EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/440905/2017
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Riximyo

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/004729/0000

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

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# List of abbreviations

| | |
|---|---|
| AC | Acceptance Criteria |
| ACR (20 /50/ 70) | American College of Rheumatology 20% (50%) (70%) Response Criteria |
| ADA | Anti-drug antibody |
| ADCC | Antibody dependent cellular cytotoxicity |
| ADCP | Antibody-Dependent cellular phagocytosis |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AF4 | Asymmetrical flow field-flow fractionation |
| Asn | Asparagine |
| AUC | Area under the concentration-time curve |
| AUC | Analytical ultracentrifugation |
| AUC(0-inf) | Area under the serum concentration-time curve from time zero to infinity |
| AUC(0-last) | AUC calculated from start of dose to the end of the dosing interval, tau |
| AUCall | AUC from the time of dosing to the time of the last observation |
| AUClast | AUC from time zero to the last measured time point |
| AUEC | Area under the effect-time curve |
| AUEC(0-t) | The area under the effect-time curve from time zero to time 't'. |
| BSA | Body surface area |
| CDAI | Clinical Disease Activity Index |
| CDC | Complement-dependent cytotoxicity |
| CEX | Cation Exchange Chromatography |
| CHO | Chinese Hamster Ovary |
| CHOP | Cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine] and prednisone |
| CI | Confidence interval(s) |
| CLL | Chronic lymphocytic leukemia |
| Cmax | The maximum (peak) observed serum concentration of rituximab |
| Cmin | Minimum observed concentration |
| CPP | Critical process parameter |
| CR | Complete response |
| CRP | C-reactive protein |
| CT | Computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough | concentration before the next infusion dose administration |
| CVP | Cyclophosphamide, vincristine, prednisone |
| Da | Dalton |
| DAS | Disease Activity Score |
| DAS28 | Disease Activity Score Based On A 28 Joint Count |
| DLBCL | Diffuse large B-cell lymphoma |
| DMARD | Disease modifying anti-rheumatic drug |
| DNA | Deoxyribonucleic acid |
| DSC | Differential Scanning Calorimetry |
| DSP | Down Stream Process |
| ECG | Electrocardiogram |
| ECL | Electrochemiluminescence |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| ELISA | Enzyme-linked immunosorbent assay |
| ESR | Erythrocyte sedimentation rate |
| EULAR | European League Against Rheumatism |
| FAS | Full Analysis Set |
| Fc | Fragment crystallisable (region of an antibody) |
| FL | Follicular lymphoma |
| FLIPI | Follicular Lymphoma International Prognostic Index |
| FMEA | Failure Mode Effects Analysis |
| FP | Finished product |
| FT-IR | Fourrier Transform Infrared Spectroscopy |
| GCP | Good clinical practice |
| GMP | Good Manufacturing Practice |
| GPA | Granulomatosis with polyangiitis |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HBV | Hepatitis B virus |
| HCP | Health Care Provider |
| HDX | Hydrogen Deuterium Exchange |
| HIV | Human immunodeficiency virus |
| HPLC | High performance liquid chromatography |
| HR | Hazard ratio |
| i.v. | Intravenous |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| Ig | Immunoglobulin |
| INN | International Nonproprietary Name |
| IPC | In-process Control |
| IRR | Infusion-related reaction |
| ITT | Intention-to-Treat |
| LLOQ | Lower limit of quantification |
| mAb | Monoclonal antibody |
| MALLS | Multi-angle Laser Light Scattering |
| MCB | Master Cell Bank |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFI | Micro-flow imaging |
| mg | Milligram |
| mL | Millilitre |
| MoA | Mechanism of Action |
| MPA | Microscopic polyangiitis |
| MRI | Magnetic Resonance Imaging |
| MTX | Methotrexate |
| NAb | Neutralizing antibody |
| NHL | Non-Hodgkin’s Lymphoma |
| NMR | Nuclear Magnetic Resonance |
| ORR | Overall response rate |
| OS | Overall survival |
| PC | Process characterization |
| PD | Pharmacodynamics |
| PD | Progressive disease |

| | |
|---|---|
| PFS | Progression free survival |
| Ph. Eur. | European Pharmacopoeia |
| PI | Package Insert |
| PK | Pharmacokinetics |
| PML | Progressive multifocal leukoencephalopathy |
| PP | Process parameter |
| PPS | Per Protocol Set |
| PR | Partial response |
| PT | Preferred term |
| PTM | Post-translational modifications |
| QbD | Quality by design |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| SA | Scientific Advice |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SD | Stable disease |
| SDAI | Simplified Disease Activity Index |
| SEC | Size-exclusion chromatography |
| SOC | System organ class |
| SPR | Surface plasmon resonance |
| T1/2 | Elimination half-life |
| TEAE | Treatment emergent adverse event |
| Tmax | The time to reach maximum (peak) serum concentration after single dose |
| TNF | Tumour necrosis factor |
| TSE | Transmissible Spongiform Encephalopathy |
| UF/DF | Ultrafiltration/diafiltration |
| US | The United States of America |
| UV | Ultraviolet |
| WCB | Working Cell Bank |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Sandoz GmbH submitted on 9 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Riximyo, through the centralised procedure falling within the Article 3(1) and point 1 of 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 applied for the following indication:

*Riximyo is indicated in adults for the following indications:*

*Non-Hodgkin's lymphoma (NHL)*

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

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

*Riximyo 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.*

*Riximyo 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.*

*Rheumatoid arthritis*

*Riximyo in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.*

*Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.*

*Granulomatosis with polyangiitis and microscopic polyangiitis*

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

This application is submitted as a multiple of Rixathon simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: MabThera, 100mg and 500mg, concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Ltd
- Date of authorisation: 02-06-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/067/001-002

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: MabThera, 100mg and 500mg, concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Ltd
- Date of authorisation: 02-06-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/067/001-002

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: MabThera, 100mg and 500mg, concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Ltd
- Date of authorisation: 02-06-1998
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/98/067/001-002

**Information on Paediatric requirements**

Not applicable.

***Information relating to orphan market exclusivity***

***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 from the CHMP on 25 June 2009 and 20 January 2011. The

Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

### *1.2. Steps taken for the assessment of the product*

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

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

- The application was received by the EMA on 9 December 2016.
- The procedure started on 16 December 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2016 as a duplicate of Rixathon.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2017
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 9 February 2017
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The CHMP adopted a report on similarity for Riximyo with Mabthera and Gazyvaro on 23 February 2017
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2017
- During the meeting on 18-21 April 2017, 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 Riximyo on 21 April 2017.

## 2. Scientific discussion

### *2.1. Problem statement*

This application concerns a centralised procedure for marketing authorisation of Riximyo, rituximab concentrate for solution for intravenous infusion of 100 mg and 500 mg, as a biosimilar product to the European reference product MabThera (EU/1/98/067/001-002).

MabThera has been registered for the treatment of non-Hodgkin lymphoma (NHL), chronic lymphatic leukaemia (CLL), rheumatoid arthritis (RA), and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Mabthera was first authorised in the European Union in 1998.

Marketing authorisation has not been applied for solution(s) for subcutaneous injection for Riximyo compared to the European reference product.

### 2.1.1. Disease or condition

Rituximab was first authorised in the European Union on 2 June 1998 under the name of MabThera. It is also marketed under the name Rituxan in the United States (US). It is currently approved for the following indications:

Non-Hodgkin's lymphoma (NHL)

- treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
- maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy.
- monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.
- 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)

- in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia.

Rheumatoid arthritis

- 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.

Granulomatosis with polyangiitis and microscopic polyangiitis

- 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 conditions covered by the above indications have been extensively analysed through the respective approval procedures of Mabthera (see Mabthera European assessment report – EPAR)

Riximyo contains rituximab intended to be approved in all the above indications with the exception of the CLL and retreatment after 24 weeks in Rheumatoid arthritis on the basis of its claimed biosimilarity to Mabthera.

### 2.1.2. Epidemiology

According to the prevalence of the indications Non-Hodgkin´s lymphoma (1-5 / 10000) and Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) (1-9 / 100000) are rare conditions. The more common condition, rheumatoid arthritis, has a prevalence of more than 1 in 1000.

## 2.1.3. Biologic features

Non-Hodgkin's lymphoma (NHL) is a form of malignant lymphoma distinguished from Hodgkin's disease only by the absence of binucleate giant cells. Follicular lymphomas are indolent (slow-growing) NHL and the second-most-common form of non-Hodgkin's lymphomas overall, defined as a lymphoma of follicle center B-cells (centrocytes and centroblasts), which has at least a partially follicular pattern. It is positive for the B-cell markers CD10, CD19, CD22, and usually CD20, but almost always negative for CD5.

B-cells also play several important roles in the pathogenesis of rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). They produce auto-antibodies such as Rheumatoid Factor (RF), anti-cyclic citrullinated protein (anti-CCP) antibody in RA or anti-neutrophil cytoplasmic antibody (ANCA) in MPA and CPA. In the synovium, RF immune complexes may mediate complement activation and the propagation of the inflammatory cascade. B-cells present in the RA synovial membrane may secrete a range of pro-inflammatory cytokines, some of which are components in the process leading to joint inflammation and damage, or to induce leukocyte infiltration. B-cells can function as antigen-presenting cells and immune-regulatory cells, leading to T-cell activation. They can also stimulate osteoclasts and synovial fibroblasts and lead to bone erosions and joint tissue remodelling.

Peripheral B cell counts decline below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/$m^2$, and remained at that level in most patients up to the 6 month time point. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.

## 2.1.4. Clinical presentation and diagnosis

Clinical presentation of the conditions covered by rituximab as well as diagnostic methods available have been extensively described in the individual applications throughout the history of the originator rituximab (Mabthera) in the EU (see Mabthera EPAR).

