containing 100 mg in a 10 ml vial or 500 mg in a 50 mL vial of rituximab as active substance. Rituximab is formulated with commonly used excipients: L-histidine, L-histidine hydrochloride monohydrate, disodium edetate, polysorbate 80, sucrose and water for injections (WFI).

Ruxience is provided in sterile, preservative-free, nonpyrogenic, single use Type I glass vials. Ruxience is supplied in packs of 1 vial for each strength.

The necessary amount of Ruxience is aseptically withdrawn from the vial and diluted to a calculated concentration of 1 to 4 mg/mL rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water.

2.2.2. Active Substance

General information

Rituximab, also referred to as PF-05280586, 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 (CHO) cell suspension culture and purified by a series of chromatography, viral inactivation and filtration steps.

The total molecular weight of rituximab with post-translational modifications is approximately 147 kDa. One N-linked glycosylation consensus site is present, which is occupied with mainly core-fucosylated,

complex-type biantennary N-linked glycans with zero or one terminal galactose residues. Each light chain consists of 213 amino acids and each heavy chain 451 amino acids.

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre B and mature B lymphocytes. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector mediated cell lysis include complement dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Manufacture, characterisation and process controls

Manufacture

The manufacturing of the active substance takes place at Boehringer Ingelheim Pharma GmbH & Co KG, Birkendorfer Straße 65, 88397 Biberach an der Riss, Germany.

Rituximab is produced using a recombinant CHO cell line. Cells are grown in suspension culture using chemically-defined (CD), animal-derived component-free (ACF) media.

The main steps of the manufacturing process are cell culture, recovery and purification.

A conventional two-tiered cell banking system is employed, consisting of a Master Cell Bank (MCB) from which Working Cell Banks (WCB) are derived.

The active substance is manufactured in production bioreactors. One production bioreactor leads to one bulk active substance lot. Bulk active substance lots are not combined at the active substance stage.

The manufacturing of rituximab PF-05280586 starts from a WCB, expansion of cell culture in flasks/bags followed by seed bioreactor, production culture in production bioreactor from which the active substance is harvested and purified using an affinity chromatography step, a virus inactivation step, ion exchange chromatography steps, virus retention filtration, ultra-/diafiltration (UF/DF) and final formulation and filtration.

The active substance is provided in appropriate container closure systems.

Control of materials

No raw materials of animal or human origin are used during the active substance manufacturing process.

The development of the dual gene expression factor for rituximab was described in sufficient detail. Key steps in the development of the PF-05280586 production cell line from the transfection event to the establishment of the WCB are described.

The Master Cell Bank (MCB) was generated in accordance with cGMP and ICH Q5D. The WCB was generated in accordance with cGMP. Testing and characterisation of MCB and WCB lots were performed according to the ICH Q5D guideline.

The sequence for rituximab was demonstrated to be present in MCB, WCB, and end-of-production (EOP) cells. The characterisation and testing of the expression constructs follow ICH Q5B.

Any new WCB will be created from MCB, following established manufacturing procedures as described and will be qualified to ensure comparability to the existing WCB.

Specifications of raw materials (compendial and non-compendial) have been provided.

Control of critical steps and intermediates

Process controls for the cell culture / harvest and purification process have been listed and their analytical procedures described.

Process validation

The validation of the PF-05280586 active substance manufacturing process has been completed and includes four process verification batches (also referred to as PPQ) that are from four independent, consecutive thaws of the WCB. Results of in-process controls (IPCs) and process parameters for all unit operations are reported and show compliance with the proposed requirements.

Removal of the following process-related impurities has been investigated: DNA, HCP, trace elements and organic compounds that were derived from the host cells, medium, or purification process. The observed levels of impurities were below acceptance criteria. Validation summaries for the analytical procedures used in these impurity removal studies have been provided.

Holding times of process materials of several stages have been established.

Transportation studies have been performed to show that a uniform temperature can be maintained to ship frozen active substance to the finished product manufacturing site.

Manufacturing process development

The applicant has developed the process in line with principles outlined in ICH Q8, Q9, Q10 and Q11. A science- and risk-based approach was used to develop the understanding of PF-05280586 critical quality attributes (CQAs) and a robust manufacturing process to consistently deliver the desired quality for this product.

The PF-05280586 active substance manufacturing process was stated to be developed using the applicant's platform host cell line and cell culture and purification processes and the applicant relied on prior knowledge. A summary of process development changes has been provided, showing that only minor changes throughout the process have been made from development batches to commercial batches. The target product quality attribute range has been established by the applicant, but proposed limits have been later amended when setting the release specification. CQAs have been defined and their criticality assessment provided, both for the active substance and finished product on their own and for similarity purposes with the licensed rituximab product. Most CQAs are controlled via release and stability testing or as IPCs. Non-criticality of other quality attributes has been adequately justified.

The applicant has provided a general discussion on how criticality assessment was performed, using Cause & Effect Matrix, experimentation and FMEA approach. Upon request, the applicant further justified the development approach, criticality assessment, and process description.

The provided information on the overall control strategy of the quality attributes is considered acceptable.

Characterisation

A comprehensive series of analytical methods have been used for the characterisation of Ruxience. These methods included state-of the art sensitive and orthogonal physicochemical and biological tests to determine the primary and higher-order structure, post-translational modifications (PTMs) and associated heterogeneities, glycan structures, charge variants, purity/impurities of Ruxience.

Functional cell-based assays and binding assays were developed and applied to characterise PF-05280586.

Forced degradation conditions were used to reveal potential PF-05280586 degradation pathways.

The removal of process-related impurities was validated through testing during process validation.

Specification

The specification for the active substance includes control of identity, purity and impurities, potency and other general tests.

The approach towards setting acceptance criteria was endorsed. Acceptance criteria for pharmaceutical/compendial tests are considered sufficiently justified in the dossier.

Analytical procedures

Validation or verification of analytical procedures was performed to ensure the control of characteristics, identity, potency, purity, product-related impurities, and safety of PF-05280586. The suitability of the analytical procedures for their intended use was performed by assessment of all relevant validation elements described in ICH Q2 (R1).

Compendial analytical procedures were verified or validated and confirmed suitable for intended use.

Non-compendial analytical procedures were validated.

The description of proposed methods and their validation was acceptable.

Batch analyses

The detail of batches manufactured for support of MAA requirements and process validation were provided together with batch analysis data. All batches met the acceptance criteria in place at the time of release. The results demonstrate consistency of the manufacturing process capabilities. All batches comply with the commercial acceptance criteria.

Reference standard

A two-tiered system for in-house PF-05280586 reference material has been implemented to support the commercial product. The existing Primary Reference Material and Working Reference Material have been suitably manufactured and characterised for their purpose. Future PRM will meet the release criteria established at the time of its manufacture. Qualification of new PRM will occur based on product understanding, appropriate analytical methods and characterisation techniques. Regulatory approval will be required for future replacement of the PRM.

Stability

The claimed active substance shelf life is supported with data and is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The PF-05280586 finished product is supplied as a liquid concentrate for solution for infusion. The active substance is formulated with L-histidine, L-histidine hydrochloride monohydrate, edetate disodium dihydrate, polysorbate 80, sucrose and water for injections.

Both the 100 mg strength in 10 mL vial and 500 mg strength in 50 mL vial of finished product presentations are supplied in a clear glass vial sealed with a chlorobutyl rubber stopper and an aluminium seal with flip-off plastic cap.

The finished product contains no preservative and is for single use only.

The composition of the finished product is sufficiently described. No novel excipients are used. The quality of the excipients is acceptable. The formulation is different from that of the reference product; the applicant sufficiently justified the proposed formulation.

The QTPP and the CQAs have been provided. Development studies support the chosen commercial manufacturing process.

Manufacture of the product and process controls

The manufacturing process is straightforward and typical for a liquid biological medicinal product and involves active substance thaw, addition of formulation buffer, sterile filtration and aseptically filling into vials Information on the sterilisation of the container closure system components (vials and stoppers), including validation of the sterilisation cycle if not according to Ph. Eur. conditions, was provided. PF-05280586 finished product presentations are manufactured using the same process steps and controls. The only differences to produce the different presentations are the fill volume and vial size.

The applicant has not identified any critical process parameters but has defined hold times and included several in-process tests. This is in line with development studies and the overall control strategy.

The manufacturing process has been validated at commercial scale and demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The specification for the finished product includes control of appearance, pH, extractable volume, sub-visible particles, protein concentration, osmolarity, charge heterogeneity, identity, purity and impurities, potency, endotoxin and sterility and other general tests.

The control of finished product is well-assured.

Upon request, several active substance and finished product specifications were tightened. Elemental impurities according to ICH Q3D are sufficiently discussed.

Analytical procedures

The description of proposed methods and their validation is acceptable.

Batch analyses

The detail of batches manufactured to support the MAA requirements and process validation were provided together with batch analysis data for the 100 mg and 500 mg presentations. All batches met the acceptance criteria in place at the time of release. The results demonstrate consistency of the manufacturing process capabilities. All batches comply with the commercial acceptance criteria.

Reference standard

The reference standard used for analysis of the finished product is the same as that used for the active substance.

Stability of the product

Stability information for PF-05280586 finished product stored under recommended long-term condition of 5 +/- 3^0 C, accelerated condition of 25 +/- 2^0 C/60 +/- 5% relative humidity (RH), as well as thermal stress, thermal cycling, and photostability conditions were provided. The stability program has been designed to follow ICH guidelines for stability of finished product.

Based on the review of the provided stability data the following shelf life and storage conditions of the unopened vial and diluted medicinal product are considered acceptable:

- Unopened vial: 24 months (2°C – 8°C) protected from light.

- Diluted medicinal product:

  - After aseptic dilution in sodium chloride solution

  The prepared infusion solution of Ruxience in 0.9% sodium chloride solution is physically and chemically stable for 24 hours at 2°C – 8°C plus an additional 24 hours at ≤ 30°C.

  - After aseptic dilution in D-glucose solution

  The prepared infusion solution of Ruxience in 5% D-glucose solution is physically and chemically stable for 24 hours at 2°C – 8°C plus an additional 24 hours at ≤ 30°C.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

No material of animal or human origin have been used in the generation and preparation of the cell banks and during the manufacturing of the active substance. The MCB, WCB and EOP cells have been screened sufficiently for adventitious viruses. These tests failed to demonstrate the presence of any viral contaminant with the exception of intracellular type A retroviral particles, which is well known for rodent cells. This is acceptable since there is sufficient capacity within the Ruxience purification procedure for the reduction of this type of viral particles. Therefore, there are no concerns for the use of the WCB in the production process of Ruxience. The unprocessed bulks are further tested to be free of adventitious viruses by *in vitro* assay including cell line for detection of a broad range of viruses including MMV. The purification process of the antibody includes several steps for inactivation/removal capacity for enveloped viruses and removal of non-enveloped viruses. The virus safety of Ruxience has been sufficiently demonstrated.

Compliance with the TSE Guideline EMEA/410/01 – rev. 3 has been sufficiently demonstrated.

Biosimilarity

General and methodological aspects

The applicant performed three comparisons to support a global development (PF-05280586 (Ruxience) to EU-originator (MabThera), also described as rituximab-EU, reference product); PF-05280586 (Ruxience) to US-originator (Rituxan, also described as rituximab-US); rituximab-EU to rituximab-US).

The originator batches were sufficiently identified and described.

A sufficient number of PF-05280586 active substance and finished product lots were produced at developmental and commercial scale and included in the similarity assessment.

Analytical methods

The applicant submitted extensive information on analytical methods, especially non-routine analytical methods, including summary information regarding qualification, in order '*to demonstrate that the selected methods used in the biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality'*.

Impurities

The general approach towards process-related impurities is considered in line with current guidance (which explicitly acknowledges that differences may be present, provided that levels are minimised as appropriate), and therefore acceptable.

Results and discussion on analytical comparability

- Identical primary structure/amino acid sequence has been sufficiently demonstrated.

- Peptide map/microheterogeneity generally supports biosimilarity. Data presentation indicates that rituximab displays limited microheterogeneity.

- Size distribution / purity is considered comparable (levels of dimers tend to be slightly lower in PF-05280586 compared to the originator).

- Comparable higher order structure has been sufficiently demonstrated.

- Charge variants / hydrophobic heterogeneity; although differences in charge variants where found, these are mainly due to variants which are well-known to be clinically irrelevant.

- Comparable strength/protein content has been sufficiently demonstrated.

- Glycan analysis: total afucosylation and total galactosylation are within the same range and from that point of view comparable.

- Binding properties have been extensively investigated in conjunction with *in vitro* biological activity/potency.

- Taken together, the data on glycosylation, FcγRIIIa-158F receptor binding and ADCC assays are consistently pointing to a slightly higher affinity and biological activity.

- *In vitro* biological activity/potency; CD20-binding and apoptosis; in *vitro* CDC and C1q binding; FcγRIIIa 158V binding and NK ADCC (V/V, V/F), FcγRIIa-binding, FcRn-binding, and a cell based antibody-dependent cellular phagocytosis (ADCP) reporter gene assay (RGA) are considered comparable.

The choice of an appropriate panel of analytical methods has been the subject of several scientific advices given by EMA and NCAs, which generally endorsed the analytical methods included in the submission.

Conclusion on analytical comparability

The analytical comparability data package is concise but covers the relevant aspects of the product and supports the conclusion that high analytical similarity exists (Table 1).

Table 1. Summary of similarity conclusions

Attribute	Analytical Procedure	Similarity Conclusion	
Primary Structure and Posttranslational Modifications (PTMs)	LC/MS/MS – Peptide Mapping with specialized bioinformatics	Identical amino acid sequence	Highly Similar
	Peptide Mapping/ Edman Degradation		
	nanoElectrospray Ionization Mass Spectrometry	Similar molecular mass at the intact molecule level.	
	nanoElectrospray Ionization Mass Spectrometry	Identical primary structure and similar posttranslational modifications at the intact molecule, subunit and peptide level.	
	LC/MS – Subunit Analysis		
	LC/MS and LC/UV – Peptide Mapping (Trypsin)		
Known MoA: Binding to CD20 Target Antigen	Binding to CD20 Target Antigen by Flow Cytometry	Similar dose response curves.	Highly Similar
Known MoA: CDC Activity	CDC Assay	Similar dose-response curves and relative potency.	Highly Similar
	C1q binding (ELISA)	Similar dose-response curves and relative potency.	
Known MoA: ADCC Activity	Primary NK Cell ADCC Assay	Similar ADCC activity.	Highly Similar
	FcγRIIIa Reporter Gene Assay	Small differences in the upper asymptote region of dose-response curves which have no impact on similarity.	
	Binding to FcγRIIIa 158V by SPR	Similar range in binding to FcγRIIIa 158V.	
	Binding to FcγRIIIa 158F by SPR	Minor differences in relative K_D values which have no impact on similarity.	
Known MoA: Apoptosis	Apoptosis assay	Similar dose response curves.	Highly Similar
Plausible MoA: ADCP	Binding to FcγRIIa 131H by SPR	Similar binding affinity and kinetics.	Highly Similar
	Binding to FcγRIIa 131R by SPR	Similar binding affinity and kinetics.	
Fcγ Receptor Binding	Binding to FcγRI, FcγRIIb, and FcγRIIIb by SPR	Similar binding affinity and kinetics.	Highly Similar

Attribute	Analytical Procedure	Similarity Conclusion	
FcRn Binding	Binding to FcRn by SPR	Similar binding affinity and kinetics.	
N-Linked Glycan Structure: Total Afucosylation	HILIC with fluorescence detection	Similar ranges of total afucosylation.	Highly Similar
N-Linked Glycan Structure: Terminal Galactosylation	HILIC with fluorescence detection	Similar ranges of terminal galactosylation.	
N-Linked Glycan Profile	HILIC/MS	Similar relative proportions of major level N-linked glycans.	
	Exoglycosidase Digestion/HILIC	Similar N-linked glycan structural assignments and glycosidic linkages.	
	Sialic Acid Assay	Similar levels of low level sialylated N-linked glycans, and sialic acid forms	
Charge Heterogeneity: Acidic Species	CEX-HPLC	Similar levels of acidic species.	Highly Similar
Charge Heterogeneity: Basic Species		Differences in levels of C-terminal lysine, amidated proline and N-terminal Q were noted, which are not considered clinically relevant.	
Charge Heterogeneity	Cation Exchange-HPLC profile characterized by MS	Similar major and minor charge isoform species. Difference in C-terminal lysine, amidated proline and N-terminal Q are not considered clinically relevant.	
	Carboxypeptidase B/CEX-HPLC	Similar charge isoform after removal of C-terminal lysine.	
Product Purity: Monomer	SE-HPLC	Higher monomer levels in PF-05280586 were noted but were observed to overlap the rituximab-US and the rituximab-EU range. For quality attributes measuring product purity and having immunogenicity risks, this is a desired result.	Highly Similar
Product Purity: HMMS	SE-HPLC	Lower HMMS levels in PF-05280586. For quality attributes measuring product purity and having immunogenicity risks, this is a desired result.	
Product Purity: HC+LC and Fragments	CGE (reducing)	Similar levels of HC + LC and fragments.	
Product Purity: Intact IgG	CGE (Non-reducing)	Higher intact IgG levels in PF-05280586. For quality attributes measuring product purity and having immunogenicity risks, this is a desired result.	
Product Purity: Western blot and SDS-PAGE	SDS-PAGE (Total protein staining and Western blotting)	Similar banding patterns.	

Attribute	Analytical Procedure	Similarity Conclusion	
Disulfide Bonds	Sulfhydryl Analysis	Similar trace level of unpaired protein sulfhydryl groups.	Highly Similar
	LC/MS – Non-reduced Peptide Mapping (Lys-C)	Identical disulfide bond connectivity.	
Higher Order Structure	Far-UV Circular Dichroism (CD) Spectroscopy	Similar secondary structure.	Highly Similar
	Fourier Transform Infrared (FTIR) Spectroscopy		
	Near-UV CD Spectroscopy	Similar tertiary structure.	
	Fluorescence Spectroscopy		
	Differential Scanning Calorimetry (DSC)	Similar thermal stability of higher order structure.	
Degradation Profile	SE-HPLC, CEXHPLC, CGE (reducing and non-reducing), CDC assay, UV spectroscopy, LC/MS –Peptide mapping (Trypsin), HIAC (elevated temperature studies only)	Similar degradation profiles.	Highly Similar

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The fermentation and purification of the active substance are adequately described, controlled and validated. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

The chemical, pharmaceutical and biological documentation comply with existing guidelines.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

From a quality point of view, biosimilarity with the reference product MabThera is considered demonstrated.

The overall quality of Ruxience is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality point of view, the marketing authorisation application for Ruxience is considered acceptable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP made recommendations for future investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

PF-05280586 is a chimeric immunoglobulin G1 kappa ($IgG1_k$) monoclonal antibody (mAb) developed as a biosimilar product to the European Union (EU) approved reference product (RP), MabThera. The nonclinical pharmacology of PF-05280586 was compared to rituximab-US and rituximab-EU in a number of *in vitro* assays that were evaluated for fragment-antigen binding (Fab) and fragment-crystallisable (Fc)-related biological activity.

2.3.2. Pharmacology

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody targeting the CD20 antigen on the surface of normal and malignant B lymphocytes. Rituximab is known to have multiple mechanisms of action (MoAs). The Fab portion of rituximab binds to CD20 target antigen and can kill target cells by apoptosis. Binding of rituximab to complement triggers Fc-mediated binding to C1q followed by CDC, which is also a known MoA for rituximab. Finally, also ADCC, which is mediated by FcγRIIIa (158V or 158F) receptors, is another known MoA for rituximab, while ADCP, mediated by the binding of FcγRIIa (131H or 131R) receptors, has been identified as a plausible MoA for rituximab.