***About the product***

Rituximab is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. CD20 is located on pre-B and mature B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal cells. CD20 is also expressed on >95% of all B-cells in non-Hodgkin lymphoma. 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. CD20 regulates an early step in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. After binding to the CD20 antigen on the cell surface, rituximab exerts its therapeutic effect by promoting B-cell lysis.

***Type of Application and aspects on development***

This application concerns a centralised procedure for marketing authorisation of Riximyo, (also referred to as GP2013), rituximab concentrate for solution for intravenous infusion of 100 mg and 500 mg, as a biosimilar product to the European reference product MabThera (EMA registration numbers EU/1/98/067/001-002).

MabThera has been registered for the treatment of non-Hodgkin lymphoma (NHL), chronic lymphatic leukaemia (CLL), rheumatoid arthritis (RA), and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Mabthera was first authorised in the European Union in 1998.

Marketing authorisation has not been requested for solution(s) for subcutaneous injection for Riximyo compared to the European reference product.

The global development program for Riximyo was designed in a stepwise approach for demonstrating comparability between Riximyo and the EU Reference Product MabThera. As a first step, structural and functional characterisation of Riximyo and the reference product was established. Riximyo was developed using the principles of a quality by design approach. A comprehensive set of binding and activity assays were conducted to gain understanding of the functionalities, and the structures underlying these functionalities of the molecule, that contribute to its modes of action.

The second step involved non-clinical testing including pharmacokinetics/ pharmacodynamics (PK/PD) and toxicokinetics studies. In addition, studies in mouse xenograft tumour disease models were conducted using a dose scaling design. Finally, assessment of effector mechanisms such as ADCC, CDC, and apoptosis was performed in a healthy volunteer whole blood assay, and in ADCC potency assays with different *in vitro* settings.

Confirmation of comparability between Riximyo and MabThera at the clinical level was based on two randomised trials: one study in patients with RA (Study GP13-201), and one study in patients with advanced Follicular Lymphoma (study GP13-301). The primary objective of Study GP13-201 was establishing bioequivalence of PK; the primary objective of Study GP13-301 was the confirmation of therapeutic equivalence. As supportive evidence, PK-PD data were provided from a small-scaled observational study in Japanese patients with indolent NHL.

CHMP guidelines

The following guidelines are considered of special interest:

**Table 1 Guidelines**

| Guideline | Document Reference | Topic |
|---|---|---|
| Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues | EMEA/CHMP/BMWP/42832/2005 Rev 1, 2014 | Development plan |
| Guideline on Similar Biological Medicinal Products | CHMP/437/04 rev 1, 2014 | Development plan |

| Guideline | Document Reference | Topic |
|---|---|---|
| Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues | EMEA/CHMP/BMWP/403543/2010 | Development plan |
| Guideline on the investigation of bioequivalence | CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** | PK trial design |
| Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins | CHMP/EWP/89249/2004 | PK trial design |
| Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins | EMEA/CHMP/BMWP/14327/2006 | PK and efficacy/safety trial design |
| Guideline on the evaluation of anticancer medicinal products in man | EMA/CHMP/205/95/Rev. 4 | Efficacy trial design |
| Draft Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis | CPMP/EWP/556/95 Rev. 2 | Efficacy trial design |
| Guideline on the choice of the non-inferiority margin | EMEA/CPMP/EWP/2158/99 | Efficacy trial design |

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as a sterile concentrate for solution for infusion containing 100 mg (in 10 mL) or 500 mg (in 50 mL) of rituximab as active substance.

Other ingredients are: sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

The product is available in 10 mL or 50 mL clear glass vials with butyl rubber stopper containing 100 or 500 mg of rituximab. Packs of 10 mL (100 mg) contain 2 or 3 vials. Packs of 50 mL (500 mg) contain 1 or 2 vials.

The formulation of the finished product was developed to maintain the similarity to the EU-marketed reference product MabThera.

### 2.2.2. Active Substance

#### *General information*

The International Nonproprietary Name (INN) of the active substance contained in Riximyo is rituximab. It is a murine/human chimeric IgG1 kappa type monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. This chimeric anti-CD20 antibody is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system. It has the characteristics which are common in monoclonal antibodies and include amino acid modifications such as deamidation, oxidation or glycation, disulfide bridging, variable N-glycosylation, N- and C-terminal heterogeneity, and molecular weight variants.

## *Manufacture, characterisation and process controls*

### *Description of manufacturing process and process controls*

The active substance is manufactured according to current Good Manufacturing Practices (cGMP) by Sandoz GmbH Schaftenau, Austria. The manufacturing process reflects a standard process used for the manufacture of monoclonal antibodies. The active substance is produced in a fed-batch process. The cell culture process involves three stages: the seed train, the inoculum train, and the production culture. The purification process consists of consecutive operations including primary separation; several chromatography steps; viral inactivation/filtration and UF/DF. Description of the active substance manufacturing process is considered adequate.

Process characterization was conducted in accordance with current ICH requirements including quality by design (QbD) principles. Process characterization included large scale and small scale data mining, risk assessments, and laboratory studies. A process risk assessment tool based on failure mode and effects analysis (FMEA) methodology was used to assess the process- and product-related risks of the active substance manufacturing process and to select the process parameters (PPs) which should be further investigated during process characterisation (PC) studies. The classification of PP is appropriate.

### *Control of materials*

As the active substance has been developed as biosimilar, the coding sequence of the expression gene was designed to achieve the identical primary amino acid sequence as the reference product.

Cell bank testing and characterisation was performed according to the requirements defined in ICH Q5A and Q5D. The data of cell bank characterisation demonstrate the absence of microbial and viral contaminants, as well as endogenously encoded retrovirus-like particles. Protocols for the preparation and testing of future Working Cell Banks are in place to ensure consistent supply.

In the manufacturing process of the active substance no material of human or TSE relevant species is used.

### *Control of critical steps and intermediates*

An extensive control strategy is proposed. Process controls performed during manufacture of the active substance are categorized.

### *Process validation*

Process validation at commercial scale was performed and process and performance parameters have been maintained within the specified acceptance ranges. Results of IPCs complied with the pre-defined limits. The release data for the three consecutive process validation batches comply with the specifications. Process-related impurities are effectively removed by the purification process. Data from manufacturing scale and results from spiking studies at small scale show that process related impurities are reduced to concentrations below the acceptable limit, which is based on worst case considerations taking a maximum intravenous dose of 1,000 mg per day into account. The removal of product related impurities was demonstrated. Overall the data show that the process is under control and suitable for consistent manufacturing. A small scale study showed that the reuse of the chromatography resins has no adverse effects on process performance and product quality including product and process related impurities and adventitious agents. Based on the results of the small scale study, the maximum number of cycles of the chromatography resins was defined. The results are supported by concurrent manufacturing scale validation activities. Hold times were established and are considered validated.

***Manufacturing process development***

In the first development phase a downstream process suitable for manufacturing of AS for preclinical and clinical studies was successfully developed. During the second development phase the downstream process was further improved. The comparability data demonstrate that the derived material is comparable to the reference material.

***Characterisation***

For the characterisation of Riximyo a comprehensive series of analytical methods have been used. These methods included state-of the art sensitive and orthogonal physicochemical and biological tests to determine the primary, secondary, and higher-order structure, post-translational modifications and associated heterogeneities, glycosylation, charge variants, purity/impurities, and quantity of Riximyo.

Molecular Mass and Primary Structure: the active substance is a 145 kDa monoclonal antibody composed of two light chains (213 amino acid) and two heavy chains (451 amino acid), which are N-glycosylated at Asn 301. Based on its theoretical sequence and characterisation studies, peptide mapping confirmed that the active substance had the expected primary structure and it can be stated that the sequence of the active substance is identical to the theoretical sequence of rituximab. In addition mass spectrometry analyses showed that all test items had the expected masses.

Disulfide bridging: All disulfide linkages could be confirmed by peptide mapping and x-ray crystallography. The levels of free thiols were comparable in all test items.

N-Glycosylation: Analyses of oligosaccharides showed that the active substance had consistent oligosaccharide distribution and expected glycosylation for an antibody produced in CHO cells, showing one single N-glycosylation site at the heavy chains (Asn301). No potentially immunogenic glycoforms such as NGNA or Gal-α1,3-Gal could be identified.

Charged variants: Charge heterogeneity was evaluated for all test items and revealed consistent values for acidic and basic peak variants, the amount of glycated variants as well as for sialylated structures.

Molecular size variants: Size heterogeneity was assessed by capillary gel electrophoresis, SEC, SEC-MALLS, AUC, AF4, MFI, light obscuration and visible particles determination according to Ph. Eur. The results show that all variants detected were of proteinous nature.

Higher order structure: Structural analyses of the active substance showed that all test items had identical higher order structures.

Biological function: Rituximab has a number of elements that are known to contribute to its mode of action. After binding of the CD20 antigen on the surface of B cells, the complement system is activated via binding of C1q to the Fc part of the antibody, leading to complement dependent cytotoxicity (CDC). In addition, the antibody can interact with FcγR positive cells and can thereby induce antibody dependent cellular cytotoxicity (ADCC). Furthermore, binding of rituximab can induce apoptosis of the target cell. All elements of these modes of action were tested using different types of assays: CD20 binding activity (binding assay), FcRn (SPR), FcγRIa (SPR), FcγRIIa (SPR), FcγRIIb (SPR), FcγRIIIa (F158) (SPR), FcγRIIIa (V158) (SPR), FcγRIIIb (SPR), ADCC activity (ADCC assay), CDC activity (CDC assay, C1q binding (C1q binding assay) and apoptosis induction (apoptosis assay). All assays revealed consistent results for the active substance tests with all values within the specified and expected ranges.

The evaluated data confirmed the capability of the active substance manufacturing process to produce consistent batches. The results obtained showed that the active substance has the expected primary, secondary and tertiary structures and physicochemical properties of a human IgG1 type antibody and all biological characteristics revealed no result being out of the specified or defined target range.

The active substance specification includes test methods for clarity, coloration, pH, identity, purity, glycosylation profile, bioburden, endotoxins, content and biological activity (potency).

Characterisation is additionally discussed in the context of biosimilarity to the reference product.

## *Specification*

The specifications set for the release of the active substance have been set taking ICH Q6B guideline into account.

Clearance validation studies have been performed to demonstrate that the manufacturing process provides adequate clearance of impurities. Process-related impurities are extensively identified and assessed. The batch results indicate that levels of process-related impurities are consistently low among the AS batches. Product-related impurities have been adequately defined and are also discussed as part of the biosimilarity data. Sufficient information is provided to substantiate that the CPPs/CIPCs guarantee satisfactory impurity removal over the whole range of the associated PARs.

### *Analytical methods*

General tests (Clarity, Colour, and pH) and Safety tests (Endotoxin and microbial enumeration) are performed according to the Ph. Eur. monographs. Non-compendial methods are briefly described including preparation, procedure, system suitability and assay acceptance criteria. The analytical methods are appropriately validated.

### *Batch analysis*

The batch results of the currently available AS batches manufactured with the proposed commercial process at the GMP manufacturing facility at Sandoz GmbH Schaftenau, Austria indicates that the manufacturing process is robust. All acceptance criteria were met. In order to establish the acceptance criteria for the commercial specifications, batch data were evaluated. Statistical analysis of the batch results has been also performed for the quantitative release tests to confirm that the proposed commercial specifications reflect assay variability, future process variability and capability appropriately.

### *Reference materials*

For active substance reference material a two-tiered approach, including primary in-house reference material and working standards, has been used. The working standards are designated to be released compared to the primary in-house standard, which should thereby last for a longer period of time.

## *Stability*

A comprehensive stability program has been provided. Results on long-term storage conditions have been provided and are considered sufficient to justify the proposed shelf-life. Evaluation of the results of the stability of the active substance at 40 ± 2°C/75 ± 5% RH showed that the selected parameters are stability indicating and appropriate to demonstrate stability of the product. A follow up stability program is proposed covering long-term storage conditions. The analytical methods cover stability indicating (including potency) and safety parameters. A photo-stability study revealed only minor effects on the purity of the active substance. Freeze-thawing and freeze-freezing studies demonstrated

the active substance stability for several cycles of alternating freezing at long-term and intermediate frozen storage conditions.

## 2.2.3. Finished Medicinal Product

### *Description of the product and pharmaceutical development*

The finished product is a sterile concentrate for solution for infusion for intravenous (IV) use after dilution. The liquid formulation is based on rituximab as the active substance at a concentration of 10 mg/mL provided in 10 mL vials (100 mg) and 50 mL vials (500 mg). The excipients for the formulation are compliant with the requirements of the Ph. Eur. and commonly used in parenteral medicinal products. The applicant sufficiently described the pharmaceutical development of the finished product (FP).

The process characterization included data mining, risk assessment, laboratory studies and technical batches manufactured at commercial scale. A process risk assessment tool based on FMEA methodology was used to assess the process-related risks of the FP manufacturing processes and to select the process parameters for characterization studies.

During development the manufacturing process of the FP has been changed. Initially the FP has been produced at the first biopharmaceuticals manufacturing site. The process was afterwards transferred to the commercial manufacturing site. Comprehensive studies have been performed to investigate the comparability of the finished product manufactured. The results showed comparable FP as all comparability assessment criteria have been met.

The primary container closure consist of a type I glass vial and a chlorobotyl rubber stopper. Both components meet the requirements of the Ph. Eur. The vials are crimped with an aluminium cap with a flip-off component. The compatibility of all constituents of the finished product with the container closure system was sufficiently demonstrated by stability data of numerous batches.

### *Manufacture of the product and process controls*

The finished product is manufactured according to current Good Manufacturing Practices (cGMP). It is released by Sandoz GmbH Schaftenau, Austria... The finished product is produced using standard manufacturing steps such as thawing of the AS, dissolving of excipients, compounding, sterile filtration and aseptic vial filling. Sterile filtration by means of bacteria-retentive membrane filters followed by aseptic filling is applied.

The process is sufficiently described including details on stirring, filtration and filling. Additionally, an overview of process parameters and their target values/acceptable ranges is provided.

The established in-process controls (IPCs) are considered as appropriate tests to monitor the process and assure a consistent performance of the manufacture of the FP. Classification of process parameters (PPs) was performed taking into account the existing product, process knowledge, and experimental data. Considering that the finished product manufacturing process is straightforward, the proposed IPCs, PPs and their ranges are acceptable. Validation of the manufacturing process was executed as prospective validation for the 100 mg and 500 mg strengths of the finished product. Process validation data / process qualification data demonstrate that when producing within the process conditions set, the predefined IPCs and product specifications are met.

The control strategy describes how QAs are addressed through different control elements. It provides a link between the finished product quality and the control elements that are established to ensure process robustness and product quality.

Subsequent to successful process validation, process performance and product quality are monitored as part of the continued process verification (CPV) to ensure that the state of control is maintained throughout the commercial manufacturing process. Continued process verification is a planned life-cycle management program to ensure that the manufacturing process remains capable and is in a state of control. This is achieved through the systematic collection, analysis and trending of product-related and process-related data.

## *Product specification*

The specifications for the release of the finished product have been set taking the principles of the guideline ICH Q6B into account. The finished product specification includes test methods for coloration, clarity, pH, extractable volume, osmolality, identity, purity, sterility, endotoxins, visible and sub-visible particles content and biological activity (potency).

Justification is presented in support of the proposed set of the finished product release / shelf life tests and their acceptance criteria.

Analytical methods specific for the FP are briefly described. For compendial methods, the applicant refers to the corresponding Ph. Eur. monographs. For methods (including validation) identical for the AS testing the applicant refers to the corresponding AS sections. The suitability of compendial methods was verified for their use. The validation of the tests was adequately completed. . Batch analyses data is provided for laboratory scale, pilot scale and commercial scale batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Each batch was tested to the specification in place at the time of manufacture and all specifications were met. For the finished product the same reference materials are used as for the active substance.

## *Stability of the product*

The applicant provided a comprehensive stability program including long-term, accelerated, stress conditions as well as freeze / thaw, out-of-the fridge, inverse out-of-the fridge and photostress studies. The stability protocols, including the selected QAs to be tested and time points for sampling, are acceptable and in accordance with ICH Q5C. For the long-term storage conditions, data were evaluated statistically using ANOCOVA for all stability-indicating parameters and a theoretical shelf-life according to ICH guideline Q1E was calculated where applicable.

The stability batches encompassed both strengths 100 mg and 500 mg. Data up to 36 months at long-term conditions have been presented for batches.

For most of the quality attributes tested the results show a highly stable finished product at the recommended long-term stability conditions (5 ± 3°C). Importantly, all results of the tested finished product 100 mg and 500 mg batches were within the shelf-life specifications during storage at 5 ± 3°C.

Evaluation of the results of the stability of the finished product at accelerated (25 ± 2°C / 60 ± 5% RH) and stressed (40 ± 2°C / 75 ± 5% RH ) conditions showed highly comparable degradation profiles.

In-use stability study

The in-use study performed with the finished product diluted in 0.9% NaCl and 5% Glucose and stored in PE bags revealed no changes for the biophysical stabilities of the FP after in-use storage under different storage conditions.

The results of the freeze / thaw studies did not reveal a significant impact on the quality attributes of the FP. Furthermore, the FP has been shown to remain stable at recommended conditions for up to 36 months after initial storage at room temperature for up to 14 days (out-of-the fridge study). The inverse out-of-the fridge study (14 days at room temperature after 36 months storage at recommended conditions) showed slight differences in the charged variants. The results stayed within the defined acceptance criteria. The results of the photostress study demonstrated that illumination slightly induces degradation in the FP.

## Adventitious agents

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The active drug substance of Riximyo is produced in a serum-free culture medium. No TSE relevant material is added during cell cultivation of the active substance. The MCB and WCB which have been established are free from TSE-risk substances.

The active substance is expressed in CHO cell using serum-free medium. The cell banking system has been extensively screened for adventitious viruses using a variety of *in vitro* and *in vivo* assays. The tests demonstrated the absence of any virus contaminants in the cell banks with the exception of intracellular type A and extracellular type C retrovirus-like particles which are well known to be present in rodent cells; this is acceptable as there is sufficient capacity within the active substance manufacturing process to inactivate/remove such virus particles. . Both enveloped and non-enveloped viruses were effectively reduced by the various unit operations including inactivation at low pH, chromatography steps and a virus filtration step. Chromatography resins are re-used during the active substance manufacturing process and both new and used resins have been investigated with very similar performance with respect to virus reduction. At the end of the active substance cell culture procedure, general testing for adventitious viruses is performed and a cell line is included to detect minute virus of mice.

## Biosimilarity

The overall strategy to demonstrate biosimilarity between Riximyo and MabThera, the EU authorised reference product, was designed in a stepwise approach: demonstrating analytical comparability between the biosimilar, the reference product (MabThera) and the US authorised Rituxan; and by generating non-clinical and clinical data.

As a first step, in an extensive structural and functional characterization, analytical comparability between the biosimilar and the reference product was established. A comprehensive set of binding and activity assays were conducted to gain a full understanding of all functionalities of the molecule and the structures underlying these functionalities that contribute to its MoAs, demonstrating that the active substance and the finished product batches of the biosimilar and MabThera/Rituxan batches are comparable on physicochemical and biological level. A sufficiently high number of the biosimilar batches manufactured by the commercial process as well as of the MabThera reference product authorised in the EU was included in the analytical similarity exercise.