Comparable results of PF-05280586 with rituximab-US, and rituximab-EU were found in terms of their ability to bind to CD20 , for inducing apoptosis and also for binding to C1q and inducing CDC .

Using a primary NK cell ADCC assay,, comparable NK ADCC V/V, V/F activity between PF-05280586, rituximab-US, and rituximab-EU was demonstrated. Also binding to FcγRIIIa 158V (by SPR) was found to be similar but with respect to the binding to the low affinity FcγRIIIa 158F receptor a higher affinity of PF-05280586 as compared to rituximab-EU was observed, which may be related to different glycosylation levels.

An ADCC FcγRIIIa-158V reporter gene assay (ADCC RGA) assay was presented to assess the downstream signaling pathway.

Binding to FcγRIIa (SPR), evaluated as a surrogate for plausible mechanisms of action of rituximab, the ADCP activity, was reported to be similar with respect to binding to FcγRIIa 131H and 131R. To assess functional ADCP activity, a cell-based FcγRIIa ADCP reporter gene assay (ADCP RGA) was developed. PF-05280586 was found to have similar effects as the rituximab-EU and the ranges in ADCP activity (% EC50) were overlapping demonstrating similar functional ADCP activity between PF-05280586 and licensed rituximab-EU.

FcRn binding may affect antibody *in vivo* half-life. Slight differences in FcRn SPR binding activity were observed but additional lot testing showed that PF-05280586 lot results fall within the quality range as established with the rituximab-EU results.

Similar binding was found to FcγRI, FcγRIIb, and FcγRIIIb receptor.

2.3.3. Pharmacokinetics

Two *in vivo* intravenously (IV) dosed monkey GLP studies were performed and toxicokinetic (TK) and anti-drug antibody (ADA) evaluations were conducted in support of single-dose TK/tolerability and repeat-dose toxicity/TK studies in cynomolgus monkeys with PF-05280586 and rituximab-EU. In these studies a commercial scale development batch of PF-05280586 in its final clinical formulation was used.

An enzyme-linked immunosorbent assay (ELISA) for the quantitation of PF-05280586 or rituximab-EU in cynomolgus monkey serum was developed and sufficiently validated. Two electrochemiluminescence (ECL) assays were developed and adequately validated to detect the presence of ADAs in cynomolgus monkey serum.

Toxicokinetic analysis was performed after a single 2, 10, or 20 mg/kg IV dose of PF-05280586 or rituximab-EU to male and female cynomolgus monkeys and after four weekly IV dosing of 20 mg/kg of PF-05280586 or rituximab-EU to cynomolgus monkeys . There were slight but not consistent differences in systemic exposure (Cmax, AUC) in both studies, which may have been influenced by ADA induction. There was a 100% (6/6 animals at each dose level) induction of ADAs to PF-05280586 or rituximab-EU in this single dose study and a 79% (11/14 animals) and 43% (6/14 animals) for PF-05280586 or rituximab-EU, respectively, in the 4 week repeated dose study. This seems lower than in the single dose study but it should be noted that the detection of ADAs appeared to be hampered by the presence of rituximab/PF-05280586 in the samples.

The ADA induction in monkeys, which occurred following single dosing, is expected given the nature of rituximab (chimeric mouse/human IgG) and is much larger than the percentage ADAs induction, which have been found in humans. Given the inter-animal variability, the small number of animals and the low predictability for humans, the ADA induction and related influence on rituximab exposure (Cmax, AUC) is not considered of relevance for biosimilarity assessment.

Overall, the systemic exposure and ADA induction for PF-05280586 and rituximab-EU seemed comparable.

No formal studies on absorption, distribution, metabolism, excretion, and drug-drug interaction were performed for PF-05280586, which is acceptable for a biosimilar and agreed by the CHMP.

2.3.4. Toxicology

In a single dose toxicity study in cynomolgus monkeys, PF-05280586 was compared to rituximab-EU. There were no adverse effects in any dose group, apart from the pharmacological effect of B-cell reduction which was similar for both PF-05280586 and rituximab-EU. Therefore, the safety profile after a single dose of rituximab up to 20 mg/kg is similar for the test item PF-05280586 as compared to the reference product rituximab-EU.

Comparative single and repeated dose toxicity study in cynomolgus monkeys were performed, to compare the safety profile of PF-05280586 with the reference product rituximab-EU. Monkeys were IV dosed with vehicle control or 2, 10 or 20 mg/kg PF-05280586 or rituximab-EU in the single dose study, and with vehicle control or 20 mg/kg PF-05280586 or rituximab-EU weekly for 5 doses in the repeated dose study. Both studies included a 13 week recovery period. No adverse effects were observed in either study apart from the expected effects related to the pharmacological effect of rituximab, which were comparable for both products. Therefore, the safety profile after single or repeated dosing of rituximab at up to 20 mg/kg/week is similar for the test item PF-05280586 as compared to the reference product rituximab-EU.

The value of these studies in terms of biosimilarity assessment is limited however, since it is questionable whether any small differences would have been detected. In addition, it is noted that these studies are not required according to current guidelines, but were initiated prior to the revision of the biosimilar guidance.

No studies assessing genotoxicity, carcinogenicity, reproductive toxicity, local tolerance, phototoxicity, immunotoxicity or other toxicity have been performed, which is according to current guidelines.

2.3.5. Ecotoxicity/environmental risk assessment

No ERA studies have been performed by the applicant (see discussion on non-clinical aspects).

PF-05280586 is a monoclonal antibody consisting of naturally occurring amino acids. As such it is not expected to have any impact on the environment. The absence of further ERA studies is sufficiently justified.

2.3.6. Discussion on non-clinical aspects

Rituximab binds to the CD20 target antigen on normal and malignant cells. Binding to CD20 is the first step of the known mechanism of action (MoA) for rituximab. This binding is then followed by antibody-dependent cell-mediated cytotoxicity (ADCC), in which antibody-coated malignant cells are killed through engagement of effector cells with active Fc receptors. In addition, the binding of the Fc portion of rituximab to the C1q molecule results in the assembly of the membrane attack complex on the cell surface (complement-mediated cytotoxicity, (CDC)). Binding of rituximab to the CD20 antigen on the target cells can also induce apoptosis via the caspase-dependent pathway. Antibody-dependent cellular phagocytosis (ADCP) has been identified as a plausible MoA, mediated by the binding of Fcγ receptors on macrophages to antibodies bound to antigens on the cell surface.

CD20 binding, C1q binding, CDC and apoptosis activity support biosimilarity. In addition, binding to FcRn, FcγRI, FcγRIIa, FcγRIIb, and FcγRIIIb receptor was found to be similar. To assess functional ADCP activity, an FcγRIIa 158V ADCP RGA was developed demonstrating similar functional ADCP activity between PF-05280586 and licensed rituximab-EU. Also binding to FcγRIIIa-158V was found to be similar but with respect to the binding to the FcγRIIIa-158F receptor a higher affinity was found.

Overall a comprehensive assessment of PF-05280586 and rituximab in multiple *in vitro* ADCC assays using various sources of effector cells and target cells was presented and the data points to similar, i.e. overlapping, ranges of responses for the ADCC assays when using the 158V/V or 158V/F genotype, except for the ADCC RGA-158V assay, for which a higher response was found with PF-05280586. NK ADCC data are in line with the FcγRIIIa-receptor binding data obtained with PF-05280586, where the binding affinity data of the 158fV genotype was overlapping with rituximab-EU, while the 158F-genotype binding data were higher and only partly overlapping with rituximab-EU data range.
In addition, the data, in line with literature reports, showed a positive correlation between glycosylation (afucosylation) and NK ADCC activity, for which the F/F genotype was found to be most sensitive for differences in glycosylation.

These differences in ADCC activity are considered minor but its clinical relevance for patients having the F/F genotype is not studied and therefore , it was agreed that ADCC t be controlled through release testing of PF-05280586.

Therefore, it can be concluded that Ruxience is biosimilar to the rituximab MabThera.

2.3.7. Conclusion on the non-clinical aspects

Biosimilarity of Ruxience to Mabthera in terms of non-clinical aspects was demonstrated.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 2. Tabular Overview of Clinical Studies Conducted for the Evaluation of Pharmacokinetics, Pharmacodynamics, Safety, Efficacy and Immunogenicity

Study No.	Protocol Title	Status	Number of Subjects or Patients Treated/PK
Study B3281001	A randomized, double-blind, study comparing the pharmacokinetics and pharmacodynamics, and assessing the safety of PF-05280586 and rituximab in subjects with active rheumatoid arthritis on a background of methotrexate (MTX) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.	Completed, final CSR issued[a]	220[b]/198[c]
Study B3281004	Extension study evaluating treatment with PF-05280586 versus rituximab in subjects with active rheumatoid arthritis who have participated in other PF-05280586 clinical trials.	Completed, final CSR issued	183[d]/183
Study B3281006	A Phase 3, randomized, double-blind study of PF-05280586 versus rituximab for the first-line treatment of patients with CD20-positive, low tumor burden, follicular lymphoma.	Completed [e], final CSR issued	393/393

Abbreviations: CSR = Clinical Study Report.

a. A supplemental CSR (sCSR) reported the post-hoc PK analysis requested by the EMA.
b. ITT (Intent-to-treat) safety population
c. Per protocol (PP) population
d. mITT (modified intent-to-treat) safety population
e. Following the CSR Primary Completion Date (PCD; cutoff date 23-Oct-2017), at Week 26, data was included in the initial submission. A full CSR (through to Week 52/study completion for all subjects) included data for all primary data endpoints and secondary endpoints.

2.4.2. Pharmacokinetics

In the pivotal biosimilarity study B3281001, Rituximab-US, rituximab-EU, and PF-05280586 exhibited similar PK profiles. More importantly, the 90% CIs for test to reference ratios of C_{max} and $AUC_{0-\infty}$ were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for all of the pair-wise comparisons among the 3 study drugs, demonstrating PK similarity among rituximab-US, rituximab-EU, and PF-05280586.

Table 3 summarises the ratios of adjusted geometric means and the corresponding 90% CIs for the primary comparisons in the PP population. For the PK similarity comparisons of PF05280586 to each of the RPs (rituximab-EU and rituximab-US), the 90% CIs for the testto reference ratios of C_{max}, AUC_{0T}, AUC_{0-2wk} and $AUC_{0-\infty}$ were within the bioequivalence acceptance criteria of 80.00% to 125.00%. For the comparison of rituximab-EU to rituximab-US, the 90% CIs of the ratios of C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$ were also within 80.00% to 125.00%.

Table 3. Summary of Statistical Comparisons of Pharmacokinetic Exposure Parameters Between Test and Reference Products, Study B3281001 (RA)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
PF-05280586 (Test) vs. Rituximab-EU (Reference)				
C_{max} (µg/mL)	432	409	105.67	(96.91, 115.21)
AUC_{0-T} (µg.hr/mL)	184000	178000	103.36	(92.81, 115.12)
$AUC_{0-\infty}$ (µg.hr/mL)	196000	188000	104.19	(92.75, 117.06)
AUC_{0-2wk} (µg.hr/mL)	49500	47700	103.74	(95.10, 113.15)
PF-05280586 (Test) vs. Rituximab-US (Reference)				
C_{max} (µg/mL)	432	405	106.62	(97.65, 116.41)
AUC_{0-T} (µg.hr/mL)	184000	181000	101.33	(90.82, 113.04)
$AUC_{0-\infty}$ (µg.hr/mL)	196000	195000	100.45	(89.20, 113.11)
AUC_{0-2wk} (µg.hr/mL)	49500	46900	105.56	(96.64, 115.30)
Rituximab-EU (Test) vs. Rituximab-US (Reference)				
C_{max} (µg/mL)	409	405	100.90	(92.38, 110.20)
AUC_{0-T} (µg.hr/mL)	178000	181000	98.03	(87.83, 109.40)
$AUC_{0-\infty}$ (µg.hr/mL)	188000	195000	96.40	(85.57, 108.60)
AUC_{0-2wk} (µg.hr/mL)	47700	46900	101.76	(93.13, 111.18)

Source: Module 5.3.3.2 B3281001 Table 14.2.1.1 and Table 14.2.1.2
Abbreviations: CI=confidence interval; C_{max}=maximum serum concentration; AUC_{0-T}=area under the serum concentration-time profile from time 0 to the last measured concentration at time T; $AUC_{0-\infty}$=area under the serum concentration-time profile from time 0 extrapolated to infinite time; AUC_{0-2wk}=area under the serum concentration-time profile from time 0 to 2 weeks.
[a] The ratios (and 90% CIs) are expressed as percentages.

Effect of ADA on PK

In RA patients (study B3281001), the serum concentrations of PF 05280586, rituximab-EU or rituximab US appeared to be lower in ADA positive subjects compared to ADA negative subjects; however, this observation should be interpreted with some caution given the small numbers of subjects who were ADA positive. The effect of ADA on PK in ADA positive subjects seems to be similar between rituximab-EU, rituximab-US, and PF-05280586.

In LTB-FL patients (study B3281006), there did not appear to be a consistent trend for a difference in mean post-dose serum concentrations between ADA positive and ADA negative subjects in either rituximab-EU or PF-05280586 treatment group. However, upon a closer look it is noted that during the Week 13 ADA sampling, serum rituximab concentrations in ADA positive subjects were roughly 1.3-fold lower than in ADA negative subjects for the PF-05280586 treatment group, whereas this decrease was 1.1-fold for the rituximab-EU treatment group. Given the small numbers of ADA positive subjects and the variability in the PK parameters, this comparison between treatments should be interpreted with caution. Overall, there does not seem to be a major difference in effect of ADA on PK between PF-05280586 and rituximab-EU.

Bioanalytical methods

All PK samples were measured with an ELISA method. This ELISA method with a calibration range of 100-5000 ng/mL has been sufficiently validated with respect to precision, accuracy, selectivity, specificity, dilution linearity, ADA-interference, and tested stability. Accuracy and precision data using validation samples (VS) for rituximab-EU, rituximab-US, and PF-05280586 prepared at 5 concentrations each met the usual acceptance criteria for ligand binding assays.

All human samples collected for evaluation of immunogenicity were analyzed using two validated assays, one specific for PF-05280586 and one specific for the licensed rituximab. The employed three-tiered strategy including a screening, confirmatory and neutralisation assay is in agreement with the

Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010). The methods were sufficiently validated and were cross-validated against the alternate antigen.

2.4.3. Pharmacodynamics

The pharmacodynamic outcome of CD19 positive B-cell count was routinely monitored in the comparative clinical trials of PF-05280586.

Methods: Study B3281001 and B3281004

The primary objective of study B3281001 was to demonstrate PK bioequivalence between PF-05280586 and rituximab-EU and rituximab-US. The secondary objective was to demonstrate equivalence regarding PD. The study was performed in RA patients. In total, 73 subjects were assigned to rituximab-US, 74 subjects to rituximab-EU, and 73 subjects to PF-05280586. The patients received a single course of 2 x 1000 mg IV infusion, with a two-week interval, in line with the posology of the reference product. Subjects with an adequate clinical response could continue three courses of further treatment in extension study B3281004. Patients who were assigned to the Rituximab-EU or rituximab-US in study B3281001 were switched randomly to PF-05280586 and patients who were assigned to PF-05280586 in study B3281001 continued on this treatment.

CD19+ cell counts of full blood samples were analyzed using a validated laser scanning cytometry (LSC) method. A secondary PD parameter was Serum IgM. CD19 positive B-cell counts and IgM were analysed on Days 1, 4, 8, 15, 22, 29, 57, 85, 113, 141, and 169. Additional samples for analysis of CD19 positive B-cell counts were collected every 3 months during the follow–up period.

Methods Study B3281006

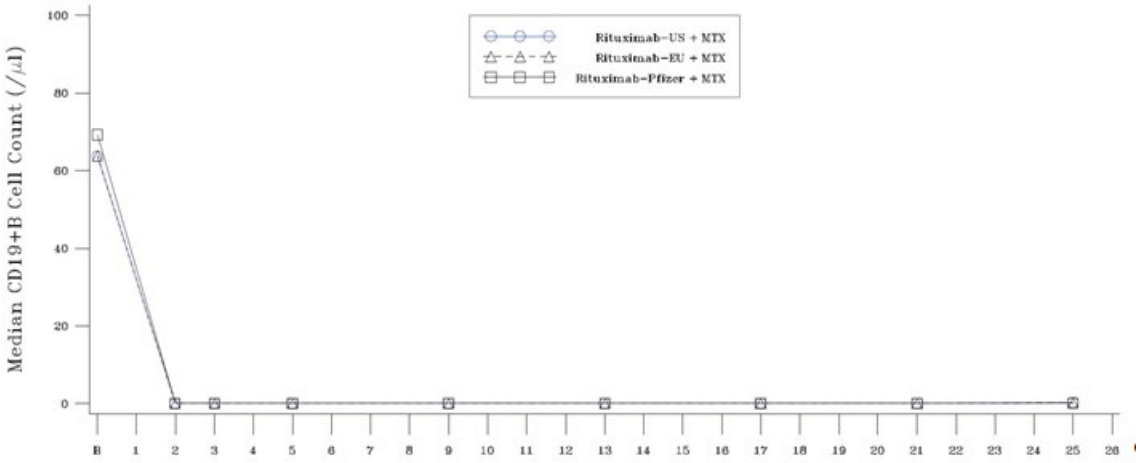
In efficacy and safety Study B3281006, 398 patients with low tumour burden follicular lymphoma (LTB-FL), were randomly assigned to PF-05280586 and rituximab-EU. The treatment consisted of 4 IV courses of 375 mg/m^2 within 22 days. PD assessment of B-cell counts was one of the secondary objectives of this study. CD19 positive B-cell counts were determined prior to dose administration on Days 1, 8, 15, and 22. In long-term follow-up period after treatment, additional samples for analysis of CD19 positive B-cell counts were collected at Weeks 5, 13, 26, 39 and 52.

Results

Study B3281001 and B3281004, RA patients

The mean (±SD, n) CD19+ B-cell counts at Baseline were 94 (± 88, n=68), and 100 (±109, n=69), respectively, for PF-05280586 and rituximab-EU. A rapid depletion of CD-19+ B-cells occurred in all 3 groups following the dose administration on Day 1. The mean CD-19+ B-cell count values decreased by 99.8% for both rituximab-Pfizer and rituximab-EU groups, at Week 25. In all groups, the CD19+ B-cell counts remained low throughout the study duration of 25 weeks. There were no obvious differences among treatment groups regarding the CD19+ B-cell counts, or the mean change from Baseline in CD19+ B-cell counts. The median CD19 counts are shown in figure 3.3.2.1.