The second step involved non-clinical testing confirming the comparability of the biosimilar and MabThera/Rituxan.

Finally, clinical comparability was based on two pivotal studies.

In order to define a biosimilarity range for the biosimilar, the applicant comprehensively analysed both the EU reference product and US Rituxan using orthogonal methods analysing specific quality attributes. The results showed high comparability between both products. Different batches of the EU reference product and Rituxan were continuously monitored to verify batch to batch consistency and showed no differences between them. This monitoring assessed the variability of the reference product over a period of approximately 9 years. A quality shift was observed in 2008 for the EU reference product and US Rituxan. Several quality attributes were affected (e.g. charge variants, glycan structures, ADCC) by this shift but both qualities were on the market simultaneously, therefore both quality profiles observed for the reference product are considered to represent a safe and effective product and considered appropriate for use in comparability assessment.

The primary structure of the biosimilar is identical to the primary structure of the reference product. Using different endoproteinases and combinations of endoproteinases with distinct substrate specificity and subsequent LC-ESIMS and MS/MS analyses 100% coverage of the amino acid sequences of the biosimilar and the reference product was achieved. Considering also the molecular mass analyses, the amino acid sequences are considered identical. In addition to X-ray crystallography, native LysC peptide mapping using RP-HPLC UV/MS revealed a similar disulphide bridge pattern in the biosimilar and the EU reference product. Analysis of the free thiols for the biosimilar was within the range of variability of the EU reference product. Post-translational modifications (PTM) as N-terminal pyroglutamate, C-terminal lysine variants and proline amide were identified in the biosimilar as well as in the EU reference product, with slight higher values for proline amide in the biosimilar. However, the small difference seen in the value of proline amide is scientifically justified to not compromise biosimilarity. Furthermore, PTMs as methionine oxidation, asparagine deamidation with or without subsequent isomerization were analysed by mass spectrometry using batches stored under stress conditions and identified identical locations on the antibodies for these PTMs in both the biosimilar and the reference product.

The higher order structure of the biosimilar and the reference product has been elucidated using orthogonal state-of the art assays. The results show highly comparable structures in terms of the secondary and tertiary structure conformation. Furthermore x-ray crystallographic analyses demonstrated similar Fab- and Fc-fragments as well as similar disulfide bridges within the fragments of the biosimilar and the reference product. Thermograms showed comparable unfolding of both mAbs further demonstrating their biosimilarity.

The elucidation of molecular size variants showed that the biosimilar has a comparable purity to the reference product. Size exclusion chromatography (SEC) results suggest a slightly higher purity, whereas orthogonal methods as analytical ultracentrifugation and SEC-MALLS show comparable purities. Furthermore, in terms of the hydrodynamic diameter or polydispersity both the biosimilar and the reference product show similar results. In addition, the enumeration of sub-visible particles measured by resonant mass measurement and micro-flow imaging demonstrated comparable results considering the high variability of these methods. Taken together the data on molecular size variants justifies a biosimilarity claim of the biosimilar to its reference product.

The pattern of charged variants is distinctive for biotechnologically manufactured mAbs. Using cation exchange chromatography, the biosimilar pattern could be resolved into acidic, main, and basic variants. The basic variants were identified to contain C-terminal lysine, proline amidation as well as N-terminal glutamine. The values lie within the upper range of the reference product. Acidic variants representing mainly molecule fragments, deamidation, glycation, and pyroglutamate are lower in the biosimilar compared to the reference product. Further analysis of the different fractions of the CEX

chromatogram (of the biosimilar and the reference product) showed that all fractions that were manageable to purify showed comparable potency values. The glycation, which has been shown to impact the potency of certain mAbs, showed a lower value for the biosimilar in comparison to its reference product. Further in depth analysis of the biosimilar and the reference product with intentionally increased glycation values did not reveal negative effects on efficacy. As the overall values are very low and the effects on efficacy and safety minor they are considered to not question the biosimilarity of the biosimilar and its reference product.

The comparison of the glycosylation pattern of the biosimilar and the reference product shows minor differences. The main glycan structures identified in rituximab are bG0, bG1 and bG2, which showed comparable values in the biosimilar and the reference product. Afucosylated structures, as well as high mannose sugars have been shown to influence Fc-mediated effector functions such as ADCC. Compared to the reference product, the glycan profile cumulates to comparable ADCC activity of the biosimilar and the reference product and, taking also the overall low content of these structures into account, no impact on efficacy/safety is expected.

The biological functions have been directly analyzed using bioassays for ADCC, CDC and Apoptosis induction or by measuring the binding of the Fc-part to the responsible receptors Fcγ-receptors for ADCC and C1q for CDC. A comparative stability study was performed for the biosimilar, the EU reference product, and US marketed Rituxan, to assess the stability under long-term, accelerated and stress conditions. The results of the studies show no significant differences in the degradation profiles of the biosimilar and the reference product.

During the comparability exercise small differences (high mannose structures, differences in charged variants) have been found between the biosimilar and the reference product. To provide further assurance that these differences in high mannose structures and charged variants do not affect biosimilarity or potency, in-depth analyses as well as forced degradation studies have been performed. The biosimilar and the reference product have been stored under stress conditions to foster degradation, and subsequently fractionated. The potency of these fractions has been analysed and a comparison between the biosimilar and the reference product was made. The results demonstrated that the biosimilar and the reference product behave similarly under stressed conditions, including the potency of the fractions. Fragments of the biosimilar have been demonstrated, as expected, to be biologically inactive and are defined as impurities. It was demonstrated that the amounts of fragments in the biosimilar and the reference product are comparable. Furthermore, process-related impurities as host cell DNA and protein that affect the safety evaluation of the medicinal products have been found to be comparably low for both products.

Summarising, a sufficiently high number of the biosimilar batches manufactured by the commercial process as well as of the MabThera reference product authorised in the EU was included in the analytical similarity exercise. As the US authorised Rituxan has been used in addition to the reference product for pre-clinical studies, investigation of Rituxan batches were also included in the analytical similarity exercise and it can be concluded that bridging between the US comparator and the EU reference product is acceptable.

Based on the comprehensive analytical comparability exercise, similarity between Riximyo and the reference medicinal product is considered demonstrated on quality level.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant provided a well-structured quality dossier. In general, high quality scientific data have been presented.

The manufacturing process reflects a standard process used for the manufacture of monoclonal antibodies and is well described, characterized and validated. The CQA assessment based on the in-house risk assessment tool is considered acceptable. The manufacturing process and associated control strategy are based on a structured process development strategy; ICH Q8 elements (e.g. risk assessment tools for identification of CQAs; systematic definition of a control strategy) have been appropriately incorporated. The data package comprises both full scale and small scale process characterisation and validation studies; in addition full scale PPQ (verification) batches are available; column/resin life time studies are addressed using continuous process verification elements. For the characterization, a comprehensive series of analytical methods have been used. These methods included state-of the art sensitive and orthogonal physicochemical and biological tests to determine the primary, secondary, and higher-order structure, post-translational modifications (PTMs) and associated heterogeneities, glycosylation, charge variants, purity/impurities, and quantity of Riximyo. The control of the AS and FP is considered sufficient.

The TSE virus safety of the finished product has been sufficiently demonstrated. Riximyo has been developed as a similar biological medicinal product to the European Union (EU)-authorised reference product MabThera (rituximab). Overall the analytical comparability data suggest that Riximyo can be considered biosimilar to the reference product. The applicant performed an extensive and structured comparability exercise in order to demonstrate analytical comparability and justify biosimilarity. This comparability exercise is supported by a risk based CQA assessment, in order to rank the attributes and assess the impact if ranges do not overlap. The comparability exercise includes different batches of reference product, and batches of the biosimilar. Most tests directly support analytical comparability, because ranges of the biosimilar are within the ranges for the reference product. In a number of cases, it is justified that ranges do not overlap because the biosimilar contains less product-related substances/impurities (e.g. aggregates).

In summary, from a quality perspective, it is considered that similarity between Riximyo and the reference product was shown. Minor differences were identified, which are not considered to impact efficacy and safety of the product nor preclude biosimilarity.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety. Based on the comprehensive analytical comparability exercise, similarity between Riximyo and the reference medicinal product is considered demonstrated on quality level. As the US authorised Rituxan has been used in addition to the reference product for pre-clinical studies, investigation of Rituxan batches were also included in the analytical similarity exercise and it can be concluded that bridging between the US comparator and the EU reference product is acceptable.

## 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

It is recommended that the active substance and finished product specifications will be re-evaluated after an appropriate and agreed number of batches becomes available using statistical tools, as

already committed by the applicant.