Figure 1. The median CD19 counts (Study B3281001)



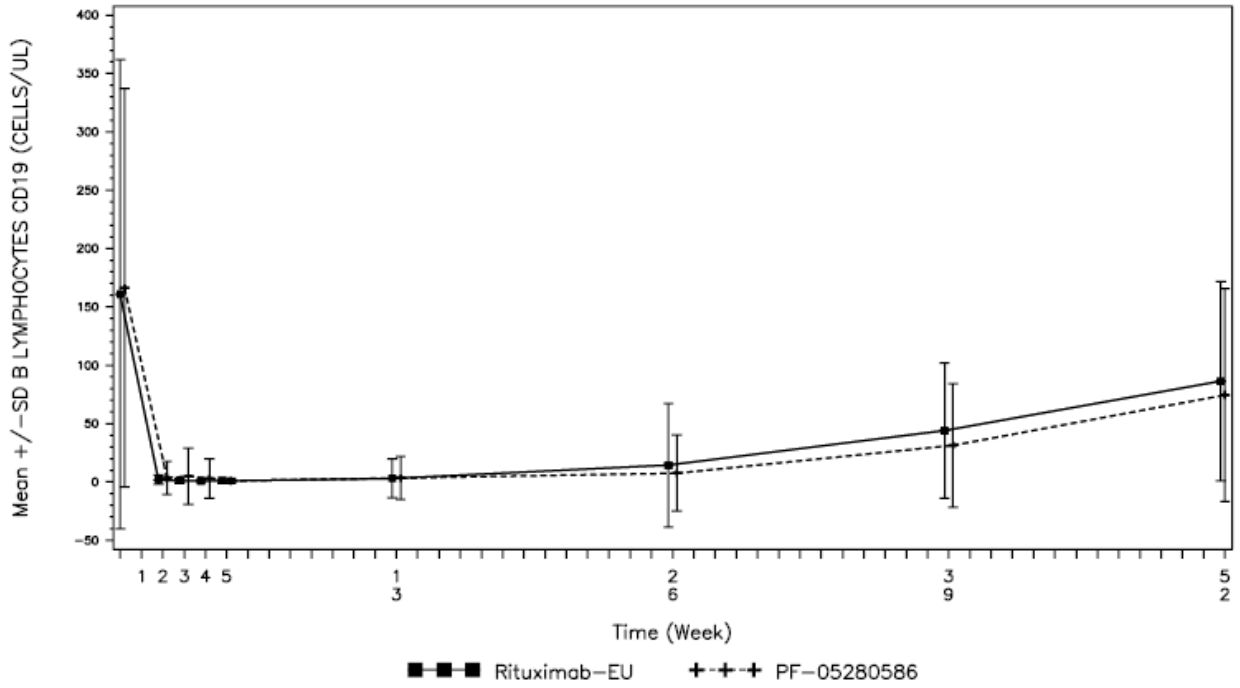
At week 13 the percentage change of IgM from baseline is -11.5% and -22.2% for PF-05280586 and Rituximab-EU, respectively. At week 25 (End Of Trial point) this percentage was -24.2 and -21.0 respectively. Similarity was shown for IgM between PF-05280586 and Rituximab-EU in the extension study.

Also, reductions in RF (rheumatoid factor), ACPA (Cyclic Citrullinated Peptide Antibody), IgM and IgG were within the same range for PF-05280586 and Rituximab-EU assignment groups.

Study B3281006 (LTB-FL patients): PD results

At baseline, the serum CD19-positive B-cell counts results ranged from 0.6 to 2313.1 cells/uL across the 2 treatment groups. The median baseline CD19-positive B-cell count was 119.9 cells/uL in the PF-05280586 group and 114.2 cells/uL in the rituximab-EU group. After the intensive treatment (4 IV courses within 21 days), CD-19-positive B-cell counts rapidly declined to near zero. The cell counts gradually recovered in the off-treatment follow-up (52 weeks).

Figure 2. Mean (SD) of CD19+ B-cell lymphocytes Study B3281006 (LTB-FL patients)



PD results in ADA positive patients

In Study B3281001, between 6-10 subjects in the three study arms were ADA positive.

In Study B3281001, the range of DAS28-CRP scores at Week 13 (mITT population) ranged from 1.15-7.13 in the PF-05280586 group, and between 1.30-7.73 in the rituximab-EU group. The individual DAS28-CRP scores for ADA positive subjects listed in Table 3.3.2.1. The subgroups are considered too small to draw meaningful conclusions on the effect of ADA formation on efficacy and PD parameters.

Table 4. Study B3281001 Individual DAS28-CRP Scores at Week 13 for the ADA Positive Subgroup

PF-05280586	Rituximab-EU*	Rituximab-US*
2.304	1.889	2.221
2.808	2.072	2.988
3.678	2.283	3.437
3.978	2.487	3.581
4.659	2.931	3.810
5.243	3.595	5.080
	3.754	5.153
	3.994	7.315
	4.158	
Source: Module 5.3.3.2 B3281001 CSR listing 16.2.6.1a *One subject (11681002) in the Rituximab-US group did not have a DAS28-CRP score past Week 5. One subject (11511001) in the Rituximab-EU group did not have a DAS28-CRP score past Week 3.		

Mechanism of Action and extrapolation to other indications

Table 5. Mechanisms of Action of Rituximab Across Diseases

Biological Activity	Mechanism of Action	RA	NHL	CLL	GPA	MPA
Fab Domain						
Binding to CD20	Apoptosis	Known[15]	Known[16]	Known[16]	Unconfirmed	Unconfirmed
Fc Domain (with prerequisite Fab binding to CD20)						
Fc Effector Function	CDC	Known[15]	Known[16]	Known[16]	Unconfirmed	Unconfirmed
	ADCC	Known[15]	Known[16]	Known[16]	Unconfirmed	Unconfirmed
	ADCP	Unknown	Plausible[17]	Plausible[17,18]	Unknown	Unknown

Abbreviations: antibody-dependent cellular cytotoxicity (ADCC); antibody-dependent cellular phagocytosis (ADCP); Chronic Lymphocytic Leukaemia (CLL); complement-dependent cytotoxicity (CDC); Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis); Microscopic Polyangiitis (MPA); non-Hodgkin's lymphoma (NHL); rheumatoid arthritis (RA)

2.4.4. Discussion on clinical pharmacology

PF-05280586 significantly and rapidly reduced CD19+ B-cell counts below the detection level, both in RA patients –with an in principle normal B-cell count at baseline-, as in patients with LTB-FL –with an increased B-cell count at baseline. PD response of PF-05280586 was overall similar to the comparator Rituximab-EU.

Rituximab is known to effectively reduce the peripheral CD19+ B–cell counts. However, there is no strong correlation between the extent of peripheral B-cell reduction and clinical response in RA, as RA disease activity may still remain even at low B-cell counts. For lymphoma, the correlation is neither clear, since circulating B-cells may not directly reflect tumour mass, and CD19+ cell counts alone cannot be considered as a surrogate for the clinical response.

Nevertheless, the comparative B-cell depletion data are considered as relevant supportive information for the assessment of bio-similarity and extrapolation to other non-investigated indications, since the B-cell levels indirectly reflect the potency of the drug of antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and programmed cell death. The mechanism of action is the same for all indications and ADCP is considered a plausible MoA relevant for CLL.

2.4.5. Conclusions on clinical pharmacology

Biosimilarity with the EU reference product MabThera has been demonstrated, based on the clinical pharmacology data.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Not applicable for biosimilar products.

2.5.2. Main study(ies)

Study B3281006

A Phase 3, Randomized, Double-Blind Study of PF-05280586 Versus Rituximab for the First-Line Treatment of Patients with CD20-Positive, Low Tumour Burden Follicular Lymphoma.

Methods

Study B3281006 is a randomised, double-blind, active controlled trial in patient with LTB-FL (low tumour burden follicular lymphoma). Patients were assigned to either the innovator product for the EU market (MabThera, called Rituximab-EU in this dossier), or the biosimilar product PF-052B0586, in a 1:1 ratio. Patients were treated with an IV (intravenous) infusion course of rituximab at Day 1, 8, 15, 22, in accordance with treatment guidelines.

After the treatment period of 22 days, a visit was scheduled at Day 29, and every 3 months thereafter. The primary endpoint assessment took place at Week 26. The end of the study was Week 52.

Figure 3. Overall Study Design of Study B3281006 in Patients With LTB-FL

Abbreviations: EU=European Union; R-EU=rituximab-EU; R-Pfizer=rituximab-Pfizer (PF-05280586)

Study Participants

Adult patients with histologically confirmed, Grade 1-3a, CD20-positive FL, containing no elements of diffuse large B-cell lymphoma, were eligible.

The diagnosis was first made by the Investigator. Low tumour burden was assessed according to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (Brice, 1997).

A nodal lesion must have been at least 11 mm x 11 mm OR ≥6 mm in the greatest transverse diameter (regardless of short axis measurement). An extra-nodal lesion must have been at least 10 mm x 10 mm.

Patients were in Ann Arbor Stage II, III, or IV.

Patients with evidence of histologic transformation to high grade or diffuse large B-cell lymphoma were excluded. Patients with poor prognostic factors, such as high lactate dehydrogenase and β2-microglobulin, and B-symptoms (>10% unintended weight loss, fever and night sweats) were excluded.

Patients had LTB-FL, defined as: a) Serum LDH ≤ 1.5 × ULN, b) β2-microglobulin ≤1.5 × ULN, c) Largest nodal or extra-nodal mass <7 cm in diameter, d) No more than 3 nodal sites with a diameter >3 cm, e) No clinically significant serous effusions detectible on chest radiography, f) Spleen enlargement ≥16 cm by computed tomography (CT) scan, g) No complications such as organ compression or impairment, h) No B symptoms (i.e. fever >38°C for 3 consecutive days; recurrent, drenching night sweats; or unintentional weight loss exceeding 10% body weight in 6 months).

Furthermore, in order to participate to the study, patients had to be in reasonably good condition, meeting performance ECOG (Eastern Cooperative Oncology Group) status of 0 to 1.

Treatments

Rituximab (PF-05280586 or rituximab-EU) was administered at a dose of 375 mg/m^2 at Visits 2, 3, 4, and 5 (Days 1, 8, 15, and 22). The maximum dose of rituximab that could be infused on 1 day was 1125 mg.

Infusion instructions were followed as per the product labelling. In order to prevent infusion reactions, precautionary measures were taken as established in the SmPC of the Innovator, such as a low infusion rate at the first administration (50 mg/hour), which can be gradually increased to a maximum of 400 mg/hour for the following administrations, if no infusion reactions occurred. Furthermore, all subjects received paracetamol, antihistaminic and prednisone (100 mg intravenous methylprednisolone or its equivalent) as a prophylaxis to prevent infusion reactions.

Objectives

Primary Objective was to compare the efficacy of PF-05280586 to rituximab-EU when administered as a first-line treatment to subjects with CD20-positive, low tumour burden follicular lymphoma (LTB-FL).

The hypothesis being tested in this study was that the efficacy (as measured by overall response rate [ORR] at Week 26) of PF-05280586 is equivalent to that of rituximab-EU.

Secondary Objectives were:

- To evaluate the safety of PF-05280586 and rituximab-EU.
- To evaluate the population pharmacokinetics (PK) of PF-05280586 and rituximab-EU.
- To evaluate the immunogenicity of PF-05280586 and rituximab-EU.
- To characterize CD19-positive B-cell depletion and recovery in patients receiving PF-05280586 and rituximab-EU.

Outcomes/endpoints

Primary efficacy outcome

The primary efficacy endpoint was ORR at Week 26, based on central review which included radiographic assessment and review of clinical data (B-cell depletion and bone marrow biopsy results).

The ORR was defined as the proportion of subjects who achieved either complete response (CR) or partial response (PR), based on the Lugano Classification (Cheson et al, 2007, 2014).

Secondary efficacy endpoints

- Complete response at Week 26 defined as per the revised response criteria for malignant lymphoma (based on central review). Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. All nodal index lesions must have regressed to the size of normal lymph nodes.

- Partial responder rates. The designation of PR at a subsequent time point requires a >50% decrease in the sum of the products of the diameters (SPD) of all index lesions.

- Overall survival (OS) defined as the time from date of randomization to death due to any cause.

- Progression-free survival (PFS) defined as the time from date of randomization to first progression of disease (PD, based on central review) or death due to any cause in the absence of documented PD.

- Time to treatment failure (TTF) defined as the time from date of randomization to progression of disease based on central review, death due to any cause, or permanent discontinuation from treatment, or discontinuation from study for any reason, whichever came first.

- Duration of response (DOR) defined as the time from date of the first documentation of overall response (CR or PR) to the first documentation of PD (central review) or to death due to any cause in the absence of documented PD.

Randomisation and blinding (masking)

Subjects were randomized in a 1:1 ratio to one of the 2 study treatment arms: arm A (PF-05280586) and arm B (rituximab-EU).

The site could randomize an eligible subject using an automated web-based randomization system (IMPALA) provided by the sponsor. A computer-generated randomization schedule was used to assign subjects to the treatment groups.

Randomization was stratified by low, medium, and high-risk subjects using the FLIPI2 score (Follicular Lymphoma International Prognostic Index 2).

Statistical methods

Analyses of the primary endpoint

The primary hypotheses were tested for ORR in order to show that PF-05280586 is equivalent to rituximab-EU, within an acceptance margin of -/+ 16%.

The primary efficacy analysis for equivalence was performed after all randomized subjects (ITT) had had the opportunity to complete their Week 26 visit and the assessment of overall response. The estimated difference in ORR between PF-05280586 and rituximab-EU was computed (based on the stratified Mantel-Haenszel method), and the asymptotic 95% CI of the difference, as proposed by Miettinen and Nurminen (1985), was constructed. The FLIPI2 categorization (low, medium, and high) was considered as the stratification factor in the Mantel-Haenszel (for the estimated treatment difference) and Miettinen and Nurminen (for the 95% CI) methods.

A missing value was defined as no post-baseline response assessment either due to loss to follow-up or withdrawal by subject or other reasons. In the primary analysis, if a post-dose response assessment was missing, the overall response was imputed as a non-responder instead of a missing value.

When the -/+ 16% acceptance criterion was met, an additional analysis was required to be conducted to test equivalence using -/+ 14.9% as criterion, in accordance to requirements from the regulatory authority in Japan.

In addition, sensitivity analyses for the primary outcome was performed in the PP-population.

The endpoints Complete Remission (CR) and Partial Response (PR) at Week 26 were analysed in a similar fashion as ORR.

A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05. Progression-free survival was also summarized using the Kaplan-Meier method. The Kaplan-Meier estimates for the 1-year PFS rates, and the 2-sided 95% CI of the rates using the Greenwood's formula were reported. In addition, a Cox model stratified by FLIPI2 was used to estimate the hazard ratio and its 95% CI for the treatment effect.

Similar methods as for PFS were used for the analyses of Overall Survival, Time to Treatment Failure and Duration of Response outcomes.

Results

Participant flow

There were 394 subjects assigned to the double-blind treatment; 196 subjects in the PF-05280586 group and 198 subjects in the rituximab-EU group. Of these, 393 subjects were actively treated including 196 treated subjects in the PF-05280586 group and 197 treated subjects in the rituximab-EU group (mITT). There was 1 subject who was assigned to the rituximab-EU group who withdrew from the study prior to receiving treatment.

In total, 194 [99.0%] subjects in the PF-05280586 group and 196 [99.0%] subjects in the rituximab-EU group completed the 4 weeks treatment course.

In total, 340 subjects had completed Week 52 of the study (170 [86.7%] subjects in the PF-05280586 group and 170 [85.9%] subjects in the rituximab-EU group.

Table 6. Subjects flow and Evaluation Groups - Study B3281006 (LTB-FL)

	rituximab-EU	PF-05280586	Total
Number (%) of subjects			
Screened			627
Assigned to study treatments	198	196	394
Treated	197	196	393
Completed treatment	196 (99.0)	194 (99.0)	390 (99.0)
Discontinued treatment	1 (0.5)	2 (1.0)	3 (0.8)
Completed study	170 (85.9)	170 (86.7)	340 (86.3)
Discontinued study	28 (14.1)	26 (13.3)	54 (13.7)
Analyzed for efficacy			
ITT	198 (100.0)	196 (100.0)	394 (100.0)
mITT[a]	197 (99.5)	196 (100.0)	393 (99.7)
PP	176 (88.9)	166 (84.7)	342 (86.8)
Response Evaluable Population	196 (99.0)	192 (98.0)	388 (98.5)
Analyzed for safety[b]			
Safety analysis	197 (99.5)	196 (100.0)	393 (99.7)
Adverse events	197 (99.5)	196 (100.0)	393 (99.7)
Laboratory data	197 (99.5)	195 (99.5)	392 (99.5)
Analyzed for PK			
PK analysis	197 (99.5)	196 (100.0)	393 (99.7)

Source: Table 14.1.1.1.

Abbreviations: ADA=anti-drug antibody; EU=European Union; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; NAb=neutralizing antibody; PK=pharmacokinetic; PP=per protocol.

a. Included biomarker analyses.

b. Analyzed for safety included ADA and NAb.

There were 54 (13.7%) subjects who discontinued from the study (23 [11.7%] subjects in the PF-05280586 group and 28 [14.1%] subjects in the rituximab-EU group). The most frequent reason for discontinuation was progressive disease as assessed by the investigator (14 [7.1%] subjects and 20 [10.1%] subjects in the PF-05280586 and rituximab-EU groups, respectively).

Table 7. Discontinuations From Study - ITT Population - Study B3281006

	rituximab-EU	PF-05280586	Total
Number (%) of subjects	198	196	394
Discontinuations	28 (14.1)	26 (13.3)	54 (13.7)
Relation to study drug not defined	27 (13.6)	23 (11.7)	50 (12.7)
Insufficient clinical response	4 (2.0)	3 (1.5)	7 (1.8)
Lost to follow-up	0	1 (0.5)	1 (0.3)
No longer willing to participate in study	3 (1.5)	4 (2.0)	7 (1.8)
Progressive disease	20 (10.1)	14 (7.1)	34 (8.6)
Protocol violation	0	1 (0.5)	1 (0.3)
AE related to study drug	0	2 (1.0)	2 (0.5)
AE not related to study drug	1 (0.5)	1 (0.5)	2 (0.5)

Source: Table 14.1.1.2.
Progressive disease was assessed by the investigator.
Abbreviations: AE=adverse event; EU=European Union; ITT=Intent-to-Treat.

Baseline data

Demographics

The study population mainly consisted of white middle-aged males and females. Slightly more females were included. About 50% of the study population had a BMI >25.

Table 8. Baseline demographic data Study B3281006

	rituximab-EU	PF-05280586	Total
Number (%) of subjects	198	196	394
Gender			
Male	92 (46.5)	86 (43.9)	178
Female	106 (53.5)	110 (56.1)	216
Age (years)			
<18	0	0	0
18-44	29 (14.6)	27 (13.8)	56 (14.2)
45-64	101 (51.0)	102 (52.0)	203 (51.5)
≥65	68 (34.3)	67 (34.2)	135 (34.3)
Mean (SD)	58.3 (12.8)	58.7 (12.1)	58.5 (12.4)
Median	60.0	59.0	60.0
Range	21-93	25-85	21-93
Race			
White	146 (73.7)	158 (80.6)	304 (77.2)
Black	0	1 (0.5)	1 (0.3)
Asian	44 (22.2)	30 (15.3)	74 (18.8)
Other	8 (4.0)	7 (3.6)	15 (3.8)
Ethnicity			
Hispanic/Latino	26 (13.1)	31 (15.8)	57 (14.5)
Not Hispanic/Latino	172 (86.9)	165 (84.2)	337 (85.5)
Weight (kg)			
N	198 (100.0)	196 (100.0)	394 (100.0)
Mean (SD)	73.2 (18.0)	73.7 (15.6)	73.5 (16.8)
Median	72.0	73.9	73.0
Range	42.2-156.0	37.6-130.0	37.6-156.0
Height (cm)			
N	195 (98.5)	194 (99.0)	389 (98.7)
Mean (SD)	166.1 (9.3)	166.0 (10.5)	166.0 (9.9)
Median	165.0	165.0	165.0
Range	146.4-190.0	137.0-195.0	137.0-195.0
Body mass index (kg/m^2)			
N	195 (98.5)	194 (99.0)	389 (98.7)
Mean (SD)	26.3 (5.2)	26.7 (4.8)	26.5 (5.0)
Median	25.9	26.0	26.0
Range	16.0-54.7	16.1-47.6	16.0-54.7

Source: Table 14.1.2.1.
Body mass index was defined as weight/(height*.01)**2
Abbreviations: EU=European Union; ITT=Intent-to-Treat; N=number of subjects in analysis population; SD=standard deviation.

Disease characteristics

The mean (SD) duration of FL since diagnosis was 0.69 (1.285) years, which was comparable between the treatment groups.