## *2.3. Non-clinical aspects*

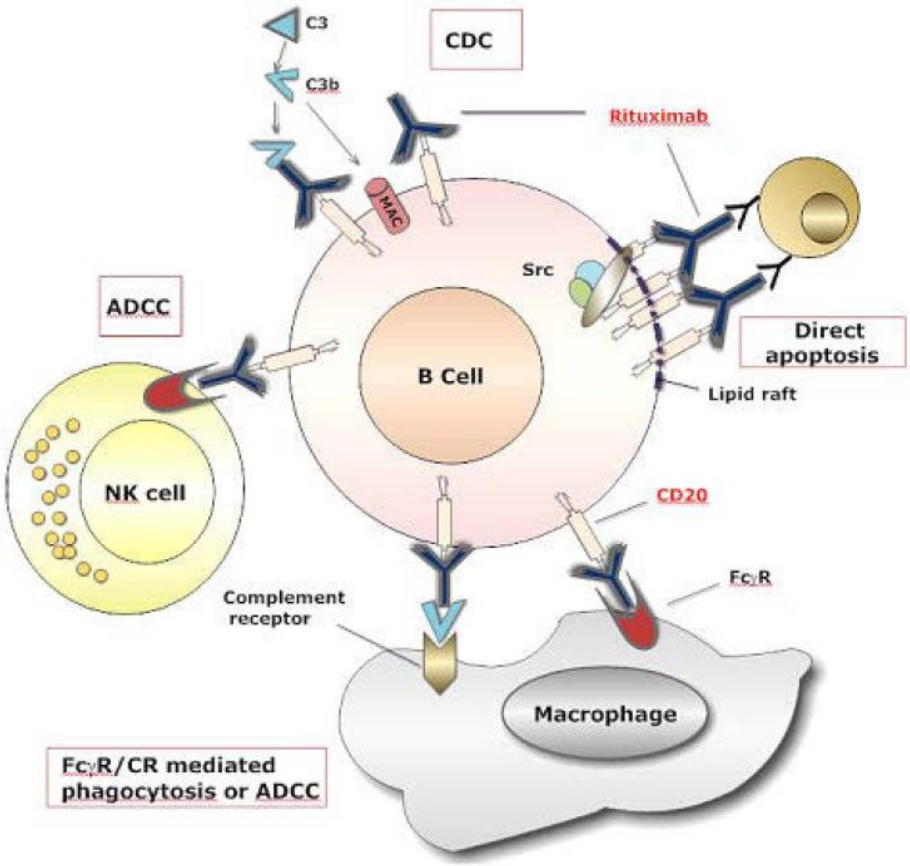
### 2.3.1. Introduction

Non-clinical animal studies included a series of studies to characterize and compare the non-clinical pharmacodynamics (PD), pharmacokinetics (PK), and safety profiles of Riximyo and MabThera including two pivotal GLP studies. The Applicant also submitted data from studies in two xenografted tumour models in mice.

### 2.3.2. Pharmacology

***Primary pharmacodynamic studies***

Rituximab binds specifically to the transmembrane antigen CD20, a non-glycosylated phosphoprotein expressed on the surface of pre-B and mature B lymphocytes, but not on hematopoietic stem cells and terminally differentiated antibody-producing plasma cells, or other tissues. While the Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, the Fc domain can recruit immune effector functions to mediate B cell lysis (resulting in B cell depletion), as well as modulating exposure. The ascribed mechanisms of effector-mediated cell lysis include antibody-dependent cellular cytotoxicity (ADCC); Complement-dependent cytotoxicity (CDC); Apoptosis and Macrophage-mediated antibody-dependent cellular phagocytosis (ADCP) – Figure 1.




- Rituximab coated B cells are killed by at least 4 different mechanisms. (A) Binding of rituximab to CD20 on B cell surface causes activation of the complement cascade, which generates the membrane attack complex (MAC) that can directly induce B-cell lysis by complement-mediated cytotoxicity (CDC). (B) Binding of rituximab allows interaction with NK cells via Fc receptors III (FcRIII), which leads to antibody-dependent cell-mediated cytotoxicity (ADCC). (C) The Fc portion of rituximab and the deposited complement fragments allow for recognition by both FcR and complement receptors on macrophages, which lead to phagocytosis and ADCC. (D) The crosslinking of several molecules of rituximab and CD20 in the lipid raft determine the interaction of these complexes with elements of a signaling pathway involving Src kinases that mediate direct apoptosis (From Jaglowski et al 2010).

**Figure 1 - Mechanisms of rituximab-mediated cell death.**

*In vitro pharmacodynamic studies*

*In* an *ex vivo* whole blood depletion assay (study GP13-021), collected human whole blood is incubated *ex vivo* with different concentrations ofRiximyo. After incubation, during which concentration-dependent B cell depletion occurs, distinct subsets of blood cells are stained with fluorescence-labelled detection antibodies and analysed on a flow cytometer. The concentration-dependent decrease of B cells within the lymphocyte populations is determined. Relative B cell depletion (BCD) is calculated. In this assay, Riximyo was shown to be similar to Rituxan and MabThera in its ability to deplete B cells, with all tested batch samples of Riximyo displaying similar biological activity at equivalent concentrations.

Study GP13-017 compared Riximyo and MabThera for *in vitro* ADCC potency of freshly-isolated human peripheral blood NK cells as the effector cells against different immortalized B cell lines and the overall results indicated that Riximyo and MabThera were similar in their ability to mediate ADCC in these cell lines. The results from study GP13-022, which was an extension of GP13-017 using one B cell line,

indicated a comparable range of EC50 values (relative to a reference standard) for MabThera and Riximyo.

The Applicant also assessed the depletion of a B cell line by Riximyo, MabThera, and Rituxan mediated by freshly isolated human PBMC. This dataset, albeit limited, confirmed comparable activity of Riximyo and the reference medicinal product.

*In vivo pharmacodynamic studies*

The pharmacodynamic effects of Rixiymo and MabThera were compared in C*ynomolgus monkeys*. After single dose iv administration of 5 mg/kg, the AUEC ratio was similar for the first 7 days, but when the whole 28 days observation period was compared the effect of Riximyo was slightly less than of Mabthera (AUEC ratio 0.92; 95% CI 0.87-0.98) for the $CD20^{low}$ B-cells, which are considered more close to human CD20 cells. For the $CD20^{high}$ B-cells, the AUEC ratio of 1 was within the 95% CI (AUEC ratio 0.94; 95% CI 0.88-1.01).

In the repeated dose toxicology study the same PD parameters were evaluated after 4 weekly iv administrations of 20 or 100 mg/kg. With these dose regimens no significant differences were observed.

In study GP13-015, a slight, but non-significant difference in survival was observed in SCID mice injected with Granta-519 cells from human mantle cell lymphoma cell line treated with 40 mg/kg Riximyo(group 3; mean survival ± S.D.: 34.9 ± 3.74 days) and 40 mg/kg Mabthera (group 5; mean survival ± S.D.: 36.1 ± 2.63 days).

In study GP13-018, where SCID mice were injected with Raji human Burkitt lymphoma cells, 1.25 mg/kg Riximyo was significantly more effective than 1.25 mg/kg MabThera (P = 0.0485). Differences between the agents at the lower and higher dose levels were non-significant and overall no dose-dependency was observed.

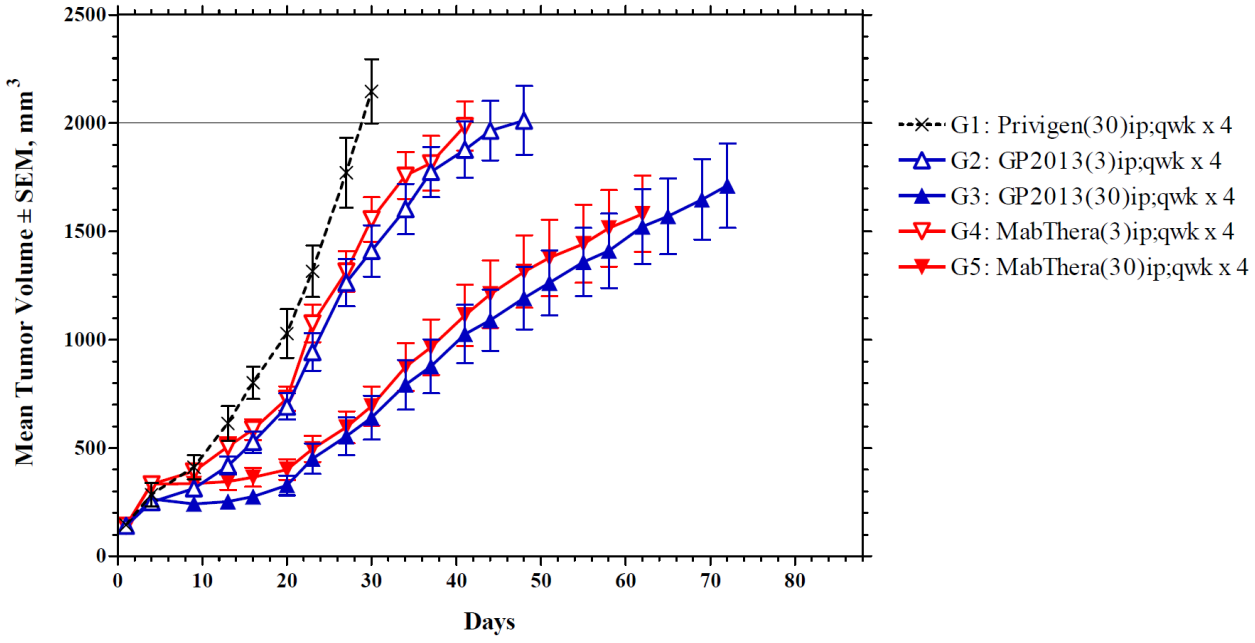
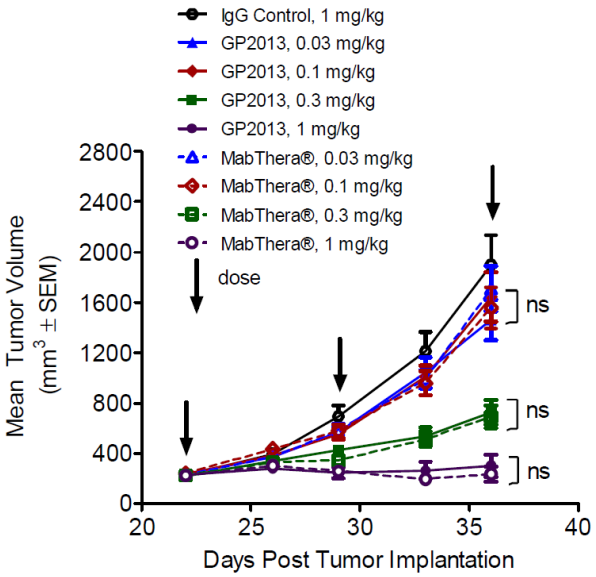



**Figure 2 - Study GP13-011 Mean Tumour Growth in SU-DHL-4-model: *In vivo* comparability of Riximyo and MabThera**




*Dose-response effects of* Riximyo *and MabThera in human mantle cell lymphoma Jeko-1 xenograft tumours.* Female SCID beige mice were implanted subcutaneously with Jeko-1 cells into the right flank. When tumours reached a certain size, mice were dosed with either Privigen (IgG control antibody) or Riximyo or MabThera at indicated doses. Arrows indicate dosing days.

**Figure 3 - Study GP13-014 Antitumour activity of Riximyo, MabThera, and Privigen (IgG control antibody) against subcutaneous Jeko-1 xenograft tumours**

Data from both Study GP13-011 and Study GP13-014 indicate that treatment with Riximyoor MabThera at sub-therapeutic dose levels results in comparable tumour growth inhibition in mouse xenograft models of NHL. The relative anti-tumour activity of Riximyoand MabThera remained comparable throughout the observation periods and at all tested dose levels in both studies, despite the increase in intra-group heterogeneity at later time points that is characteristic of these xenograft models.

**Secondary Pharmacodynamics**

Dedicated secondary PD studies have not been submitted (see discussion on non-clinical aspects).

There were no reports of toxicity caused by a lack of specificity for the primary target (i.e. there are no known off-target effects of rituximab) and there was no off-target binding of Riximyoin an in vitro cross-reactivity study performed in a comprehensive panel of human tissues.

**Safety Pharmacology**

Dedicated safety pharmacology studies have not been submitted (see discussion on non-clinical aspects).

## 2.3.3. Pharmacokinetics

Pharmacokinetic/toxicokinetic response was evaluated in C*ynomolgus monkeys* after a single 5 mg/kg dose for 9 days and after two weekly doses of 20 or 100 mg/kg for 14 days.

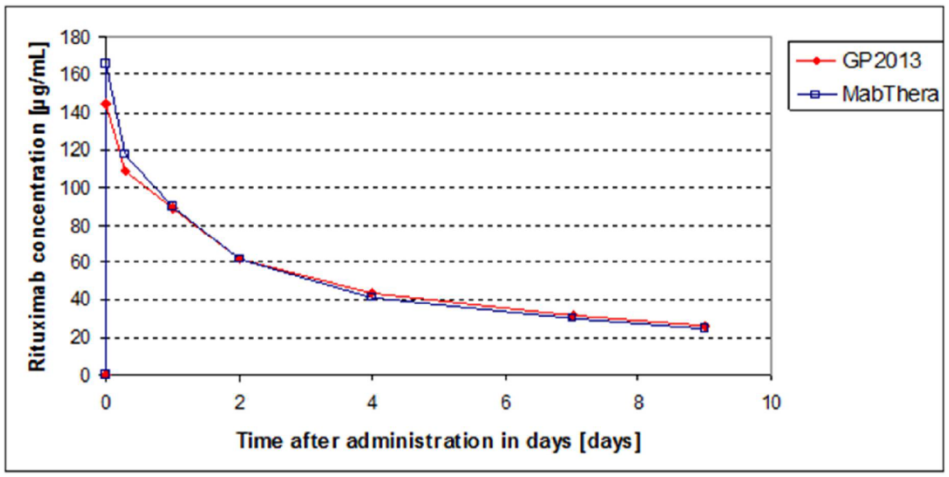



**Figure 4 - Study GP13-007: Geometric mean serum concentration of rituximab in male *cynomolgus monkeys* over nine days after a single intravenous dose of Riximyoor MabThera (5 mg/kg)**

**Table 2 Study GP13-007: Pharmacokinetic parameters in male *cynomolgus monkeys* after a single intravenous administration of Riximyoor MabThera (5 mg/kg)***

| Test Item | $t_{max}$ (days)#1 | $C_{max}$ (mcg/mL) | $AUC_{0-7d}$ (mcg*day/mL) | $AUC_{0-9d}$ (mcg*day/mL |
|---|---|---|---|---|
| GP2013, 5 mg/kg Geometric mean (CV%) | 0.0035 | 144.8 (87.7) | 400.5 (337.8) | 458.0 (391.2) |
| MabThera, 5 mg/kg Geometric mean (CV%) | 0.0035 | 165.7 (142.8) | 399.8 (327.8) | 454.0 (368.7) |
| Ratio GP2013/MabThera Geometric mean | 0#2 | 0.87 | 1.00 | 1.01 |
| 90% CI Lower limit | 0 | 0.79 | 0.93 | 0.94 |
| 90% CI Upper limit | 0 | 0.97 | 1.07 | 1.08 |

*: 14 animals per group

#1: Median values for time to reach maximum observed serum concentration ($t_{max}$) are reported.

#2: Ratio of this parameter was not determined; rather, the difference was determined between the time to reach maximum observed serum concentration ($t_{max}$) values for GP2013 and MabThera.

**Table 3 - Study GP13-008: Ratio of area under the serum concentration-time curves and of maximum serum concentration in *cynomolgus monkeys* after once-weekly repeated intravenous doses of Riximyo or MabThera**

| Dose | Observation period | Parameter | Ratio[#1, #2] GP2013/MabThera | 90% CI Lower limit | 90% CI Upper limit |
|---|---|---|---|---|---|
| 20 mg/kg | 0 to 7 days | $AUC_{0\text{-}7d}$ | 0.98 | 0.84 | 1.14 |
| | | $C_{max1}$ | 0.80 | 0.64 | 1.00 |
| | 0 to 14 days | $AUC_{0\text{-}14d}$ | 0.95 | 0.80 | 1.12 |
| | | $C_{max2}$ | 0.85 | 0.70 | 1.04 |
| | | $C_{max}$ | 0.82 | 0.68 | 0.99 |
| 100 mg/kg | 0 to 7 days | $AUC_{0\text{-}7d}$ | 1.00 | 0.85 | 1.18 |
| | | $C_{max1}$ | 0.90 | 0.66 | 1.23 |
| | 0 to 14 days | $AUC_{0\text{-}14d}$ | 1.01 | 0.84 | 1.22 |
| | | $C_{max2}$ | 0.95 | 0.76 | 1.20 |
| | | $C_{max}$ | 0.94 | 0.74 | 1.20 |

[#1]: Ratio of geometric means of area under the serum concentration-time curves and of maximum serum concentration for GP2013 and MabThera, and the corresponding lower and upper limits of the 90% confidence intervals.

[#2]: Data from 4 animals/sex/group

## 2.3.4. Toxicology

***Single dose toxicity***

No dedicated single-dose toxicity studies were performed forRiximyo.

In a single dose PK/PD study in male *cynomolgus monkeys* a dose of 5 mg/kg of each product was administered i.v. to 14 animals per group. Both test items showed comparable safety profiles consistent with the pharmacology of rituximab when evaluated for up to ten weeks following dose administration.

***Repeat dose toxicity***

***Study GP13-008 Riximyo / MabThera: Comparative repeated dose toxicity study in cynomolgus monkeys***

This was a 4 week study with the purpose to compare the safety profile of Riximyo(commercial scale quality), to that of MabThera, following repeated iv administration to *cynomolgus monkeys* on the days 1, 8, 15, and 22 of the study period plus a 4-week dosing-free period, and, in a subset of the animals, to assess comparability of the reversibility of the effects observed during a 6 month recovery phase.

There were no detectable differences between test and reference item. Neither substance induced any toxicologically relevant findings in weekly dosing of 20 or 100 mg/kg for 4 weeks. Pharmacological findings were a massive but not total reduction of B lymphocytes starting on day 2 of dosing, which resulted in shifted immunophenotyping values and correlated with lacking germinal centres in lymphatic organs, accessory in single animals a lymphoid depletion of spleen or axillary lymph node. The recovery of B cell reduction was seen in all groups and comparable in test and reference item

dosed animals. The no observed adverse effect level (NOAEL) can be defined at the high dose of 100 mg/kg for the test item.

Immunogenicity evaluations were included in the comparative single- and repeat-dose studies with Riximyo and MabThera. In both studies, *cynomolgus monkey* serum samples were analysed for the presence of anti-rituximab antibodies using an ELISA method.

In the single-dose study all animals developed anti-rituximab antibodies between nine to 14 days after treatment with either Riximyo or MabThera, each of which was evaluated at a dose of 5 mg/kg.

In the comparative repeat-dose toxicity study the number of animals that developed anti-rituximab antibodies were comparable at equivalent dose levels of Riximyo and MabThera. Anti-rituximab antibodies were detected in the 20 mg/kg Riximyo and MabThera groups starting on Day 15 (or 14 days after the first dose); as a result, TK analyses were only performed up to Day 15. Antibodies were directed against the murine F(ab')2 fragment of the drug and/or the Fc fragment of the drug. In the 100 mg/kg treatment groups, most of the animals showed no (or only a marginal) immune response, which was likely a result of rapid and marked depletion of B cells and/or a high drug concentration-induced tolerance.

***Genotoxicity***

Dedicated genotoxicity studies have not been submitted (see discussion on non-clinical aspects).

***Carcinogenicity***

Dedicated carcinogenicity studies have not been submitted (see discussion on non-clinical aspects).

***Reproduction Toxicity***

Dedicated reproductive and developmental toxicity studies have not been submitted (see discussion on non-clinical aspects).

***Toxicokinetic data***

Toxicokinetic data have not been submitted.

***Local Tolerance***

No injection site findings were noted in the repeat-dose i.v. toxicity study in which Riximyo or MabThera were administered to monkeys once-weekly for four weeks.

***Other toxicity studies***

No other toxicity studies were submitted.