The randomisation stratification factor FLIPI2 was balanced between the treatment groups. The majority had a FLIPI2 risk classification of medium and low at baseline. In line with inclusion criteria, LDH was normal or marginally increased. About 28% had bone marrow involvement.

Table 9. Baseline disease characteristics, Study B3281006

	Rituximab-EU (N=198)		PF-05280586 (N=196)		Total (N=394)	
Number (%) of Subjects	n	(%)	n	(%)	n	(%)
Ann Arbor Stage						
Stage I	0		0		0	
Stage II	54	(27.3)	52	(26.5)	106	(26.9)
Stage III	85	(42.9)	89	(45.4)	174	(44.2)
Stage IV	59	(29.8)	55	(28.1)	114	(28.9)
ECOG Performance Status						
0	169	(85.4)	171	(87.2)	340	(86.3)
1	28	(14.1)	25	(12.8)	53	(13.5)
2	0		0		0	
3	0		0		0	
4	0		0		0	
Not Reported	1	(<1.0)	0		1	(<1.0)
FLIPI Risk Classification						
Low	89	(44.9)	91	(46.4)	180	(45.7)
Medium	77	(38.9)	72	(36.7)	149	(37.8)
High	32	(16.2)	33	(16.8)	65	(16.5)
FLIPI2 Risk Classification						
Low	58	(29.3)	54	(27.6)	112	(28.4)
Medium	127	(64.1)	133	(67.9)	260	(66.0)
High	13	(6.6)	9	(4.6)	22	(5.6)
Bone Marrow Biopsy Lymphoma Results						
Positive	56	(28.3)	53	(27.0)	109	(27.7)
Negative	142	(71.7)	142	(72.4)	284	(72.1)
Not Done	0		0		0	
Indeterminate	0		1	(<1.0)	1	(<1.0)
LDH Normal?						
Yes	193	(97.5)	192	(98.0)	385	(97.7)
No	5	(2.5)	4	(2.0)	9	(2.3)
Not Assessed	0		0		0	
Beta 2-Microglobulin Level <= 1.5ULN?						
Yes	198	(100)	196	(100)	394	(100)
No	0		0		0	
Not Assessed	0		0		0	

Co-morbidity

About 25% of the population had a history of cardio-vascular disorders. The use of any prior drug treatments was comparable between the 2 treatment groups, reported by 140 subjects (71.4% and 71.1%) in the PF-05280586 group and rituximab-EU group, respectively.

The most frequently reported concurrent drug treatments were agents acting on the renin-angiotensin system (23.9% and 20.9%), beta-blockers (9.6% and 13.3%), simvastatin (8.2 and 5.6%), and acetylsalicylic acid (11.7 and 8.6%) in the PF-05280586 group and Rituximab-EU group, respectively.

Numbers analysed

The ITT Population (394 [100.0%] subjects) was used for the primary efficacy analyses of the primary and secondary endpoints.

The PP Population (342 [86.8%] subjects) was used for sensitivity analyses of the primary and secondary efficacy endpoints at Week 26. Reasons for exclusion from the PP Population are provided in the table below. The most frequent reason for exclusion from the PP Population was no evaluable Week 26 assessment (based on central review) with 20 (10.2%) subjects in the PF-05280586 group and 14 (7.1%) subjects in the rituximab-EU group.

Table 10. Per Protocol population, Study B3281006

	Rituximab-EU N=198 n (%)	PF-05280586 N=196 n (%)
Number (%) of patients excluded from the PP Population	22 (11.1)	30 (15.3)
A subject was excluded from the PP analysis population if the following applied:		
Did not take the treatment to which the subject was randomized to	1 (0.5)	0
No baseline or no adequate baseline disease assessment (based on central review), unless the subject died on/before Week 26	1 (0.5)	0
A subject was excluded from the PP analysis population if the following reasons applied, unless the subject either died on/before Week 26 or had an Overall Response of PD (central review) on/before the Week 26 time point:		
For subjects that had an adequate baseline disease assessment (based on central review), no measureable disease at baseline as assessed by the central reader selected after the adjudication step	9 (4.5)	13 (6.6)
No evaluable Week 26 assessment (based on central review, defined as the following: either missing, UE, or not available)	14 (7.1)	20 (10.2)
Any concomitant medication violation that could have significantly impacted the Week 26 Overall Response assessment, which occurred on/before the Week 26 time point	0	0

Source: Table 14.2.7.2
Abbreviations: EU=European Union; n=number of subjects with observation; N=number of subjects in analysis population; PD=progressive disease; PP=per protocol; UE=unevaluable.

Outcomes and estimation

Primary outcome

The primary endpoint, i.e. the ORR by central review in the ITT population at Week 26, was 148 (75.5%) subjects in the PF-05280586 group, and 140 (70.7%) subjects in the rituximab-EU group. The analysis of ORR showed an estimated difference of 4.66% (PF-05280586 minus rituximab-EU), with a 95% CI of (-4.16%, 13.47%), which fell within the -16.0% to 16.0% pre-specified equivalence margin agreed to by the FDA and EMA. See Table below.

Table 11. Summary of Primary endpoint (Overall Response Rate at Week 26 - Central Review Assessment - ITT Population - Study B3281006 (LTB-FL)

	Rituximab-EU (N=198)	PF-05280586 (N=196)	Difference (PF-05280586 minus Rituximab-EU)
Overall Response Rate (%)			
n (%)	140 (70.7)	148 (75.5)	4.66
(95% CI)	(63.8, 76.9)	(68.9, 81.4)	(-4.16, 13.47)

The 95% CI of the difference in ORR was also within the -14.9% to 14.9% margin agreed to by the Japanese authority PMDA.

The equivalence criteria were also met for the PP-analysis of the primary endpoint ORR (see Table below).

Table 12. Summary of Overall Response Rate (ORR) at Week 26 - Central Review Assessment - PP Population

	Rituximab-EU (N=176)	PF-05280586 (N=166)	Difference (PF-05280586 minus Rituximab-EU)
Overall Response Rate, n (%)	138 (78.4)	143 (86.1)	7.49
(95% CI)	(71.6, 84.2)	(79.9, 91.0)	(-0.67, 15.80)

Secondary outcomes

Complete Remission (CR) at Week 26 was also similar between EU-Rituximab (28.3%, 95% CI 22.1,35.1) and biosimilar product PF-05280586 (26.0, 95% CI 20.0,32.8), difference -2.31, 95% CI -11.09, 6.50), ITT-analyses.

Partial Response (PR) rates were 42.4% (95% CI 35.4-49.6) and 49.5% (95% CI 42.3-56.7) forEU-Rituximab and biosimilar product PF-05280586, respectively (difference 6.975 (-2.91-16.71),ITT-analyses.

Table 13. Summary of Complete Response (CR) and Partial Response (PR) at Week 26 - Central Review Assessment - ITT Population

	Rituximab-EU (N=198)	PF-05280586 (N=196)	Difference (PF-05280586 minus Rituximab-EU)
Complete Response			
n (%)	56 (28.3)	51 (26.0)	-2.31
(95% CI)	(22.1, 35.1)	(20.0, 32.8)	(-11.09, 6.50)
Partial Response			
n (%)	84 (42.4)	97 (49.5)	6.97
(95% CI)	(35.4,49.6)	(42.3, 56.7)	(-2.91, 16.71)

Also, the PP-analyses of CR and PR, supported equivalence:

Table 14. Summary of Complete Remission (CR) and Partial Response (PR) at Week 26 - Central Review Assessment - Per Protocol Population

	Rituximab-EU (N=176)	PF-05280586 (N=166)	Difference (PF-05280586 minus Rituximab-EU)
All Subjects			
Complete Remission (CR) (%)	54 (30.7)	46 (27.7)	-3.28
95% CI (%)	(24.0,38.1)	(21.1,35.2)	(-12.85, 6.40)
Partial Response (PR) (%)	84 (47.7)	97 (58.4)	10.77
95% CI (%)	(40.2,55.4)	(50.5,66.0)	(0.13, 21.17)

Long-term ORR outcomes (Week 52).

Table 15. Summary of ORR, Complete Remission (CR) and Partial Response (PR) at Week 52- Central Review Assessment - ITT Population

	Rituximab-EU (N=198)	PF-0528086 (N=196)	Difference
ORR	126 (63.6) (56.5,70.3)	123 (62.8) (55.6,69.5)	0.84 (-10.38, 8.71)
Complete Remission	63 (31.8) (25.4,38.8)	62 (31.6) (25.2,38.6)	0.05 (-9.07, 9.18)
Partial response	63 (31.8) (25.4,38.8)	61 (31.1) (24.7,38.1)	-0.89 (-10.02, 8.24)

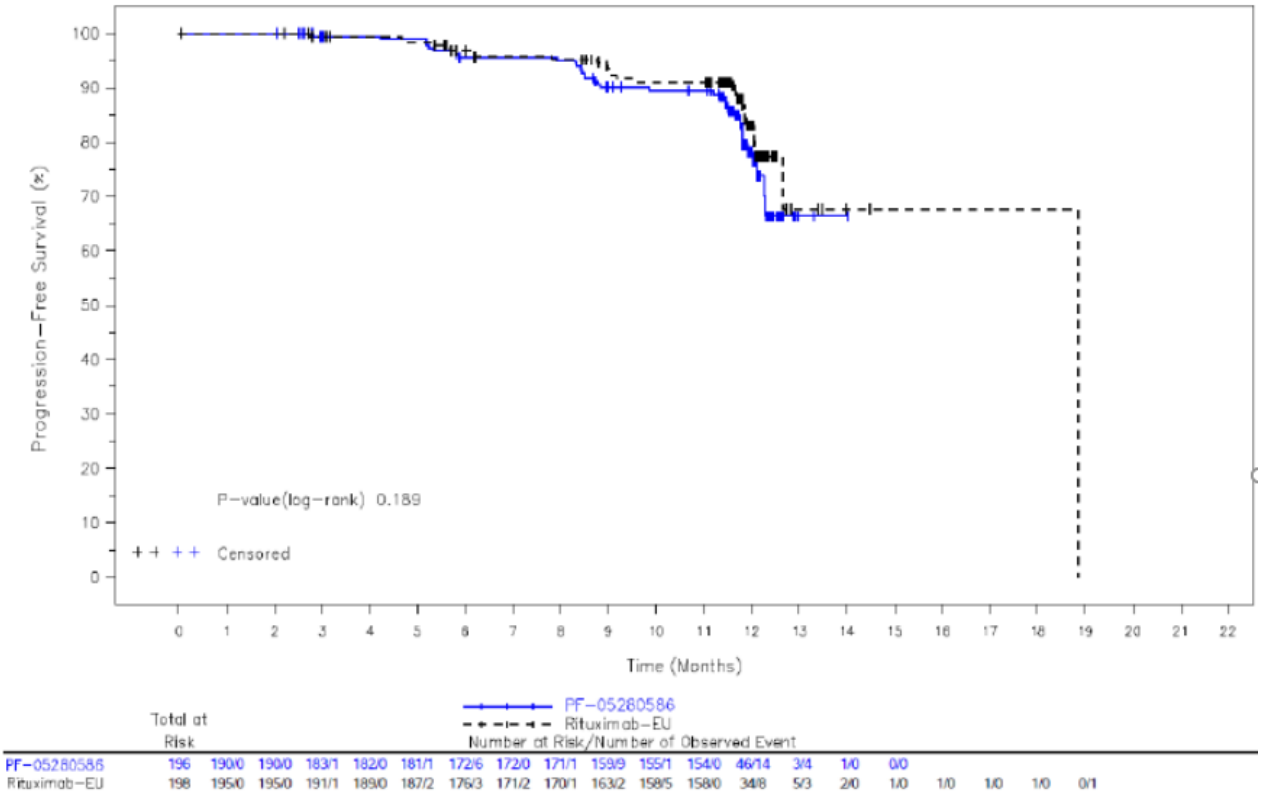
Progression-Free Survival (PFS)

After of 52 weeks follow-up, there were 37 (18.9%) subjects in the PF-05280586 treatment group and 28 (14.1%) subjects in the rituximab-EU treatment group who had an event. A total of 159 (81.2%) subjects in the PF-05280586 treatment group and 170 (85.9%) subjects in the rituximab-EU group were censored. Using a Cox Proportional Hazards model with FLIPI2 categorization (low, medium, and high) as strata, the hazard ratio when comparing PF-05280586 and rituximab-EU was 1.393, with a 95% CI of (0.847, 2.291) for ITT population. Similar outcomes were reported for the PP-population (HZ 1.381, with a 95% CI of (0.835, 2.284), and a p-value of 0.207).

Table 16. Progression-Free Survival (PFS) - Central Review Assessment - ITT Population

	rituximab-EU (N=198)	PF-05280586 (N=196)
Number with event, n (%)	28 (14.1)	37 (18.9)
Type of event, n (%)[a]		
Progression	27 (96.4)	36 (97.3)
Death without progression	1 (3.6)	1 (2.7)
Number censored, n (%)	170 (85.9)	159 (81.1)
Reason for censorship[b]		
Ongoing at data cutoff	0	0
No baseline assessment (or not adequate), no death	1 (<1.0)	0
No post-baseline assessment (or not adequate), no death	2 (1.2)	6 (3.8)
Early study discontinuation without progression/death	17 (10.0)	14 (8.8)
Study completion without progression/death	150 (88.2)	139 (87.4)
Probability of being event-free at 1 year[c] (95% CI)[d]	83.0 [75.0, 88.6]	78.2 [70.2, 84.2]
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[e]		
25%	12.6 [12.1, 18.9]	12.1 [11.8, -]
50%	18.9 [12.6, 18.9]	-
75%	18.9 [- , -]	-
Versus rituximab-EU		
Hazard ratio[f]		1.393
95% CI of hazard ratio		0.847 - 2.291
P-value[g]		0.189

Figure 4. Kaplan-Meier Plot, Progression-Free Survival (PFS) - Central Review Assessment - ITT Population



Source: Figure 14.2.2.1.
P-value from 2-sided log-rank test stratified by FLIPI2 risk categorization.
Abbreviations: EU=European Union; FLIPI2= Follicular Lymphoma International Prognostic Index 2; ITT=Intent-to-Treat.

Overall Survival (OS)

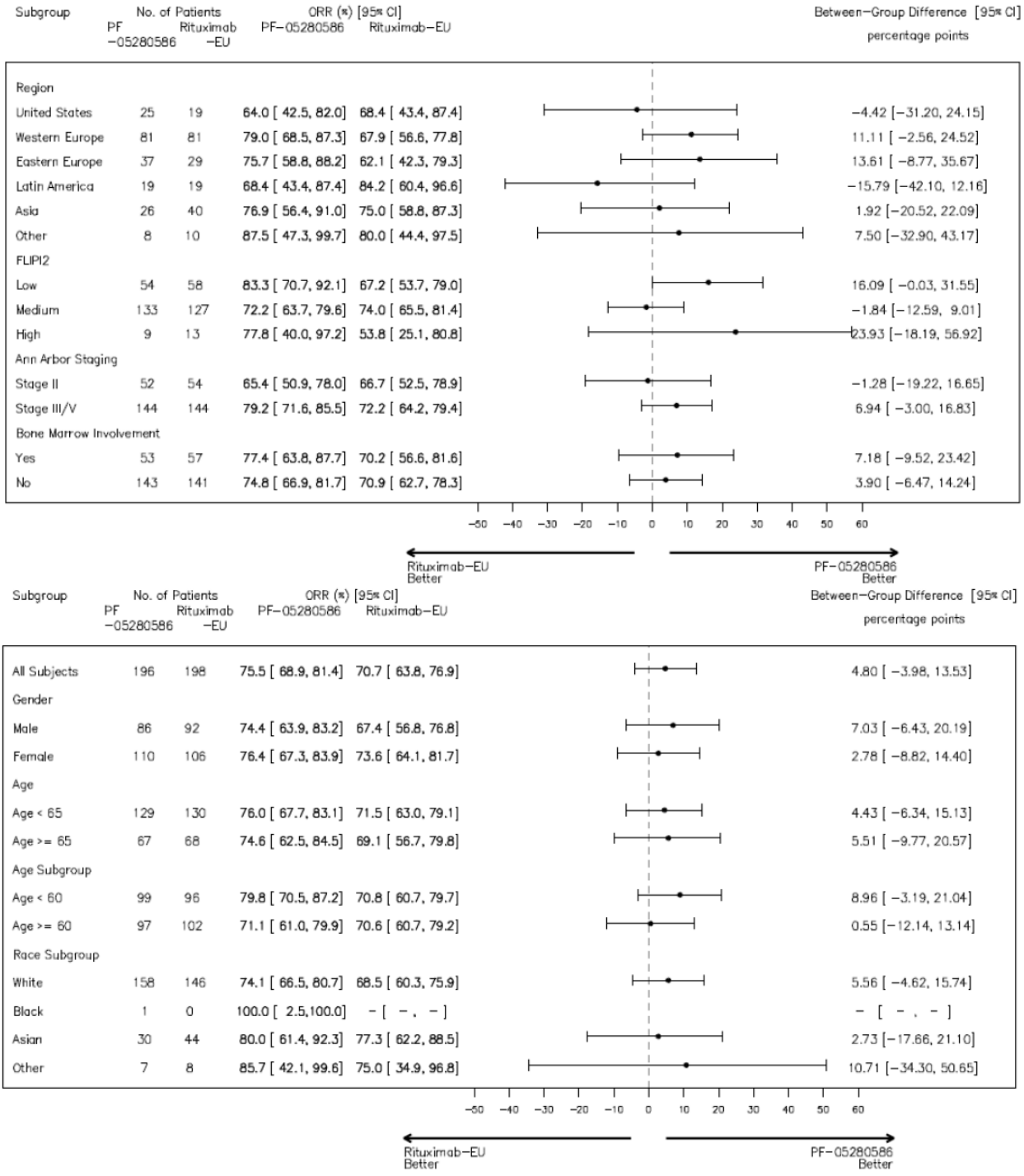
In the ITT Population, there was one (0.5%) subject who died in each treatment group. The cause of death was reported as disease progression for the subjects in both the PF-05280586 group and the rituximab-EU group. Neither event was considered by the investigator as related to treatment. Both cases were reported outside the protocol-specified active reporting period (through and including 28 calendar days after the last study visit).

For Time to Treatment Failure and Duration of Response outcomes, a reference is made to the Clinical Assessment Report.

Ancillary analyses

Subgroup analyses by age, gender, race and region, Ann Arbor Staging classification, bone marrow involvement, as well as by baseline FLIPI2 categorization were performed on the primary endpoint, the ORR at Week 26 (ITT). See plots in figure 3.3.5 and 3.3.6 below. In addition, also in a subgroup of very elderly, the data pointed at equivalence.

Figure 5 and 6. Subgroup analyses, Study B3281006



Summary of main study(ies)

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

Table 17. Summary of efficacy for trial B3281006

Title: A Phase 3, Randomized, Double-Blind Study of PF-05280586 Versus Rituximab for the First-Line Treatment of Patients With CD20-Positive, Low Tumour Burden, Follicular Lymphoma			
Study identifier	Study B3281006		
Design	Randomised, active-controlled. double-blinded, parallel, multi-centre,		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks not applicable 26 weeks
Hypothesis	Equivalence		
Treatments groups	PF-05280586		Dose: 375 mg/m2 BSA, Days 1, 8, 15, and 22, number randomized 196 (ITT)
	rituximab-EU (MabThera)		Dose: 375 mg/m2 BSA, Days 1, 8, 15, and 22, number randomized 198 (ITT)
Endpoints and definitions	Primary endpoint	ORR	Overall Response Rate (%), sum of Complete Responder + Partial responder rates, as established by central readers, at Week 26, ITT
	Secondary endpoint	CR	Complete Response rate
	Secondary endpoint	PR	Partial Response rate
	Secondary endpoint	PFS	Progression Free Survival
Database lock	18 May 2018 (last randomised subject had completed end-of-study at Week 52) visit)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intention to treat (all randomised subjects), Week 26		
Descriptive statistics and estimate variability	Treatment group	rituximab-EU	PF-05280586
	Number of subjects	198	196
	ORR (%)	140 (70.7)	148 (75.5)
	95% CI	63.8-76.9	68.9-81.4
	CR (%)	56 (28.3)	51 (26.0)
	95% CI	22.1-35.1	20.0-32.8
	PR (%)	84 (42.4)	97 (49.5)

	95% CI	35.4-49.6	42.3-56.7
	PFS, number of events, %) Week 52	28 (14.1)	37 (18.9)
Effect estimate per comparison	Primary endpoint	Comparison groups	PF-05280586 *minus* Rituximab-EU
		difference between groups	4.66
		95% confidence interval of the difference between groups	-4.16-13.47*
	Secondary endpoint CR	Comparison groups	PF-05280586 *minus* Rituximab-EU
		difference between groups	-2.31
		95% confidence interval of the difference between groups	-11.09-6.50
	Secondary endpoint PR	Comparison groups	PF-05280586 *minus* Rituximab-EU
		difference between groups	6.97
		95% confidence interval of the difference between groups	-2.91, 16.71
	Secondary endpoint PFS (Week 52)	Comparison groups	PF-05280586 *versus* Rituximab-EU
		Hazard ratio (HR)	1.393
		95% CI of the HR	0.847, 2.291
		P-value	0.189
Notes	*The equivalence criteria (+/- 16%) were met for the primary endpoint		
Analysis description	**Per protocol set (pre-specified)**		
Primary endpoint ORR at Week 26	Treatment group	rituximab-EU	PF-05280586
	Number of subjects	176	166
	ORR: n (%)	138 (78.4)	143 (86.1)
	95% CI	71.6-84.2	79.9-91.0
Effect estimate per comparison: Primary endpoint	Comparison groups	PF-05280586 *minus* Rituximab-EU	
	difference between groups	7.49	
	95% confidence interval of the difference between groups	-0.67,15.80	
Notes	**The equivalence criteria (+/- 16%) were met for the primary endpoint in the PP analysis as well.		

Supportive study(ies)

Study B3281001 and its extension study B3281004 were conducted to compare the PK-PD and immunogenicity of PF-05280586 with the EU and US rituximab innovator products.

Study B3281001

Study B3281001 was a blinded randomized study, in which subjects were randomly assigned in a 1:1:1 ratio to one of the three treatment groups (PF-05280586, rituximab-EU, or rituximab-US).

Primary objective of Study B3281001 was demonstrating PK bioequivalence. Secondary efficacy endpoints were disease activity scores using DAS28-CRP (mean change from Baseline), LDAS (Low Disease Activity, defined as DAS28-CRP ≤3.2), Remission (defined as DAS28-CRP <2.6), EULAR responses , EULAR Response (categorized as no response, good response, and moderate response), HAQ-DI and ACR assessments (ACR20, ACR50, and ACR70 responder rates).

All randomized subjects (220 cases) received the study drug; 73 subjects (33%) rituximab-US, 74 subjects (34%) rituximab-EU, and 73 subjects (33%) PF-05280586. A total of 192 of the 220 randomized subjects (87.3%) completed the study. A total of 16 (7.3%) subjects discontinued before completing the study, including 5 (6.8%) rituximab-US subjects, 3 (4.1%) rituximab-EU subjects, and 8 (11.0%) PF-05280586 subjects. The most frequent reasons for discontinuation from the study were 'no longer willing to participate in the study' (6 [2.7%] subjects) and AEs (5 [2.3%] subjects).

Statistics

Descriptive statistics of all efficacy endpoints were provided without reporting confidence intervals. Additionally, the relative risk and its 95% confidence interval were computed for LDAS rate and DAS28-CRP remission rate for each pair-wise treatment comparison by visit, from the mITT population (defined as each randomised subject who received at least one dose of the study treatment). Missing data were imputed as non-responder for LDAS and remission rates.

Results regarding efficacy Study 001:

At inclusion, the mean DAS2CRP scores varied between 5.68 -6.22 between subgroups, indicating moderate-severe active disease stage. An imbalance in RA disease activity parameters at baseline was noted in Study B3281001, which was considerable higher for Rituximab-US versus the PF-05280586 group. There was no relevant difference between Rituximab-EU group and PF-05280586 group in baseline disease activity.

As after 16 weeks patients were able to leave for study B3281004, if the results of last visit before 16 weeks (in this study week 13) were considered most relevant for efficacy assessment.

The mean DAS28-CRP decreased from baseline with about 2 points and reached its plateau at Week 13 in all 3 treatment groups. Such an improvement is considered a clinically relevant effect. The results were similar for PF-05280586 and Rituximab-EU. The 95% CIs of the differences between treatment groups regarding the decline of efficacy endpoints from baseline was not provided for any of these endpoints in the applicants dossier.

Table 18. Summary of DAS28-CRP baseline and change from baseline by visit (mITT Population)- Study B3281001

	Rituximab-US N=73	Rituximab-EU N=74	PF-05280586 N=73
Baseline			
N	73	74	73
Mean (SD)	6.22 (0.89)	5.79 (0.95)	5.68 (0.86)
Median	6.23	5.75	5.65
Min, Max	4.00, 8.25	3.58, 7.95	3.99, 7.34
Change from Baseline at Week 13			
N	67	72	67
Mean (SD)	-2.3 (1.34)	-2.1 (1.33)	-2.0 (1.43)
Median	-2.4	-2.2	-2.0
Min, Max	-5.0, 0.0	-6.1, 0.9	-5.1, 0.9
Change from Baseline at Week 17			
N	67	71	66
Mean (SD)	-2.4 (1.35)	-2.1 (1.39)	-2.0(1.32)
Median	-2.3	-1.9	-1.8
Min, Max	-5.5, 0.2	-5.2, 0.6	-5.2, 0.7
Change from Baseline at Week 25 (EOT)			
n[a]	55	58	50
Mean (SD)	-2.5 (1.30)	-2.0 (1.30)	-1.7 (1.25)
Median	-2.5	-2.1	-1.6
Min, Max	-5.2, -0.0	-5.1, 1.0	-5.1, 0.7

Source: Module 5.3.3.2 Study B3281001 Table 18

a. The number of subjects in each treatment group decreased on and after Week 17 because they could rollover to the extension study.

Abbreviations: DAS28-CRP=Disease Activity Score in 28 joints - C-reactive protein; EOT=End of Treatment; EU=European Union; Max=maximum; Min=minimum; mITT=modified intent-to-treat; n=number of subjects; N=number of subjects randomized; SD=standard deviation; US=United States

From other secondary endpoints, LDAS scores, DAS remission rates and EULAR responses showed the same results as DAS28-CRP. At week 13, both LDAS rates and EULAR response for PF-05280586 and Rituximab-EU were 41.8% and 44.4% respectively. DAS remission rates at week 13 were 29.2% and 28.4% for Rituximab-EU and PF-05280586 respectively. These remain stable till end of study at Week 25. Relative risk analyses showed no statistical differences for LDAS and remission rates between treatments.

Also, HAQ-DI and ACR responders (ACR20, 50 and 70) decline from baseline in all study groups, although at a lower extent for PF-05280586. At week 13 the percentage change in HAQ-DI scores for PF-05280586 was -14.6% and for Rituximab-EU -39.5%. ACR20 measures (non-responder imputation) for PF-05280586 and Rituximab-EU were 50.7% and 70.3% at week 13 respectively. At Week 25, the were 50.0% and 60.3%, respectively.

Post-hoc analyses

To match the subjects regarding the baseline in disease activity, applicant has conducted a post hoc Propensity Score (PS) analysis on request of the FDA, based on swollen joint count (66) and subject's assessment of arthritis pain (VAS), and combined the rituximab-EU and rituximab-US groups. After propensity score matching, the baseline values and the outcomes regarding mean change from baseline of DAS28-CRP and HAQ-DI were similar for US reference product and PF-05280586. Also, efficacy responder rates indicated similarity. These data are only considered as supportive, as direct comparisons to the Rituximab-EU reference product are considered more relevant to establish biosimilarity for the EU target population and similarity was demonstrated as compared to the EU reference product).

Study B3281004

Design

This was an extension study for subjects who had participated for in the prior Study B3281001. The objectives of the study were to provide access to continuous rituximab treatment in the participating RA patients, and to evaluate the overall safety, tolerability and immunogenicity of PF-05280586 occurring after transition from a licensed rituximab product to PF-05280586.

Patient were eligible who completed the full study period for Study B3281001. In addition, patients could escape earlier to participation in extension study B3281004 after least 16 weeks, based on Investigator's judgement and patient's willingness to comply with the extension study protocol. All subjects were offered three courses of study treatment. Subjects assigned to PF-05280586 in Study B3281001 continued to receive PF-05280586 throughout this study. Subjects who were assigned to the licensed products (Rituximab-EU or US) in Study B3281001 were assigned in a blinded manner (1:1) to receive either the previously assigned licensed product Rituximab-EU (E) or PF-05280586 (P) for the first course of treatment (E-PPP arm). The subjects who in the first instance were assigned to receive Rituximab-EU in Study B3281004, were also switched to PF-05280586 (E-EPP) in following courses.

Results regarding efficacy Study B3281004:

Overall, 185 subjects from 220 B3281001 Study subjects were randomized and included in Study B3281004. In total, 48/59 subjects completed the study for study arm P-PPP, and 30/33 for both study arms E-PPP and E-EPP, respectively. P-PPP refers to the group which received PF-05280586 in both Study B3281001 and extension study B3281004 (3 treatment courses) and were not switched, E-PPP group are the subjects which received Rituximab-EU in study B3281001 and PF-05280586 from the start of extension study. E-EPP refers to the group of subjects who received Rituximab-EU during study B3281001 and first course of Study B3281004, and then were switched to PF-05280586.

Change from Baseline for DAS28-CRP score at course 3/ week 25 (end of trial) is shown below. The mean percentage changes in DAS28-CRP were -41.56%, -42.40% and -45.09% for P-PPP and E-EPP and E-PPP groups, respectively.

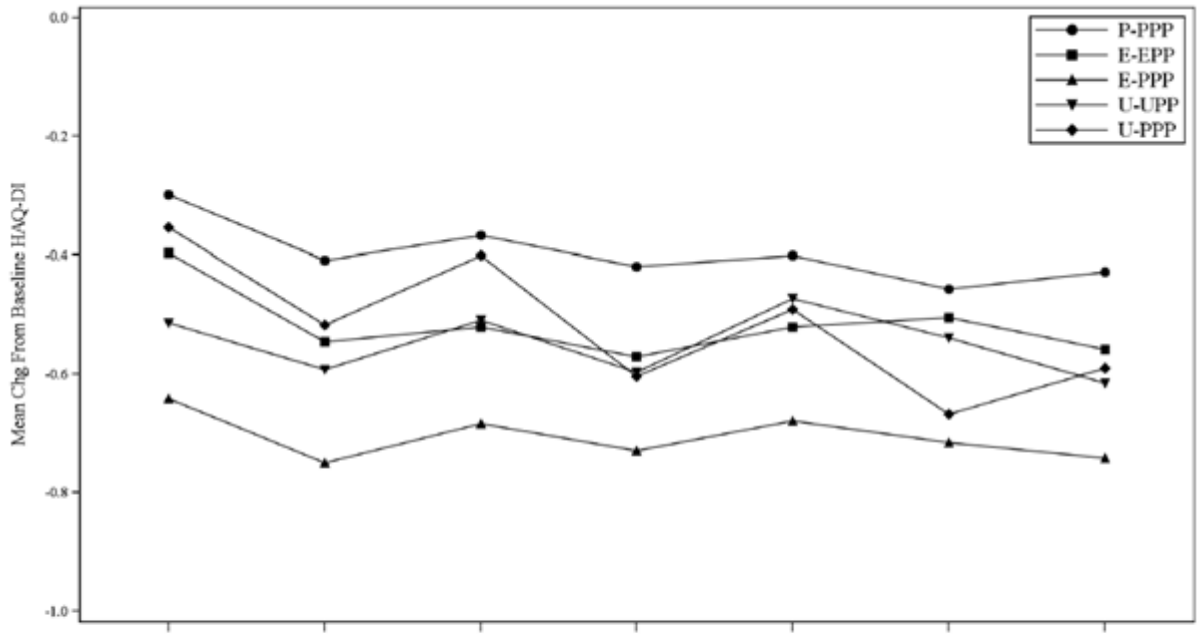
Table 19. Summary of overall DAS28 and its components by treatment sequence and visit – by the end of course 3, mITT population

	B3281001 Randomization					
	PF-05280586	Rituximab-EU		Rituximab-US		
Component Visit Statistics	PPP (N=48)	EPP (N=30)	PPP (N=30)	UPP (N=27)	PPP (N=29)	Total (N=164)
Overall DAS28-CRP[a]						
Course 3/ Week 25| (EOT)						
n	47	29	29	27	29	161
Mean (Std Dev)	3.22 (1.322)	3.23 (1.333)	3.15 (1.320)	3.26 (1.212)	3.24 (1.364)	3.22 (1.297)
Median	3.46	3.24	2.95	3.25	3.19	3.16
Min, Max	1.12, 6.22	1.41, 6.46	1.25, 6.28	1.14, 5.16	1.47, 6.48	1.12, 6.48
Change from Baseline at Course 3/ Week 25 (EOT)						
n	47	29	29	27	29	161
Mean (Std Dev)	-2.30 (1.245)	-2.53 (1.641)	-2.59 (1.314)	-2.88 (1.127)	-2.86 (1.392)	-2.59 (1.348)
Median	-2.32	-3.04	-2.23	-2.69	-3.15	-2.68
Min, Max	-5.15, 0.96	-5.30, 1.18	-5.34, 0.08	-4.92, -0.59	-4.67, 0.57	-5.34, 1.18
Percentage Change from Baseline at Course 3/ Week 25 (EOT)						
n	47	29	29	27	29	161
Mean (Std Dev)	-41.56 (22.824)	-42.40 (26.290)	-45.09 (20.163)	-47.29 (17.810)	-46.75 (22.300)	-44.24 (22.046)
Median	-42.43	-45.87	-43.04	-46.72	-50.82	-46.10
Min, Max	-82.08, 21.80	-77.34, 25.94	-77.25, 1.33	-78.48, -10.29	-71.71, 9.59	-82.08, 25.94

Similarly, to Study B3281001, LDAS rates, DAS remission rates in all groups showed equivalent efficacy regarding the mean changes from baseline in DAS28-CPR in Study B3281004. LDAS rates at week 25 (EOT) for P-PPP, E-EPP and E-PPP were 48.9%, 48.3% and 58.6% respectively (CIs are not provided). For the subjects who took all 3 courses of treatment, all treatment groups showed comparable profiles in DAS remission rate. The DAS remission rates at Course 3, Week 25 were 34.0%, 37.9% and 41.4% in the P-PPP, E-EPP and E-PPP treatment groups, respectively.

HAQ-DI mean percentage changes from baseline at week 25 (EOT) for P-PPP, E-EPP and E-PPP were -23.7%, -37.7% and -48.7% respectively. At Course 3, Week 25 the ACR20 responders, for P-PPP, E-EPP and E-PPP were 59.6%, 66.7% and 89.7% respectively.

Figure 7. Mean Change From Baseline in HAQ-DI by Treatment Sequence and Visit - mITT Population



N							
P-PPP	48	48	48	48	48	46	47
E-EPP	30	30	30	30	30	30	30
E-PPP	30	30	30	30	30	29	30
U-UPP	27	27	27	27	27	26	27
U-PPP	29	29	29	29	29	29	29

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study B3281006 in Patients With LTB-FL

One pivotal randomised, double-blind, active controlled study was performed in an oncology model, to demonstrate equivalence of efficacy of the biosimilar product and the EU reference product. In addition, a randomised single dose study, followed by its extension study was performed in RA as a model of an auto-immune disorder. The RA study was only considered as supportive, since it was not powered to demonstrate equivalence of efficacy, while it was powered to demonstrate bioequivalence of PK.

The pivotal study enrolled subjects with LTB-FL (low-tumour burden follicular lymphoma) who were asymptomatic for lymphoma specific B-symptoms, an early disease stage where either WW (watchful waiting without active treatment), radiotherapy or rituximab monotherapy could be applied according to the ESMO European treatment guideline (Annals of Oncology 27 (Supp 5): v83–v90, 2016). There is no clear evidence that starting rituximab early would improve overall survival. However, according to the European treatment guideline ESMO (2016), rituximab monotherapy could be an option for LTB-FL when taking into account the patient's perspective, who may prefer early rituximab treatment as WW brings along uncertainties. In addition, radiotherapy may be associated with side-effects at certain locations, such as e.g. sicca syndrome or hypothyroidism at cervical location, or mucositis or myeloablative suppression due to abdominal radiation.

The choice of the LTB-FL as a model is supported, as rituximab monotherapy allows for the assessment of biosimilarity without the potentially confounding factors that would be introduced by combining rituximab with chemotherapy in more advanced stage patients. MabThera is not authorised for the treatment of LTB-FL. However, the SAWP/CHMP agreed with the choice of LTB-FL as a mode to investigate equivalence, as it was considered as a more sensitive model to detect potential differences between the reference product and the biosimilar product.

The design of the pivotal study (randomised, double blind) is considered adequate, and in accordance to the SAWP advice. The choice of the comparator, EU-sourced Rituximab, is supported; the lack of a placebo arm is considered acceptable, however, as assay sensitivity can be assumed given the large treatment effect (ORR difference versus placebo of >70%) that has been reported for rituximab in a similar population in literature (Ardeshna, 2014, Kahl, 2014). Notably, the ORR rates in the pivotal trial were similar as reported in studies from the literature.

The choice of the primary endpoint (ORR at Week 26) is considered adequate for a biosimilar exercise. ORR is a sensitive and well-established endpoint for follicular lymphoma studies. Since overall survival is expected to be high in LTB-FL, it would require a very large and long-term study to establish an effect on overall survival. The end-of-treatment after 4 courses is already at Day 22, conform treatment guidelines. However, as the PD effects of rituximab are prolonged and it may take time before the tumours resolve. Therefore, it is agreed that the primary analyses were scheduled at Week 26.

As discussed in the SAWP in 2014, the equivalence margin of +/- 16 % was based on a single randomised controlled study in LTB-FL patients by Ardesha. The Ardesha study showed a large treatment effect of Rituximab versus the control of Watchful Waiting (78% versus 7%). The proposed equivalence margin of +/- 16% was based on both statistical and clinical arguments. The +/- 16% margin was agreed by the SAWP/CHMP in the scientific advice from 2014, provided that the ORR responder rates with PF-05280586 and EU-Rituximab would be in the same range as reported for Rituximab in the Ardesha study. This was indeed the case, which provides confirmation that differences within the equivalence margin of 16% will not likely overlap with the control. In addition, the clinical relevance of the confidence interval of -4.14% to 13.47 of the ORR was discussed. Considering the treatment effect observed for rituximab in LTB-Fl patients, differences within the equivalence margin of 16% is considered reasonable from a clinical perspective. A slightly (numerically) higher ORR response was observed for the biosimilar product PF-05280586 versus the EU innovator product. However, this was not associated with differences in quality, PK, PD or Safety.

The primary endpoint was assessed centrally by two independent readers. When there was disagreement between the two readers, a third adjudicated reader made the final diagnoses. The inter-rater agreement of radiographic outcomes between the two readers was 80.2%. Treatment group differences in ORR at Week 26 were consistent with the total group analysis, with or without agreement among raters.