## 2.3.5. Ecotoxicity/environmental risk assessment

N/A – see discussion on non-clinical aspects

## 2.3.6. Discussion on non-clinical aspects

According to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1, the applicant used a stepwise approach in order to demonstrate the Riximyo is comparable to MabThera with respect to PD/PK and toxicity.

Studies regarding secondary pharmacology, safety pharmacology, reproduction toxicology, and carcinogenicity and on local tolerance are not required for non-clinical testing of biosimilars.

A comprehensive program of studies provided extensive data that indicate an overall comparability between Riximyo and MabThera. Physicochemical assays have indicated that Riximyo is comparable to MabThera/Rituxan with regard to primary and higher order structure, post-translational modifications, and size variants. Functional characterisation included CD20 binding, C1q binding, and surface plasmon resonance (SPR) Fc receptor affinity assays complemented by in vitro cell-based bioassays (ADCC assay, CDC assay, apoptosis assay).

Additional whole blood and ADCC potency *in vitro* non-clinical studies were conducted and B cell depletion and ADCC potency of Riximyo was compared to both MabThera and Rituxan. Comparable B-cell depletion was demonstrated. Different ADCC assay formats were used and the overall data indicate that EC50 values are similar.

The ADCP assay is a Reporter Gene Assay (RGA) in which FcγRIIa-mediated activation of nuclear factor of activated T-cells (NFAT) is measured through the luciferase gene expression. The FcγRIIa-receptor is considered an important mediator in eliciting ADCP when phagocytes interact with antibody-opsonised target cells. Other Fcγ-receptors are expressed as well by macrophages. However their contribution to ADCP is less certain. Furthermore, the functional activity of FcγRIIIa has already been captured by the comparative ADCC assays performed by the Applicant. The ADCP assay developed by the Applicant is considered appropriate to evaluate and compare the ADCP activity of Riximyo, Mabthera and Rituxan. The results of the ADCP assay support the conclusion of biosimilarity.

Data submitted in support of this application are related to the comparison between the biosimilar and the US rituximab (Rituxan); this approach was acceptable and relevant for the EU since the bridge between the US and EU product has been sufficiently justified from analytical studies, structural and functional data (see discussion on quality).

The PD profiles of Riximyo and MabThera were compared in a single-dose i.v. PK/PD and in a four-week repeat-dose i.v. toxicity study in healthy *Cynomolgus monkeys*.

The comparison of Riximyo and MabThera over 8 weeks revealed comparable AUECs for Riximyo and for MabThera for both B cell subpopulations with ratios around 1.0 for both B cell subpopulations. With respect to total exposure to rituximab, the results of the non-compartmental PK analysis confirmed bioequivalence between Riximyo and MabThera with similar AUCs and 90% CIs lying entirely within the standard bioequivalence acceptance range of 0.8 to 1.25.

The Applicant also included data from studies in two xenografted tumour models in mice. In these two different mouse xenograft models of human lymphomas both Riximyo and MabThera showed positive effects on animal survival compared to animals in the control groups. Animal survival was comparable between Riximyo and MabThera and clinical signs and body weight changes were comparable among all Riximyo and MabThera groups in both studies. Data from both studies demonstrate that treatment with Riximyo or MabThera results in comparable tumour growth inhibition in mouse xenograft models of NHL. In the SU-DHL-4 human B cell lymphoma CB17 SCID mouse xenograft model Riximyo

appeared to be slightly more active than MabThera during the dosing period. But the overall outcome shows that treatment with Riximyo or MabThera showed no significant differences in short-term and overall efficacy results, early tumour growth and progression, and relative anti-tumour efficacies.

Pharmacokinetic parameters were evaluated in the single dose study in monkeys and after once-weekly i.v. (bolus) administrations of Riximyoor MabThera to male and female monkeys at dose levels of 20 mg/kg or 100 mg/kg given over a four-week period. A competitive ELISA method for the bioanalysis of rituximab in cynomolgus monkey serum was validated. A lower limit of quantification (LLOQ) was established. The validated ELISA method is acceptable. The results show comparable PK profiles at equivalent dose levels when evaluated for up to 14 days following the initial dose administration. Lower Cmax values (by 6 to 20%) were observed for Riximyocompared to MabThera at both dose levels which were attributed to intrinsic heterogeneity among individual monkeys and variations in the initial sampling time point. The justification is considered sufficient since the analysis showed comparable AUC values for the two treatment groups at equivalent dose levels, with 90% CI ratios within the standard acceptance range of 0.8 to 1.25. Furthermore B cell depletion seems not to be impacted by the lower Cmax.

There were no signs of toxicity and no detectable differences between groups administered equivalent dose levels of Riximyoand MabThera in the four week repeat dose i.v. toxicity study in monkeys. The no observed adverse-effect level (NOAEL) for Riximyoin the four week study was reported to be 100 mg/kg, the highest dose level evaluated and which exceeds clinical dose levels of MabThera/Rituxan.

There was no off-target binding of Riximyo in an in vitro cross-reactivity study performed in a comprehensive panel of human tissues. All binding was related to the expected pharmacology of Riximyo and its ability to bind CD20 expressing B lymphocytes, consistent with the reversible effects that were observed on B cell numbers in the single and repeat dose studies in monkeys and with the beneficial effects of Riximyo in mouse xenograft human B cell models of NHL.

### 2.3.7. Conclusion on the non-clinical aspects

In the light of the overall *in vitro* and *in vivo* non-clinical data , Riximyo (rituximab) can be considered similar to the reference product Mabthera. The non-clinical information under section 5.3 of the Mabthera SmPC applies also to Riximyo.

## *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 4 - Tabular overview of clinical studies**

| Study No. | Study title | Study population | Treatment duration | Dosage and [batch numbers] |
|---|---|---|---|---|
| GP13-201 (Part I- comparing GP2013 vs. MabThera- included in the dossier)[1] (pivotal) | A randomized, double-blind, controlled study to evaluate PK, PD, safety and efficacy of GP2013 and rituximab in patients with active RA refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies | Patients with active RA<br>Total: N = 173 (149f, 24m)<br>GP2013: N = 86 (76f, 10m)<br>MabThera: N = 87 (73f, 14m)<br>Age mean (range) = 53.71 (21-82) years | 52 weeks plus up to 26-weeks after first infusion of second treatment, if necessary | GP2013 or MabThera: 1000 mg (10 mg/L in 500 mg (50 mL) single use vials), two single iv infusions, two weeks apart in combination with MTX<br>Optional 2nd course of GP2013 or MabThera after week 24 (2x 1000 mg i.v., 2 weeks apart) |
| GP13-301 (data until cut-off 10 Jul 2015 included in the dossier; (pivotal) | A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus cyclophosphamide, vincristine, prednisone vs. MabThera plus cyclophosphamide, vincristine, prednisone, followed by GP2013 or MabThera maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma (ASSIST-FL trial) | Patients with previously untreated, advanced stage FL<br>Combination phase: Total: 627 (2 of the 629 randomized patient were not treated);<br>Maintenance phase: Total: 462;<br>N (f/m) = 350/277<br>Age mean (range) = 56.9 (23–84) years | Up to 3 years (Combination Treatment Period: 6 months, Maintenance Treatment Period and/or Follow-up Period: 2.5 years). | Combination Treatment Period: Total 8 cycles of GP2013 or MabThera 375 mg/m² (10 mg/L in 500 mg (50 mL) single use vials) i.v. on Day 1 of each cycle +CVP administered every 21 days (±3 days)<br>Maintenance Treatment Period (patients with PR or CR after 8 cycles of combination treatment): 8 treatment cycles - GP2013 or MabThera 375 mg/m² i.v. administered every 3 months (±14 days) for a further 2 years[2]. |
| GP13-101 (supportive) | Phase I trial to assess the safety and pharmacokinetics of GP2013 monotherapy administered weekly in Japanese patients with CD20 positive low tumor burden indolent B-cell non-Hodgkin's lymphoma | Japanese patients with CD20 Positive low tumor burden indolent B-cell NHL<br>Total: 6;<br>N (f/m) = 4/2<br>Age mean (range) = 59 (41-69) years | 12 weeks (Treatment Period: 8 weeks, Follow-up Period: 30 days) | GP2013: 375 mg/m² (10 mg/L in 500 mg (50 mL) single use vials), single i.v. infusions on Day 1 of each week for up to 8 weeks |

CR = Complete response; CVP = cyclophosphamide, vincristine, prednisone; DMARDs = Disease modifying anti-rheumatic drugs; EU: European Union; f = female; FL = Follicular lymphoma; i.v. = intravenous(ly); m = male; MTX = Methotrexate; N = number of patients or subjects; NHL = non-Hodgkin's lymphoma; PK = Pharmacokinetics; PD = Pharmacodynamics; PR = Partial response; RA = Rheumatoid arthritis; TNF = Tumor necrosis factor

[1] Part II of GP13-201 study (comparison of GP2013 with Rituxan) is ongoing.

[2] For Italy only, consists of 12 treatment cycles of single agent GP2013/MabThera administered every 2 months (± 14 days) for a further 2 years

## 2.4.2. Pharmacokinetics

Three studies were submitted to support the pharmacokinetics part of the application: the pivotal study GP13-201-Part 1 compared the PK profiles of Riximyoand MabThera in patients with rheumatoid arthritis (RA), the supportive study GP13-301 compared the PK profiles of Riximyo and MabThera in a subset of patients with follicular lymphoma (FL) and the other supportive study GP13-101 compared the PK profiles of Riximyo and Rituxan studied in 6 Japanese patients with indolent Non-Hodgkin's lymphoma (NHL).