For the primary analyses, the ITT population was chosen. PP-analyses were performed as sensitivity analyses. However, according to ICH E9 guideline, the use of the full analysis set in an equivalence trial is generally not conservative, and therefore, the differences between the ITT and PP analyses were further explored. A total of 22 (11.1%) and 30 (15.3%) of randomized subjects in the rituximab-EU and PF-05280586 groups, respectively, were excluded from the PP analysis population. This included subjects without a measurable disease at baseline, as assessed by the central reader, i.e. 13 (6.6%) of subjects in the PF-05280586 group and 9 (4.5%) of subjects in the rituximab-EU group. Given that response is expected to be high in subjects with no measurable disease at baseline, this may have slightly favoured the ITT population as compared to the PP population.

On the other hand, disproportionally more patients were excluded in the PF-05280586 arm because their radiography was considered invaluable by the central readers at Week 26. This occurred in 20 (10.2%) subjects in the PF-05280586 group and 14 (7.1%) subjects in the rituximab-EU group. Given that subjects with no evaluable Week 26 assessment were imputed as non-responders in the ITT analysis but removed from the PP analysis, may have resulted in a favour of ORR the PF-05280586 group in the PP analysis. Despite the different approaches across the ITT and PP analyses, the conclusions from both analysis populations are consistent. Altogether, there is no indication of systematic bias regarding reasons for exclusion from the PP- analysis and the potential favourable/unfavourable effects for the PP and ITT populations appear to be balanced. Protocol deviations were reported, as might be expected in a multiple centre clinical setting. These did not impact the final results.

The RA studies were only supportive for evaluating efficacy and safety. This can in principle be agreed, given that an adequately powered study has been performed in a sensitive model of lymphoma, without interference of background chemotherapy. For biosimilar products, it is not required to evaluate equivalence of efficacy in each indication separately, and extrapolation of studies in other models can be accepted, if adequately justified. For RA treatment, the same mode of action of rituximab applies, as for the lymphoma indication. For conclusions see also under Section 6 of this report, Biosimilarity assessment.

The design of the RA studies, i.e. randomised and double-blinded, is considered adequate. The comparators (EU and US sourced Innovator product) are considered appropriate.

In accordance with the labelling of the Innovator product, patients irresponsive to prior TNF-inhibitor treatment were included, indicating that the patients had quite advanced RA at baseline. Only sero-positive patients (RF, or ACAP) were included, whereas the Reference product labelling does not exclude sero-negativity. Considering that seronegative RA patients are reported to have a lower response to rituximab, the study population is not fully representative for the whole RA population. However, because seropositive patients are more sensitive to the treatment, it is justified to exclude seronegative RA subjects from the study which is intended to show similarity.

Primary endpoint of B3281001 study was determining PK parameters Cmax and AUC0-∞. Explorative efficacy outcomes were mean change of DAS28-CRP (and their mean change from baseline), DAS28-CRP responder rates (LDAS ≤3.2, and remission <2.6), ACR responder rates and HAQ-DI were determined as secondary endpoints. However, DAS28-CRP as a continuous endpoint, has been recommended by the CHMP as a sensitive endpoint to establish biosimilarity in the Scientific Advice for this product. Post-hoc analyses indicated similarity of DAS28-CRP scores between PF-05280586 and rituximab-EU, within the margins of 0.6 points difference –which is generally considered as not clinically relevant.

Efficacy data and additional analyses

Study B3281006 in Patients With LTB-FL

In total, 196 subjects were randomly assigned to PF-05280586 and 198 subjects to rituximab-EU treatment. Baseline demographic and disease characteristics were balanced between the two treatment groups.

The vast majority completed the four weekly courses of rituximab monotherapy. The primary endpoint, i.e. the ORR by central review in the ITT population at Week 26, was 75.5% in the PF-05280586 group, and 70.7% subjects in the EU-Rituximab group. The analysis of ORR showed an estimated difference of 4.66% (PF-05280586 minus rituximab-EU), with a 95% CI of (-4.16%, 13.47%), which fell within the -16.0% to 16.0% pre-specified equivalence margin agreed to by the CHMP.

The ORR consist of two components: complete responders (CR) and partial responders (PR, defined as >50% clearance of the tumours). These separate endpoints CR and PR also supported equivalence. Furthermore, equivalence criteria were also met for ORR in the sensitivity analysis (per-protocol), indicating robustness. Subgroup analyses also showed that the conclusions regarding equivalence were similar across subgroups.

Another secondary outcome is PFS. The number of events (disease progression) was numerically higher for PF-05280586 (37 (18.9%) versus 28 (14.1%)) at Week 52. The hazards ratio of PFS was not statistically significant different in either ITT or PP analyses. In each study arm, there was one fatal case of disease progression. Censoring occurred in about 80% in each treatment arm.

Extrapolation to other indications

To what extent the *equivalence* of efficacy between a rituximab biosimilar and reference product –thus not the response itself- can be extrapolated from a lymphoma to auto-immune disorders is a matter of debate. On one hand, rituximab specifically targets the transmembrane CD20 antigen, in both normal as well as malignant B-cells, and binding to the CD20 epitope is similar for normal as well as malignant B-cells. This was demonstrated by the fact that CD19 cell counts –as a marker of CD20+ cells- rapidly declined to detection in both the RA studies, as well in the LTB-FL study that are part of this dossier.

As discussed in the non-clinical section, binding of rituximab to CD20 leads to direct apoptosis, or Fc receptor mediated lyses (CDC, ADCC). Both ADCC and CDC are considered relevant for RA and NHL/CLL. ADCP may be relevant for CLL indication specifically.

Considering this, it is accepted that only a single pivotal study in an oncology model, with an additional PK-PD study in RA, were chosen to demonstrate equivalence in efficacy for all indications in the study program of PF-05280586. The CHMP considered extrapolation of similarity to all indications for the other rituximab biosimilar products acceptable, based on those studies and the totality of evidence from Quality and in-vitro binding and functional assays.

RA studies

In general, the efficacy outcomes of Week 13 of Study B3281001 were considered most informative, given that patients could escape to the extension study early from Week 16.

Although not formally tested, the following results supports the equivalence in efficacy between PF-05280586 and MabThera: in study B3281001 for DAS28 (CRP) the mean changes at 13th week were -2.0 for Ruxience and -2.1 for Rituximab-EU, LDAS rates were 44.4% for Ruxience and 41.8% for Rituximab-EU at the 13th week of the study. Also, DAS28-CRP remission responder rates were highly similar. In general, maintenance of response was observed in the extension studies for the efficacy outcomes, also after switching from Rituximab-EU to PF-05280586. However, the data should be interpreted carefully and rather considered as supportive, given that a selected population will continue treatment in the extension phase. Also, carry-over effects of prior treatment cannot be excluded after switching.

A response in HAQ-DI and ACR20 response was observed in the studies, however, to a lesser extent for PF-05280586 as compared to Rituximab-EU. E.g. in Study B3281001, ACR20 was 70.3% in the rituximab-EU group versus 50.7% in the PF-05280586 group, and 60% versus 50% at Week 25. For HAQ-DI, a functional outcome, at week 13 the percentage change for Ruxience was -14.6% and for rituximab-EU -39.5%. The differences between ACR and DAS28 responder rates are probably due to HAQ-DI, as ACR includes HAQ-DI scores as a part of this composite endpoint, whereas the DAS28-CRP score does not include this scale. For other individual endpoints that are shared for the DAS28-CRP and ACR composite scores, such as number of painful/swollen joints, CRP-response, similar results were shown between treatment arms.

Reassuringly, patients who were switched from Rituximab-EU to PF-05280586 in Study B3281004, maintained their relatively high HAQ-DI and ACR20 response as obtained after the first course of treatment with Rituximab-EU. This indicates that this apparent difference may be due to incomplete randomisation, rather than a true treatment effect. Notably, there were no differences observed in PK-PD, ADA formation, and the more sensitive RA outcomes (DAS28-CRP), and these outcomes all support similarity. Furthermore, the study population included patients in advanced treatment stage (irresponsive to TNF-inhibitors), and there might have been limited room for improvement of physical function in these patients, due to permanent structural joint damage at baseline.

2.5.4. Conclusions on the clinical efficacy

Overall, the pre-defined criteria for equivalence were met for the primary endpoint ORR in the pivotal trial in patients with LTL-FL. The outcomes of the RA studies were supportive for similar efficacy for Ruxience and the innovator product.

2.6. Clinical safety

Comparative safety data of the biosimilar product and the European innovator product MabThera were obtained from three randomised clinical trials: one in low tumour burden follicular lymphoma (LTB-FL, Study B3281006), and two in RA (i.e. a single treatment course trial, followed by an extension trial with 3 other courses, including a switching arm).

Safety data of the lymphoma study and the RA studies were not pooled, because of the differences in dosing schedule (an intense 3 weeks treatment course for LTB-FL, versus a relatively low dose chronic treatment for RA), and background therapy (none for LTB-FL, MTX for RA) of these two disorders.

Patient exposure

Study B3281006, in patients with low tumour burden follicular lymphoma

Study B3281006 has a total of 394 subjects assigned to the double-blind treatment; 196 subjects in the PF-05280586 group and 198 subjects in the rituximab-EU group. Of these, 393 subjects were actively treated including 196 subjects in the PF-05280586 group and 197 subjects in the rituximab-EU group. No background therapy of cytostatic drugs was given. All subjects randomized and treated with at least 1 dose of study drug were included in all safety analyses.

Overall, 390 subjects had completed study treatment (subjects would have completed protocol specified 4 weekly cycles of study treatment on Days 1, 8, 15, and 22).

Table 20. Treatment Duration- Safety Population, Study B3281006

	Rituximab-EU N=197	PF-05280586 N=196
Total number of doses received		
1 dose	0	2 (1.0)
2 doses	1 (0.5)	0
3 doses	0	0
4 doses	196 (99.5)	194 (99.0)
Duration of treatment (days)		
Mean	22.1	21.9
SD	1.18	2.33
Median	22.0	22.0
Min, Max	10, 29	1, 29

Table 21. Patients exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term 12 months safety data
Active – controlled: LTB-FL Study	PF-05280586: 196 rituximab-EU: 198	196 197	194 196	170170
Active–controlled: B3281001	PF-05280586: 73 rituximab-EU: 74	73 74	71 72	61 69
Active –controlled: B3281004	PF-05280586: 58 rituximab-EU: 65	58 65	48 60 (30 in E-PPP and 30 in E-EPP group)	48 60
Open studies	Not applicable			
Post marketing	Not applicable			
Compassionate use	Not applicable			

Study B3281001 and Study B3281004, RA Studies:

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 115 subjects were switched to PF-05280586 during either Course 1 or 2 of the trial after initially receiving commercially available rituximab, from which 60 were switched from Rituximab-EU to PF-05280586 in total.

Adverse events

Study B3281006 – Subjects With LTB-FL

The majority of all subjects experienced at least 1 TEAE, with 156 (79.6%) subjects in the PF-05280586 group and 145 (73.6%) subjects in the rituximab-EU group reporting a total of 607 and 670 events, respectively.

Table 22. Treatment-Emergent Adverse Events (All Causalities) - Safety Population, Study B3281006

	rituximab-EU n (%)	PF-05280586 n (%)
Number (%) of subjects:		
Subjects evaluable for adverse event	197	196
Number of adverse event	670	607
Subjects with adverse event	145 (73.6)	156 (79.6)
Subjects with serious adverse event	15 (7.6)	17 (8.7)
Subjects with grade 3 or higher adverse events[a]	26 (13.2)	28 (14.3)
Subjects discontinued due to adverse events[b]	2 (1.0)	3 (1.5)
Subjects with dose reduced due to adverse events	0	0
Subjects with temporary treatment discontinuation due to adverse events[c]	51 (25.9)	37 (18.9)

The incidence of TEAEs (treatment emergent AEs) was generally comparable between treatment groups. The most frequently reported TEAEs by PT were infusion related reaction (49 [25.0%] subjects in the PF-05280586 group and 59 [29.9%] subjects in the rituximab-EU group), pruritus (13 [6.6%] subjects in the PF-05280586 group and 22 [11.2%] subjects in the rituximab-EU group), and headache (16 [8.2%] subjects in the PF-05280586 group and 19 [9.6%] subjects in the rituximab-EU group).

The percentage of patients with grade 3-4 AEs were low a similar between groups. The most frequently reported Grade 3 TEAEs by PT were infusion related reactions in the PF-05280586 group (4 [2.0%] subjects) and hypertension in the rituximab-EU group (4 [2.0%] subjects). The only Grade 4 TEAE was neutropenia reported in 1 (0.5%) subject in the rituximab-EU group, which was considered related to treatment but was not associated with any signs or symptoms of infection. No Grade 5 events were reported in this study.

Table 23. Treatment-Emergent Adverse Events by System Organ Class, Preferred Term for ≥2% of Patients in Either Treatment Group (All Causalities) - Safety Population, Study B3281006

System Organ Class Preferred Term	rituximab-EU n (%)	PF-05280586 n (%)
Number (%) of subjects:		
Evaluable for adverse event	197	196
With adverse event	145 (73.6)	156 (79.6)
Discontinued due to adverse event	2 (1.0)	3 (1.5)
Number (%) of subjects with adverse events:		
Injury, poisonings and procedural complications	**65 (33.0)**	**61 (31.1)**
Infusion related reaction	59 (29.9)	49 (25.0)
Fall	2 (1.0)	5 (2.6)
Infections and infestations	**63 (32.0)**	**52 (26.5)**
Upper respiratory tract infection	5 (2.5)	9 (4.6)
Nasopharyngitis	9 (4.6)	5 (2.6)
Bronchitis	7 (3.6)	3 (1.5)
Influenza	6 (3.0)	4 (2.0)
Urinary tract infection	5 (2.5)	5 (2.6)
Sinusitis	2 (1.0)	5 (2.6)
Pharyngitis	4 (2.0)	4 (2.0)
Gastrointestinal disorders	**52 (26.4)**	**58 (29.6)**
Nausea	17 (8.6)	15 (7.7)
Diarrhoea	12 (6.1)	14 (7.1)
Abdominal pain upper	5 (2.5)	9 (4.6)
Constipation	8 (4.1)	8 (4.1)
Abdominal pain	3 (1.5)	8 (4.1)
Vomiting	7 (3.6)	3 (1.5)
Dyspepsia	2 (1.0)	5 (2.6)
Respiratory, thoracic and mediastinal disorders	**56 (28.4)**	**46 (23.5)**
Throat irritation	10 (5.1)	14 (7.1)
Cough	11 (5.6)	11 (5.6)
Oropharyngeal pain	10 (5.1)	2 (1.0)
Dyspnoea	9 (4.6)	6 (3.1)
Oropharyngeal discomfort	1 (0.5)	4 (2.0)
General disorders and administration site conditions	**53 (26.9)**	**52 (26.5)**
Fatigue	13 (6.6)	12 (6.1)
Asthenia	13 (6.6)	9 (4.6)
Pyrexia	11 (5.6)	12 (6.1)
Oedema peripheral	7 (3.6)	2 (1.0)
Influenza-like illness	4 (2.0)	2 (1.0)
Skin and subcutaneous tissue disorders	**47 (23.9)**	**39 (19.9)**
Pruritus	22 (11.2)	13 (6.6)
Rash	8 (4.1)	10 (5.1)
Erythema	2 (1.0)	7 (3.6)
Urticaria	6 (3.0)	3 (1.5)
Musculoskeletal and connective tissue disorders	**42 (21.3)**	**38 (19.4)**
Back pain	10 (5.1)	8 (4.1)
Myalgia	5 (2.5)	9 (4.6)
Arthralgia	6 (3.0)	7 (3.6)
Pain in extremity	4 (2.0)	7 (3.6)
Nervous system disorders	**33 (16.8)**	**34 (17.3)**
Headache	19 (9.6)	16 (8.2)

System Organ Class Preferred Term	rituximab-EU n (%)	PF-05280586 n (%)
Dizziness	6 (3.0)	2 (1.0)
Psychiatric disorders	**17 (8.6)**	**15 (7.7)**
Insomnia	8 (4.1)	5 (2.6)
Anxiety	7 (3.6)	6 (3.1)
Investigations	**14 (7.1)**	**15 (7.7)**
Neutrophil count decreased	0	5 (2.6)
White blood cell count decreased	1 (0.5)	4 (2.0)
Vascular disorders	**15 (7.6)**	**11 (5.6)**
Hypertension	7 (3.6)	5 (2.6)
Flushing	4 (2.0)	1 (0.5)
Metabolism and nutrition disorders	**12 (6.1)**	**13 (6.6)**
Hyperglycaemia	4 (2.0)	1 (0.5)
Cardiac disorders	**9 (4.6)**	**7 (3.6)**
Palpitations	2 (1.0)	5 (2.6)

AEs of special interest* (*Study B3281006 – Subjects With LTB-FL)

Adverse events of special interest were pre-defined by the applicant (Tier-1) as infections, infusion related reactions, neutropenia, progressive multifocal leukoencephalopathy (PML), and tumour lysis syndrome. These events were selected based on the established safety profile of rituximab.

Infections (grade 3-4)

In the PF-05280586 treatment group there were 5 subjects (2.3%) who experienced a Grade 3 infection, including a Clostridium difficile infection, which was considered serious and treatment related. Three (1.5%) subjects in the rituximab-EU group experienced 4 Grade 3 infection events, none of which were considered related to treatment.

No cases of PML occurred.

Neutropenia

Neutropenia was reported in one (0.5%) subject in the PF-05280586 group and three (1.5%) subjects in the rituximab-EU group. The one subject in the rituximab-EU group had a Grade 4 event of neutropenia, which was considered related to treatment but was not associated with any signs or symptoms of infection.

Infusion-related reactions

The most frequently reported TEAEs of special interest were infusion-related reactions (IRRs). IRRs were reported for 49 [25.0%] subjects in the PF-05280586 group and 59 [29.9%] subjects in the rituximab-EU group.

Tumour lysis

No cases occurred.

Study B3281001 and Study B3281004, RA Studies:

AEs of special interest

Though not pre-defined as an AE of special interest in the protocol of Study B3281001 and B3281004, infections, IRR, PML and neutropenia are also considered of special interest for these studies by the assessors.

Study B3281001

Non-serious AE of special interest were defined as urticaria. There was a one case of urticaria in this study which happened in Rituximab-US group.

Grade 3 treatment-related infections occurred in 4/73 (5.5%) patients in PF-05280586 group and 0/74 (0.0%) patients in Rituximab-EU group. These 4 AEs consisted of: arthritis bacterial, bronchitis, bacterial sepsis and septic shock and sinusitis.

Infusion-related reactions (IRRs) occurred in 10/73 (13.7%) patients in PF-05280586 group and 5/74 (6.8%) patients in Rituximab-EU group.

Study B3281004

Rash popular and hot flush were pre-defined as AEs of special interest in this study. There were 1 case of each rash popular and hot flush in P-P and U-UPP groups, respectively.

Grade 3 infections:

Course 1

Grade 3 treatment-related infections occurred in 2/58 (6.9%) patients in P-P group, 0/32 (0.0%) patients in E-E group and 2/33 (12.0%) in E-P group. In both P-P and E-P groups 1 incidence of pneumonia and UTI had occurred.

Course 2

Grade 3 treatment-related infections occurred in 4/54 (7.5%) patients in P-PP group, 0/30 (0.0%) patients in E-EP group and 3/31 (9.5%) in E-PP group. Four cases in P-PP group consisted of 1 case of cellulitis, postoperative wound infection, subcutaneous abscess and viral gastroenteritis, each. 3 cases in E-PP group consist of 1 bronchitis and 2 cases of pneumonia.

Course 3

Grade 3 treatment related infections occurred in 2/48 (2.9%) patients in P-PPP group, 0/30 (0.0%) patients in E-EPP group and 3/30 (6.8%) in E-PPP group. 2 cases in P-PP group consisted of 1 case of arthritis infective and postoperative wound infection, each. 6 cases in E-PPP group consist of 1 case of bronchitis, wound infection staphylococcal, sinusitis and UTI, each and 2 cases of pneumonia.

Infusion related reactions:
In total, 6 subjects experienced an IRR during the study that were all assessed as related to the study treatment (3, 2 and 1 in the P-PPP, E-PPP, and U-PPP group, respectively). Five subjects who experienced IRRs that resulted in a dose reduction or temporary discontinuation, one of the subjects was withdrawn permanently.

Course 1

Among the subjects who received treatment during Course 1, the number of subjects (exposure-adjusted incidence) reporting IRRs were 2/58 (6.9%), 0/32 (0.0%) and 0/33 (0.0%) subjects in the P-P, E-E and E-P groups, respectively.

Course 2

Among the subjects who received treatment during Course 1 and Course 2, the number of subjects (exposure-adjusted incidence) reporting IRRs were 2 (3.8%), 0 (0.0%) and 1 (3.2%), subjects in the P-PP,E-EP and E-PP groups, respectively, by the end of Course 2.

Course 3

Among the subjects who received 3 courses of treatment, the number of subjects (exposure adjusted incidence) reporting IRRs were 2 (2.9%),0 (0.0%) and 1 (2.3) subjects in the P-PPP,E-EPP and E-PPP groups, respectively, by the end of Course 3. The IRRs were throat irritation and infusion related reaction (1 subject each in P-PPP group) and infusion related reaction (1 subject in E-PPP).

Neutropenia:
In Study B3281004, during Course 2 there was a single case of neutropenia in P-PP group. (1/54)

Progressive multifocal leukoencephalopathy (PML):
PML was not reported in none of the RA studies.

Other common TEAEs (not pre-defined as of special interest), Study B3281006 – Subjects With LTB-FL

Tier-2 events were those that occurred in at least 6 subjects (3% or higher) in either treatment group and that were not Tier-1 events.

The most frequently reported Tier-2 TEAEs by PT were headache (16 [8.2%] subjects in the PF-05280586 group and 18 [9.1%] subjects in the rituximab-EU group), nausea (15 [7.7%] subjects in the PF-05280586 group and 16 [8.1%] subjects in the rituximab-EU group), diarrhoea (13 [6.6%] subjects in the PF-05280586 group and 12 [6.1%] subjects in the rituximab-EU group), and fatigue (12 [6.1%] subjects in the PF-05280586 group and 13 [6.6%] subjects in the rituximab-EU group).

Serious adverse event/deaths/other significant events

SAEs Study B3281006 – Subjects With LTB-FL

Overall, 17 (8.7%) subjects in the PF-05280586 group and 15 (7.6%) subjects in the rituximab-EU group experienced at least 1 treatment-emergent SAE. The highest incidence of SAEs reported occurred in the Infections and infestations SOC (4 [2.0%] subjects in the PF-05280586 group and 3 [1.5%] subjects in the rituximab-EU group)

Concurrent solid tumours were reported for 3 [1.5%] subjects in the PF-05280586 group and 1 [1.0 %] subjects in the rituximab-EU group.

The Investigators considered the following SAE treatment related: Clostridium difficile infection and pyrexia (reported for PF-05280586), and a single case of Serious infusion reaction and serum sickness for rituximab-EU. The sponsor concurred with these assessments, except for the pyrexia case, as the reported event occurred after study drug was discontinued for 1 month.

Table 24. Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum CTCAE Grade (All Causalities) - Safety Population, Study B3281006

System organ class	Rituximab-EU (N=197) n (%)	PF-05280586 (N=196) n (%)
Any SAE	15 (7.6)	17 (8.7)
Cardiac disorders	**2 (1.0)**	**1 (0.5)**
Angina unstable	1 (0.5)	
Atrial fibrillation	0	1 (0.5)
Intracardiac thrombus	1 (0.5)	
Gastrointestinal disorders	**1 (0.5)**	**3 (1.5)**
Abdominal pain	0	1 (0.5)

System organ class	Rituximab-EU (N=197) n (%)	PF-05280586 (N=196) n (%)
Ileus	0	1 (0.5)
Mesenteric artery stenosis	1 (0.5)	0
General disorders and administration site conditions	**2 (1.0)**	**2 (1.0)**
Disease progression	1 (0.5)	1 (0.5)
Non-cardiac chest pain	1 (0.5)	0
Pyrexia	0	1 (0.5)
Hepatobiliary disorders	**1 (0.5)**	**0**
Cholelithiasis	1 (0.5)	**0**
Immune system disorders	**1 (0.5)**	**0**
Serum sickness	1 (0.5)	0
Infections and infestations	**3 (1.5)**	**4 (2.0)**
Appendicitis	0	1 (0.5)
Clostridium difficile infection	0	1 (0.5)
Diverticulitis	0	1 (0.5)
Escherichia sepsis	1 (0.5)	0
Hepatitis B	1 (0.5)	0
Kidney infection	1 (0.5)	0
Peritonitis	0	1 (0.5)
Urinary tract infection	0	1 (0.5)
Viral sinusitis	1 (0.5)	0
Injury, poisoning and procedural complications	**1 (0.5)**	**1 (0.5)**
Contusion	0	1 (0.5)
Infusion related reaction	1 (0.5)	0
Musculoskeletal and connective tissue disorders	**2 (1.0)**	**1 (0.5)**
Intervertebral disc disorder	0	1 (0.5)
Polyarthritis	1 (0.5)	0
Spinal column stenosis	1 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.0)**	**4 (2.0)**
Bladder cancer	1 (0.5)	0
Colon adenoma	0	1 (0.5)
Lung adenocarcinoma stage I	0	1 (0.5)
Prostate cancer	0	1 (0.5)
Squamous cell carcinoma of lung	1 (0.5)	0
Uterine cancer	0	1 (0.5)

System organ class	Rituximab-EU (N=197) n (%)	PF-05280586 (N=196) n (%)
Nervous system disorders	**0**	**2 (1.0)**
Paraesthesia	0	1 (0.5)
Transient ischaemic attack	0	1 (0.5)
Respiratory, thoracic and mediastinal	**2 (1.0)**	**0**
Dyspnoea	1 (0.5)	0
Pulmonary embolism	1 (0.5)	0

Fatal cases, Subjects With LTB-FL

Two deaths were reported (one for each study drug), and disease progression was described for each of the cases. The two cases are summarized below;

Subject 10291002, a 65-year-old male in the PF-05280586 group, died on Day 128 due to disease progression. The last dose of study treatment was administered on Day 20. Approximately 2 months after the last dose of study treatment, the subject was hospitalized due to disease progression and died. An autopsy was not performed.

Subject 11081001, a 76-year-old male in the rituximab-EU group, died on Day 573 due to disease progression. The subject had a medical history of papillary cystadenoma lymphomatosum and squamous cell carcinoma of the skin. The last dose of study treatment was administered on Day 22. On Day 485, the subject was diagnosed with high grade transformation to diffuse large B-cell lymphoma (stage 4) and commenced treatment. He did not respond well to treatment and subsequently died. An autopsy was not performed.

RA studies

An analysis with regard to the incidence of Grade 3 or higher treatment-related AEs is provided by the applicant. Treatment-related Grade 3 AEs were reported in a total of 6 subjects: 2 subjects in the rituximab-US group and 4 subjects in the PF-05280586 group. All AEs were assessed as non-serious and none of them were reported as Grade 4 or Grade 5. All AEs were considered recovered/resolved with the exception of 2 AEs of local swelling and bronchitis, both in the PF-05280586 group.

B3281001:

A total of 4 subjects (1.8%) were withdrawn from treatment due to an AE: 1 subject (1.4%),1 subject (1.4%), and 2 subjects (2.7%) receiving rituximab-US, rituximab-EU, and PF-05280586, respectively.

A total of 10 (4.5%) subjects had an SAE including 1 (1.4%) subject receiving rituximab-EU, and 5 (6.8%) subjects receiving PF-05280586 (Table 31). The one rituximab-EU subject had an SAE of thrombocytopenic purpura. Five PF-05280586 subjects had SAEs of cardiac failure (1 subject), intentional self-injury (1 subject), presumed bone neoplasm (1 subject), bacterial arthritis (1 subject), and bacterial sepsis and septic shock in 1 subject.

Table 25. Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (mITT Population)

System Organ Class Preferred Term	Rituximab-US N=73 n (%)	Rituximab-EU N=74 n (%)	Rituximab-Pfizer N=73 n (%)	Total N=220 n (%)
Subject with any serious TEAE[a]	4 (5.5)	1 (1.4)	5 (6.8)	10 (4.5)
Blood and lymphatic system disorders				
Thrombocytopenic purpura	0	1 (1.4)	0	1 (0.5)
Cardiac disorders				
Cardiac failure	0	0	1 (1.4)	1 (0.5)
Cardiac failure congestive	1 (1.4)	0	0	1 (0.5)
Atrial flutter	1 (1.4)	0	0	1 (0.5)
Infections and infestations				
Arthritis bacterial	0	0	1 (1.4)	1 (0.5)
Bacterial sepsis	0	0	1 (1.4)	1 (0.5)
Septic shock	0	0	1 (1.4)	1 (0.5)
Pyelonephritis	1 (1.4)	0	0	1 (0.5)
Musculoskeletal and connective tissue disorders				
Arthropathy	1 (1.4)	0	0	1 (0.5)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)				
Bone neoplasm	0	0	1 (1.4)	1 (0.5)
Psychiatric disorders				
Intentional self-injury	0	0	1 (1.4)	1 (0.5)

Source: Table 14.3.1.3

There was 1 death in Study B3281001. Subject 11611005, a 66-year-old White female, was receiving PF-05280586 and experienced a Grade 5 presumed bone neoplasm 51 days after the first dose of study drug. The patient was discontinued from the study due to this AE and subsequently died.

B3281004:

The most frequent SAE was pneumonia in all 3 courses. Other SAEs in Ruxience and MabThera groups included anaemia, febrile neutropenia, pericarditis, bronchitis, subcutaneous abscess, UTI, staphylococcal wound infection, viral gastroenteritis, syncope, TIA, hydronephrosis, ureterolithiasis, COPD. In total in course 1 incidence of SAEs for PP group was 4/58 (13.7 n/PY*100), for EE group 2/32 (13.7 n/PY*100) and for EP group 2/33 (13.7 n/PY*100). In course 2 total incidence of SAEs for PPP group was 6/54 (11.3 n/PY*100), for EEP group 1/30 (3.6 n/PY*100) and for EPP group 4/31 (12.7 n/PY*100). In course 3 total incidence of SAEs for PPPP group was 4/48 (5.7 n/PY*100), for EEPP group 1/30 (2.4 n/PY*100) and for EPPP group 4/30 (9.1 n/PY*100) (Table 31).

Table 26. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term – Subjects who received Courses 1, 2 and 3 treatment (mITT Population)

B3281001 Treatment B3281004 Treatment System organ class Preferred term	PF-05280586 PPP (N=48) (69.678 PY) n (n/PY*100)	Rituximab-EU EPP (N=30) (41.958 PY) n (n/PY*100)	Rituximab-EU PPP (N=30) (44.016 PY) n (n/PY*100)	Rituximab-US UPP (N=27) (37.451 PY) n (n/PY*100)	Rituximab-US PPP (N=29) (41.832 PY) n (n/PY*100)	Total (N=164) (234.935 PY) n (n/PY*100)
Subjects with Any Serious TEAE	4 (5.7)	1 (2.4)	4 (9.1)	1 (2.7)	1 (2.4)	11 (4.7)[a]
Blood and lymphatic system disorders	1 (1.4)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	2 (0.9)
Anaemia	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Febrile neutropenia	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Pericarditis	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	1 (1.4)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.4)	3 (1.3)
Pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.4)
Diaphragmatic hernia	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.4)
Umbilical hernia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.4)
Infections and infestations	2 (2.9)	0 (0.0)	2 (4.5)	0 (0.0)	0 (0.0)	4 (1.7)
Arthritis infective	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Bronchitis	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Pneumonia	1 (1.4)	0 (0.0)	2 (4.5)	0 (0.0)	0 (0.0)	3 (1.3)
Wound infection staphylococcal	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Sinusitis	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)
Renal and urinary disorders	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hydronephrosis	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Ureterolithiasis	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Chronic obstructive pulmonary disease	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

No new or unexpected safety concerns emerged from Study B3281004, including in those subjects who switched from reference product to PF-05280586. There were 2 subjects experiencing AEs of malignant events in Study B3281004, basal cell carcinoma (Grade 2, non-serious and event considered not related to study treatment) was reported in a subject randomized to the E-PPP group. This case was a continuation of an event that began in Study B3281001; and squamous cell carcinoma (Grade 3, non-serious and considered related to study treatment) was reported in a subject randomized to the E-PPP group.

No death was reported for this study.

Laboratory findings

In general, there were no meaningful differences in clinical chemistry and haematology parameters between PF-05280586 and rituximab-EU in the pivotal trial in LTB-FL patients. LFT (liver function test) abnormalities were uncommon, as expected since rituximab is not thought to be hepatotoxic. Mild lymphopenia was commonly reported in this study (17.8% and 19.1%, for rituximab-EU and PF-05280586, respectively), as may be expected considering the mode of action of rituximab.

As reported before for rituximab therapy, neutropenia was common (18.8% and 20.6 for rituximab-EU and PF-05280586, respectively), although grade 3 was only reported for one subject in the PF-05280586 group (0.5%). In the rituximab-EU group, grade 3 neutropenia was reported for two cases (1.0%), and one grade 4 case was reported (0.5%).

There were no meaningful differences between clinical chemistry and haematology results in different groups in both 001 and 004 studies.

Safety in special populations

One pregnancy occurred in the RA trial.

One subject in the U-UPP treatment group of Study B3281004 reported a pregnancy which was found to be a blighted ovum later. The onset of the serious adverse event was 154 days after the most recent dose of study medication (PF-05280586). Concomitant therapy taken within 2 weeks before the onset of the event of blighted ovum included Cilest (norgestimate/ethinyl estradiol), folic acid, methotrexate, and naproxen. Subject had an obstetric history which included 1 miscarriage and 1 normal birth. PF-05280586 was permanently discontinued in response to the event and the subject was discontinued from the study due to pregnancy. The case was not considered PF-05280586 treatment-related by the Investigator.

Immunological events

Subjects with LTB-FL (Study B3281006)

Overall, 38 (19.5%) subjects in the PF-05280586 group and 37 (18.8%) subjects in the rituximab-EU group had at least 1 post-dose sample that tested positive for ADA.

Overall, the percentage of subjects reporting immune-based adverse effects was comparable across both treatment groups, and also between ADA positive and ADA negative subjects (See Table 3.3.8.9 below).

Table 27. Summary of immunogenicity data and related events_ Subjects with LTB-FL (Study B3281006) at Week 26

	PF-05280586	EU-Rituximab
ADA positive	**38/195 (19.5 %)**	**37/197 (18.8 %)**
IRR reported	11/38 (28.9%)	10/37 (27.0%)
Anaphylaxis/hypersensitivity	7/38 (18.4%)	5/37 (13.5%)
ADA negative	**157/195 (80.5 %)**	**160/197 (81.2 %)**
IRR reported	37/157 (23.6 %)	46/160 (28.8 %)
Anaphylaxis/hypersensitivity	22/157 (14.0)	35/160 (21.9)

The number of ADA-positive patients (i.e. post-treatment ADA) was comparable for both treatment arms in the final Week 52 data set (PF-05280586: n=43 [22.1%]; rituximab-EU: n=39 [19.8%]).

RA studies:

B3281001:

Samples that tested ADA positive after the first dose only (post-baseline only, at any time during the study) were reported for 10.9% and 10.8% of the subjects in the PF-05280586 and rituximab-EU groups, respectively.

Of the 2 subjects with persistent ADA and the highest titres, 1 subject had CD19+ B-cells depleted post-dose for the entire study duration up to Day 169, while the CD19+ B-cells for the other subject were undetectable following dosing, and became detectable again after Day 85, reaching approximately 5% of the pre-treatment baseline on Day 141.

B3281004:

At EOT point there was one ADA positive case in P-PPP group (N=48). There were no ADA positive cases reported for other arms of the study.

No samples were tested postivie for Neutralizing Antibody (Nab) in any of the studies.

Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars. Reference is made to the reference product.

Discontinuation due to adverse events

Permanent discontinuations from the study due to AEs were low and comparable between the two treatment groups in each of the clinical studies.

Study B3281006 – Subjects With LTB-FL

There were 3 (1.5 %) subjects in the PF-05280586 group and 2 (1.0 %) subject in the rituximab-EU group who permanently discontinued the study due to AEs. For PF-05280586, this was a single case of infusion reaction including angioedema symptoms, and a case of maculopapular rash, and Grade 2 Non-Hodgkin's lymphoma, which was not considered as related to study treatment by the investigator. For rituximab-EU, this was a SAE of serum sickness, and a SAE of bladder cancer, which was not considered by the investigator as related to study treatment.

RA studies:

Study B3281001:

One rituximab-EU subject discontinued due to a TEAE of thrombocytopenic purpura, and two PF-05280586 subjects discontinued due to AEs of bacterial sepsis and upper respiratory tract infection, respectively.

Study B3281004:

The TEAEs leading to withdrawal from study treatment among the subjects that received Course 1 treatment were the following: 1/58 subject in the P-P group (rash papular),1/32 E-E group (transient ischaemic attack) and 1/30 U-P group (bacterial arthritis). Among the subjects that received treatment in Course 1 and Course 2, withdrawal cases were 1/54 subject in the P-PP group (cellulitis) and 2/29 subjects in the U-UP group (oral candidiasis and blighted ovum). Among the subjects that received 3 courses of treatment, there was 1/29 subject in the U-PPP group (cellulitis).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety database size is rather small, and only provides insight in common AEs. For a biosimilar application, the numbers of subjects are considered acceptable and sufficient. Reference should be

made to the innovator for rare events, as these could not be evaluated in the relatively small equivalence studies.

In Study B3281006 – Patients With LTB-FL, 1-year safety and immunogenicity data have been provided. Overall, the incidence, and nature of the AEs and SAE were similar between PF-05280586 and rituximab-EU, in the pivotal trial in LTB-FL. The safety profile is in line what has been reported before for the innovator MabThera, with infusion reactions, infections and neutropenia as most common findings.

Rituximab monotherapy is not specifically indicated for the treatment of LTB-FL according to the SmPC of MabThera. No unexpected safety issues emerged for rituximab in this setting.

The rates of ADA-formation were balanced between PF-05280586 and rituximab-EU, As reported before for rituximab, there was no clear relationship between ADA-formation and infusion reactions.

For historic data of NHL studies, lower rates of ADA were reported than in this study in LTB-FL. However, it is noted that for NHL, rituximab is given on top of combination chemotherapy, which was not provided in the LTB-FL study, combination chemotherapy may suppress ADA-formation. The rates of ADA-formation of rituximab monotherapy in *patients with LTB-FL* of Study B3281006 was however within limits as reported before for auto-immune disorders.

Overall the safety profile of PF-05280586 was comparable with Rituximab-EU during RA studies. The safety profile was in line with the innovator rituximab-EU and no new concerns emerged from this study regarding rituximab. Although these studies in RA patients were not powered to confirm safety, the outcomes of them are considered relevant. In line with earlier experiences, infections and potential infusion reaction related events were the most commonly reported AEs in the RA population. These were equally distributed in study arms. In the RA studies, the rate of ADA formation was higher for rituximab-EU than for PF-05280586 (6/73 versus 10/74). However, this does not necessarily indicate that similarity is at stake. The number of neutralising ADA was null for all the study arms. There was no clear relationship between ADAs and safety/efficacy.

In the RA studies, there were numerically less ADA positive subjects in the PF-05280586 arm (10.9%) than in the two rituximab-arms (EU: 14.9%, US: 15.1%). No NAbs were detected in ADA positive subjects.

2.6.2. Conclusions on the clinical safety

In general, the incidence and nature of the AEs were similar between biosimilar product and the Reference product. There were no new safety signals or unexpected findings. Immunogenicity was moderate and similar to the innovator product. The safety aspects as in the Mabthera PI are applicable to the product information of Ruxience.

2.7. Risk Management Plan

Safety concerns

Table 28. Summary of Safety Concerns

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.

Pharmacovigilance plan

Routine pharmacovigilance, with specific adverse reaction follow-up (FU) questionnaires for the following safety concerns:

All indications

- Progressive Multifocal Leukoencephalopathy
- Off-Label Use in Paediatric Patients

Non-oncology indications

- Malignant Events

The specific adverse drug reaction follow-up forms were provided in Annex 4. The proposed questionnaires are similar to the questionnaires in use for the reference product.

The proposed routine PhV activities are in line with the reference product and considered acceptable.

Risk minimisation measures

Table 29. Summary of Risk Minimisation Measures

Safety Concern	**Risk Minimisation Measures**
Important Identified Risk	
IRRs (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: None.
Infections, including serious infections	Routine risk minimisation measures:

Table 29. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures
(All Indications)	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 (Non-oncology indications): Patient alert card (PAC). The PAC is supported by educational material developed for patients and healthcare professionals. The text of the PAC is included in the PI Annexes.
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 (Non-oncology indications): PAC. The PAC is supported by educational material developed for patients and healthcare professionals. The text of the PAC is included in the PI annexes.
Hepatitis B reactivation (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: None.
Hypogammaglobulinaemia (Non-oncology 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: None.
Important Potential Risk	
Malignant events (Non-oncology indications)	Routine risk minimisation measures: EU SmPC Section 4.4 Special warnings and precautions for use EU SmPC Section 4.8 Undesirable effects Medicine's legal status: Medicinal product subject to restricted medical prescription. Additional RMMs: None.

Table 29. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures
Impact on CV disease (Non-oncology indications)	Routine risk minimisation measures: EU SmPC Section 4.2 Posology and method of administration 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: None.
Relapses (GPA/MPA only)	Routine risk minimisation measures: EU SmPC Section *5.1 Pharmacodynamic properties* Medicine's legal status: Medicinal product subject to restricted medical prescription. Additional RMMs: None.
Off-label use in paediatric patients (All Indications)	Routine risk minimisation measures: EU SmPC Section 4.1 Therapeutic indications EU SmPC Section 4.2 Posology and method of administration PL Section 2 Warning and precautions Medicine's legal status: Medicinal product subject to restricted medical prescription. Additional RMMs: None.
Administration route error (NHL/CLL)	Routine risk minimisation measures: EU SmPC Section 1: Name of the Medicinal Product EU SmPC Section 4.2: Posology and method of administration. PL Section 3 The outer carton as well as the vial label of the product states: For intravenous use after dilution. Medicine's legal status: Medicinal product subject to restricted medical prescription. Additional RMMs: The Physician information about Ruxience will contain Information that the product should be administered intravenously (IV) only to avoid administration route errors.
Missing Information	
Use in pregnancy and lactation (All Indications)	Routine risk minimisation measures: EU SmPC Section 4.6, Fertility, pregnancy and lactation PL Section 2 Warnings and precautions Medicine's legal status: Medicinal product subject to restricted medical prescription. Additional RMMs: None.
Long-term use in GPA/MPA patients (GPA/MPA only)	Routine risk minimisation measures: EU SmPC Section *5.1 Pharmacodynamic properties* Medicine's legal status:

Table 29. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures
	Medicinal product subject to restricted medical prescription. <u>Additional RMMs</u>: None.

Abbreviations: ADR = adverse drug reaction;, CLL = chronic lymphocytic leukaemia; CV = cardiovascular; DCA = data capture aid; GPA = granulomatosis with polyangiitis; HBV = hepatitis B virus; IRR = infusion related reaction; IV = intravenous; MPA = microscopic polyangiitis; NHL = Non-Hodgkin's lymphoma; PAC = patient alert card; PI = package insert; PL = package leaflet; PML = progressive multifocal leukoencephalopathy; RMM = risk minimisation measure; SmPC = summary of product characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Mabthera and Rixathon,-another approved products' format . The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ruxience (rituximab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

PF-05280586 (also called rituximab-Pfizer in the dossier) has been developed as a biosimilar product of MabThera (also called Rituximab-EU in this report).

The same indications are claimed as established for the EU reference product MabThera, i.e. non-Hodgkin lymphoma (advanced stage III-IV follicular lymphoma) on top of chemotherapy, CLL (chronic lymphatic leukaemia), moderate-severe rheumatoid arthritis (RA), in the second line after TNF-inhibitor failure, Granulomatosis with polyangiitis and microscopic polyangiitis (GPA and MPA) and Pemphigus vulgaris (PV).

At the time of this opinion MabThera is indicated for the treatment of adults only.

Summary of biological data (Quality & Non-Clinical)

An extensive physicochemical comparability exercise has been presented.

Comparative *in vitro* data were presented on:

- Binding of PF-05280586 and rituximab (EU/US) to the target, CD20 binding.
- Effects on Fab-related functionality due to the binding of CD20. This was evaluated in an assay measuring induction of apoptosis.
- Binding to relevant Fc receptors (FcRn, FcγRI, FcγRIIa (R131 & H131), FcγRIIb, FcγRIIIa (V158 & F158) and FcγRIIIb.
- Binding to Complement component 1q (C1q).
- Effects on Fc-related functionality: CDC, NK cell ADCC, ADCC 158V Reporter Gene Assay, ADCP 131H Reporter Gene Assay.

The *in vitro* data were presented by the applicant in Module 3, however, some functional data were assessed in the non-clinical AR.

Comparative *in vivo* data were presented on:

- Toxicokinetics, safety, B-cell count and immunogenicity in cynomolgus monkeys (SD and 4 week repeated dose).

Clinical studies

In total, three clinical trials were performed.

Study B3281006 was a 52-week, randomised, double blind, controlled study in low-tumour burden follicular lymphoma (LTB-FL). The primary objective of this was to evaluate equivalence of efficacy. Patients were eligible in case of histologically confirmed, Grade 1-3a, CD20-positive FL, containing no elements of diffuse large B-cell lymphoma. The largest nodal mass was not allowed to exceed 7 cm in diameter, and the maximum number of nodal sites was 3. Patients with poor prognostic factors like B-symptoms (fever, night sweats and weight loss), or high lactate dehydrogenase at baseline were excluded. Patients were randomly assigned to rituximab monotherapy with four weekly infusions of 375 mg/m^2 (n=198 to Rituximab-EU and n=196 to PF-05280586). Stratification factor was FLIPI1 risk category. The primary endpoint ORR (Overall Responder Rate, i.e. the sum of Complete Responders (CR) and Partial Responders PR (>50% reduction of the tumour load)), was established by two independent central reviewers at Week 26, based on radiological imaging. If there was no agreement,

a 3rd reviewer was assigned for final decision, taking into account clinical features such as CD19+ cell counts and bone-marrow involvement as well.

In RA patients, Study B3281001 where a single treatment course was given, and its extension study B3281004 were submitted. The primary objective of Study 001 was to establish biosimilarity of PK, based on $AUC_{0-\infty}$ and C_{max} as primary outcomes. PD measurement by CD19+ cell counts was secondary objective. The primary objective of Study 004 was to evaluate the effect of switching from licensed rituximab to PF-05280586.

Study B3281001 was a randomised, double blind, study of 25 weeks duration. A standard dosage of two rituximab IV infusions (1000 mg) with a 14-day interval was given. Seventy-three subjects were assigned to Rituximab-US, 74 to Rituximab-EU, and 73 to PF-05280586. After 16-24 weeks, subjects from Study B3281001 could continue rituximab treatment in extension study B3281004. In total, 59/73, 66/74 and 58/73 subjects from the Rituximab-US, Rituximab-EU ad PF-05280586 arms of Study B3281001 enrolled into Study B3281004, where three treatment cycles were given with a 16-24 weeks interval, at the discretion of the prescriber. Subjects who received Rituximab-EU or Rituximab–US at baseline of Study 004 were randomly switched to PF-05280586 in subsequent cycles.

The RA studies were not powered to establish equivalence of efficacy, and only descriptive data were provided of secondary efficacy outcomes, such as disease activity scores DAS28-CRP (mean changes form baseline), its responder rate LDAS (low disease activity, defined as DAS28-CRP ≤ 3.2) and remission (DAS28-CRP < 2.6), ACR20 responders and the functional score HAQ-DI.

The clinical development plan was in accordance with the CHMP scientific advice.

3.2. Results supporting biosimilarity

Quality and in vitro pharmacology data

- Identical primary structure/amino acid sequence has been sufficiently demonstrated.

- Size distribution / purity is considered comparable (levels of dimers tend to be slightly lower in PF-05280586 compared to the originator).

- Comparable higher order structure has been sufficiently demonstrated.

- Charge variants / hydrophobic heterogeneity; although differences in charge variants where found, these are mainly due to variants which are well-known to be clinically irrelevant.

- Comparable strength/protein content has been sufficiently demonstrated.

- Glycan analysis: Total Afucosylation and Total Galactosylation are within the same range and in that respect comparable.γ. - *In vitro* biological activity/potency related to Fab functionality (CD20-binding, induction of apoptosis) or Fc functionality (C1q binding & CDC; FcγRIIa binding & ADCP 131H RGA; FcγRIIIa 158V & NK cell ADCC (V/V, V/F) and FcRn, FcγRI, FcγRIIb, and FcγRIIIb) are considered comparable.

In conclusion, the analytical comparability data package is concise, and covers most of the relevant aspects of the product.

Results supporting biosimilarity; Non clinical

No significant differences in toxicokinetics, immunogenicity (ADA), safety and reduction in B-cell count were apparent in the single dose or 4 week repeated dose cynomolgus monkey study, and although limited the non-clinical data are considered supportive of the biosimilarity of the product to the originator.

Results supporting biosimilarity; Clinical Pharmacology

In the pivotal biosimilarity study B3281001, the 90% CIs for test to reference ratios of C_{max} and $AUC_{0-\infty}$ were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for all of the pair-wise comparisons among the three study drugs, demonstrating PK similarity among rituximab-US, rituximab-EU, and PF-05280586. Furthermore, in all comparison cases, one (i.e. 100%) was always included in the 90% confidence interval (thus there were no "statistically significant differences in 90% CIs") and all confidence intervals were in general evenly spread around one (100%).

Therefore, based on the pharmacokinetics of this study B3281001 it is concluded that PF-05280586 and rituximab-MabThera are biosimilar in RA patients.

Drug concentration data from the Week 26 report for the Phase 3 study B3281006 in LTB-FL patients indicate similar rituximab serum concentrations at each time point between the two treatment groups and support the conclusion that PF-05280586 is biosimilar to rituximab-MabThera (EU) also in this disease population.

Both in RA patients –with an in principle normal B-cell counts at baseline-, as in patients with LTB-FL – with increased B-cell count at baseline, PF-05280586 significantly and rapidly reduced CD19+ B-cell counts below the detection level. In both disease models, the reduction of CD19+ B-cells was persistent for a long-term, for both PF-05280586 and Rituximab-EU. E.g. the CD19+ cell count remained reduced near detection level over 1.5 years of continued treatment (4 courses) of PF-05280586 in Study B3281004.

ADA (anti-drug antibody) formation was overall modest and balanced over the treatment groups; 19.5% in the PF-05280586 vs 18.8% in the Rituximab-EU arm in LTB-FL patients at Week 26. and in 8.2% in the PF-05280586 vs 13.5% in the Rituximab-EU arm, in RA patients with no impact on infusion related reactions or CD19+ B-cell depletion or efficacy.

Results supporting biosimilarity; Clinical Efficacy

Study 006, LTB-FL patients

In the pivotal efficacy trial 006, the primary outcome of ORR at Week 26 as established by central readers, was 75.5% in the PF-05280586 group, and 70.7% in the rituximab-EU group. The analysis of the ORR showed an estimated difference of 4.66% (PF-05280586 minus rituximab-EU), with a 95% CI of (-4.16%, 13.47%) (analyses in the ITT population). The difference of the primary endpoint ORR at Week 26 and its 95% CI were within the predefined equivalence margin of -/+ 16%.

Equivalence of ORR was further supported by similarity of secondary endpoints (CR, PR, PFS) between the treatment groups, and the ancillary analyses demonstrating robustness of the primary endpoint over the diverse subgroups. The equivalence criteria were also met for the primary endpoint in the sensitivity analyses in the PP-subset (estimated difference 7.49, 95% CI -0.67, 15.80).

Also at long-term follow up till 52 weeks, ORR and PFS remained similar between treatment groups. In the PP-analyses, ORR at 52 weeks was 68.2% for rituximab-EU and 68.1% for PF-052805 (difference -0.15 (95% CI -10.10, 9.76). Hazard ratio of PFS after 52 weeks was 1.393 (95% CI 0.847-2.291) for the ITT population, with a p-value of 0.189. A similar outcome was reported for the PP population.

Study B3281001 and B3281004, RA patients

These studies were considered as supportive for efficacy. In Study 001, the mean change (SD) from baseline of DAS28-CRP was similar for PF-05280586 and Rituximab-EU at the short term at Week 13 (-2.0 (1.43) and -2.1 (1.33), respectively, no formal statistic comparisons were performed). Clinical response reached its plateau at Week 13. The effect size is considered clinically meaningful, given mean baseline DAS28-CRP values of 5.68 (0.86) and 5.79 (0.95) for PF-05280586 and Rituximab-EU,

indicating moderate-severe disease activity. Clinical relevance and similarity are further illustrated by LDAS responder rates of 41.8% and 44.4% for PF-05280586 and Rituximab-EU, respectively, and DAS28-CRP remission rates of 29.2% and 28.4%, respectively. Maintenance of efficacy for these endpoints was observed in extension Study 004.

Results supporting biosimilarity; Clinical Safety

Overall, the nature and incidence of the adverse events was balanced between the study arms in the study in LTB-FL, as well as in the RA studies.

As could be expected given the known safety profile of rituximab, infections and infusion reactions were commonly reported. In study B3281006, the incidence of infusion reactions was 29.9% and 25.0%, for rituximab-EU and PF-05280586, respectively. Infections occurred in 32.0% and 26.5% of the subjects, respectively. Similar incidences were reported in the RA studies. These events were rarely reported to be serious. No new treatment related events emerged.

3.3. Uncertainties and limitations about biosimilarity

- ***Uncertainties; Quality and in vitro pharmacology***

  There are no uncertainties in terms of quality and *in vitro* pharmacology aspects.

- ***Uncertainties; Non-clinical in vivo data***

  There are no uncertainties in terms of biosimilarity on the non-clinical aspects.

- ***Uncertainties; Clinical Pharmacology***

  There are no uncertainties in clinical pharmacology aspects.

- ***Uncertainties; Clinical efficacy and safety***

  There are no uncertainties regarding clinical efficacy and safety data.

3.4. Discussion on biosimilarity

Quality

The analytical comparability data package covers the relevant aspects of the product and supports the conclusion that high analytical similarity exists. The applicant satisfactorily addressed the Other Concerns raised during the procedure. From a quality point of view, biosimilarity with the reference product MabThera is considered demonstrated.

In vitro Pharmacology

The *in vitro* biological (pharmacological) activity of PF-05280586 was compared with Rituximab-EU, including most of the relevant modes of action (MoA) (apoptosis, CDC, ADCP and ADCC). It can be concluded that both compounds display similarity with respect to the ADCC F/F MoA.

Clinical Pharmacology

No relevant differences were noted regarding immunogenicity. There does not seem to be a major difference in effect of ADA on PK between PF-05280586 and rituximab-EU. Biosimilarity in terms of PK and PD was demonstrated.

Clinical efficacy & Safety

In the RA studies, efficacy and safety were secondary objectives, and not formally tested. Bioequivalence of PK and PD was established in these studies. and the more sensitive RA outcome DAS28-CRP support similarity.

There were no differences observed in PK-PD, ADA formation, other more sensitive RA outcomes and the study in LTB-FL, and these outcomes all support similarity.

3.5. Extrapolation of safety and efficacy

Extrapolation of equivalence has to be made from the clinical studies in RA and LTB-FL, to approved indications NHL (higher grade than LTB-FL), CLL and the auto-immune disorder ANCA-vasculitis (GPA and MPA).

On one hand, bioequivalence in PK and similarity in PD (reduction of B-cell counts), efficacy and safety has been demonstrated for PF-05280586 and Rituximab-EU, in two models (auto-immune disorder RA and haemato-oncology model LTB-FL). Similar study programs as for Ruxience, consisting of a supportive PK-PD study in RA and a pivotal clinical efficacy and safety in a lymphoma model, have been accepted before by the CHMP for other rituximab biosimilar products. The CHMP considered extrapolation of similarity to all indications for the other rituximab biosimilar products acceptable, based on those studies and the totality of evidence from Quality and in-vitro binding and functional assays.

The comparative B-cell depletion, efficacy and safety and bio-equivalence between PF-05280586 and Rituximab-EU is considered relevant for the assessment of bio-similarity and extrapolation to other non-investigated indications, since this indirectly reflect the potency of the drug of antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) and programmed cell death (apoptosis). These mechanisms of action may be applicable to all indications, irrespective whether these are malignant CD20+ B-Cells or normal CD20+ B-cells, as in auto-immune disorders. Yet, their relative contributions may vary among the different indications, e.g. ADCP may be more relevant for response in CLL (chronic lymphatic leukaemia).

According to in-vitro assays, similarity between PF-05280586 and Rituximab was shown regarding these actions. .

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ruxience is considered biosimilar to Mabthera. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ruxience is not similar to Imbruvica, Gazyvaro, Kymriah, Yescarta and Polivy within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of Ruxience is favourable in the following indications:

Ruxience is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

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

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

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

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

Chronic lymphocytic leukaemia (CLL)

Ruxience 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.

See section 5.1 for further information.

Rheumatoid arthritis

Ruxience 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.

Ruxience 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

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

Pemphigus vulgaris

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

Additional risk minimisation measures

Non-oncology indications:

The MAH must ensure that all physicians who are expected to prescribe Ruxience are provided with the following:

Product information

Physician information

Patient information

Patient Alert card

The Physician information about Ruxience should contain the following key elements:

- The need for close supervision during administration in an environment where full resuscitation facilities are immediately available
- The need to check, prior to Ruxience treatment, for infections, for immunosuppression, for prior/current medication affecting the immune system and recent history of, or planned, vaccination
- The need to monitor patients for infections, especially PML, during and after Ruxience treatment
- Detailed information on the risk of PML, the need for timely diagnosis of PML and appropriate measures to diagnose PML
- The need to advise patients on the risk of infections and PML, including the symptoms to be aware of and the need to contact their doctor immediately if they experience any.
- The need to provide patients with the Patient Alert Card with each infusion

The Patient information about Ruxience should contain the following key elements:

- Detailed information on the risk of infections and PML
- Information on the signs and symptoms of infections, especially PML, and the need to contact their doctor immediately if they experience any
- The importance of sharing this information with their partner or caregiver
- Information on the Patient Alert Card

The Patient Alert Card for Ruxience in non-oncology indications should 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

Oncology indications:

The MAH must ensure that all physicians who are expected to prescribe Ruxience are provided with the following:
Product information
Physician information

The Physician information about Ruxience should contain the following key elements:

- Information that the product should be administered as IV only to avoid administration route errors.

The Physician information, Patient information and Patient Alert Card must be agreed with the National Competent Authorities prior to distribution.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.