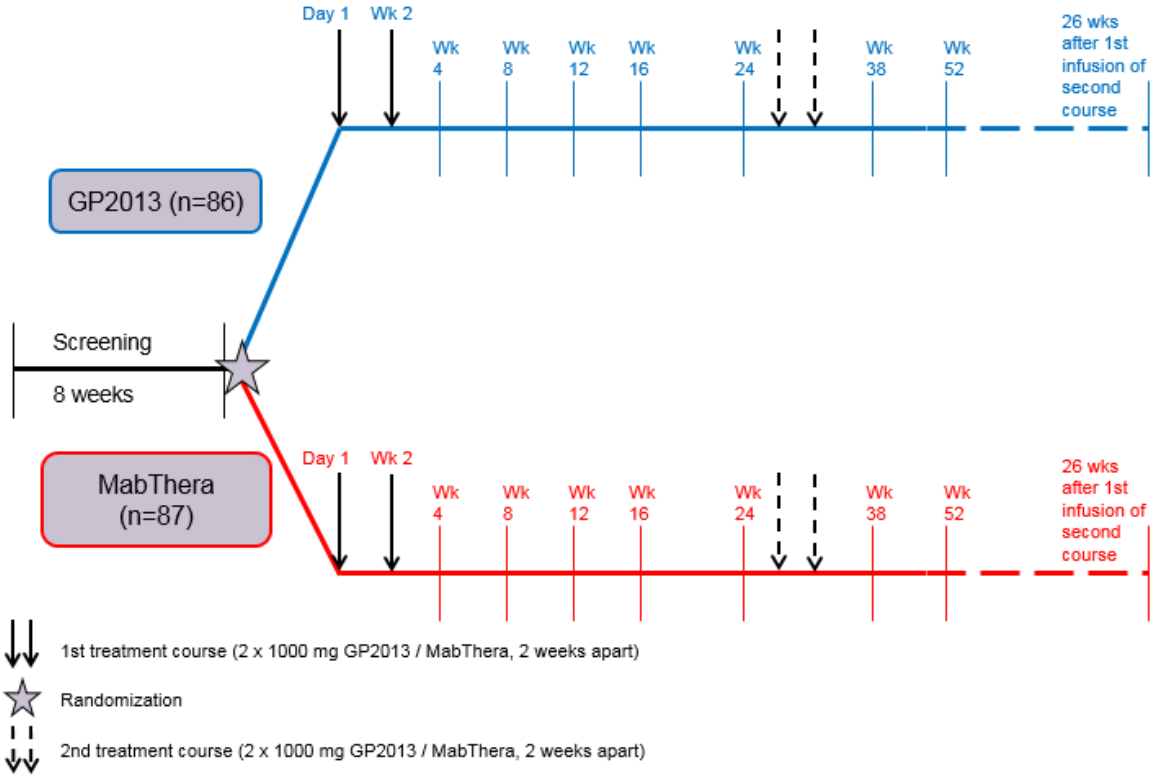
***Analytical methods***

ELISA was used for the determination of rituximab concentrations in human RA and FL serum. For the determination of immunogenicity an affinity capture elution (ACE) ELISA for detection of antibodies against rituximab in human RA serum and an electrochemiluminescence (ECL) bridging immunogenicity assay for detection of antibodies against rituximab in human FL serum were used. In order to determine neutralizing antibodies a cell-based complement-dependent cytotoxicity (CDC) assay for detection of neutralizing antibody (NAb) in RA serum and a cell-based competitive ligand binding assay (CLB) assay for detection of NAb in FL serum. The assay methods were validated separately using the respective patient-specific serum matrix (i.e. serum of RA and FL patients) as serum of patients suffering from either RA or FL can differ in their matrix composition.

***Pharmacokinetics in target population***

*Pivotal PK/PD bioequivalence study GP13-201 in patients with RA (GP13-201 Study Part I)*

The purpose of this clinical PK/PD study was to assess bioequivalence between Riximyo and EU-approved MabThera as well as US-licensed Rituxan in patients with active RA. Therefore the study was set up in two parts, Part I for assessing bioequivalence between Riximyo and MabThera and Part II for assessing bioequivalence between Riximyo and Rituxan. Study Part I is completed; an overview of the study design for Study Part I is shown in the figure below.




n=number of patients randomized; Wk=Week

**Figure 5 - Study design for GP13-201 Part 1**

The study included male and female patients ≥ 18 years of age with a ≥ 6 months' diagnosis of RA based on the American College of Rheumatology (ACR) 1987 criteria. Patients had to be seropositive for rheumatoid factor (RF) and/or anti-CCP antibodies, had an inadequate response or intolerance to non-biologic DMARDs and one or up to three TNF antagonists, and had been receiving MTX (7.5 mg to a maximum of 25 mg per week) for at least 4 months; stable dose for 4 weeks prior to randomization.

The eligible patients were randomized (1:1) to receive the first course of study medication (a 1000 mg i.v. infusion of Riximyo or MabThera on two separate occasions, two weeks apart (i.e., on Day 1 and on Day 15)). The duration of the first study drug infusion (Day 1) was approximately 4 h 15 min and the duration of the second study drug infusion (Day 15) was approximately 3 h 15 min (if the first infusion was uneventful). After the first treatment with study medication on Day 1, patients were followed for 52 weeks. Samples for comparative PK and PD assessments were collected until Week 24 and Week 52, respectively. Efficacy and safety data were assessed on a regular basis until Week 52 and were used to evaluate the similarity of the efficacy and safety between Riximyo and MabThera.

***Results***

A total of 302 patients were screened, of which 173 patients met the eligibility criteria and were randomized to either Riximyo (n=86) or MabThera (n=87) treatment group. The majority of randomized patients (n=142, 82.1%) completed the study up to 52 weeks and few patients (n=31, 17.9%) discontinued the study. The most common reasons for premature discontinuation across both

treatment groups were adverse events (n=8, 4.6%), unsatisfactory therapeutic effect (n=8, 4.6%) and withdrawal of consent (n=6, 3.5%).

All patients in the Full Analysis Set (FAS = 86 patients for study drug, 87 patients for Mabthera) received study drug at least once and are therefore also included in the Safety (SAF) Analysis Set. Patients with major protocol deviations such as C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) values who did not meet the criteria either at baseline or at the unscheduled reassessment visit, patients having negative RF and negative ACPA at the screening visit or patients not been treated with randomized treatment, were excluded from the PK or Per Protocol (PP = 85 for study drug, 82 patients for Mabthera) or both analysis sets. Pharmacokinetic analysis Set (PAS; 86 patients for study drug, 86 patients for Mabthera) was used for the analyses of PK, PD parameters.

**Baseline and disease characteristics**

**Table 5 - Demographics by treatment (Full Analysis Set)**

| Variable category / Statistics | GP2013 N=86 | MabThera® N=87 | Total N=173 |
|---|---|---|---|
| Age (years) | | | |
| n | 86 | 87 | 173 |
| Mean | 54.72 | 52.71 | 53.71 |
| SD | 12.135 | 12.531 | 12.341 |
| Median | 54.50 | 54.00 | 54.00 |
| Min | 26.0 | 21.0 | 21.0 |
| Max | 82.0 | 79.0 | 82.0 |
| Age groups - n(% ) | | | |
| 18-<45 | 15 (17.4) | 21 (24.1) | 36 (20.8) |
| 45-<65 | 51 (59.3) | 50 (57.5) | 101 (58.4) |
| ≥ 65 | 20 (23.3) | 16 (18.4) | 36 (20.8) |
| Sex - n(% ) | | | |
| Female | 76(88.4) | 73(83.9) | 149(86.1) |
| Male | 10(11.6) | 14(16.1) | 24(13.9) |
| Predominant race - n(% ) | | | |
| Caucasian | 72 (83.7) | 68 (78.2) | 140 (80.9) |
| Black | 1 (1.2) | 6 (6.9) | 7 (4.0) |
| Asian | 12 (14.0) | 12 (13.8) | 24 (13.9) |
| Native American | 0 (0.0) | 1 (1.1) | 1 (0.6) |
| Other | 1 (1.2) | 0 (0.0) | 1 (0.6) |
| Weight (Kg) | | | |
| n | 86 | 86 | 172 |
| Mean | 71.71 | 72.47 | 72.09 |
| SD | 16.635 | 17.171 | 16.860 |
| Median | 68.50 | 69.40 | 69.10 |
| Min | 42.0 | 45.0 | 42.0 |
| Max | 139.4 | 128.0 | 139.4 |

| Variable category / Statistics | GP2013 N=86 | MabThera® N=87 | Total N=173 |
|---|---|---|---|
| BMI ($kg/m^2$) | | | |
| n | 86 | 85 | 171 |
| Mean | 27.20 | 27.25 | 27.23 |
| SD | 6.121 | 6.000 | 6.043 |
| Median | 26.35 | 27.20 | 26.60 |
| Min | 17.0 | 16.5 | 16.5 |
| Max | 47.7 | 48.2 | 48.2 |

1. Age is calculated at visit 1 using date of birth.
2. Body Mass Index: BMI ($kg/m^2$) = weight(kg)/[(height(cm)/100)$^2$].
Source: Table 14.1-3.1

**Table 6 - Baseline disease history by treatment (Full Analysis Set)**

| Variable Category / statistic | GP2013 N=86 | MabThera® N=87 | Total N=173 |
|---|---|---|---|
| **Duration of RA (years)** | | | |
| n | 86 | 86 | 172 |
| Mean | 9.34 | 10.81 | 10.07 |
| SD | 6.818 | 7.137 | 6.998 |
| Median | 7.81 | 8.68 | 8.12 |
| Min | 1.0 | 1.0 | 1.0 |
| Max | 34.0 | 32.1 | 34.0 |
| **Number of prior non-biologic DMARDs** | | | |
| 1 | 31 (36.0) | 30 (34.5) | 61 (35.3) |
| 2 | 29 (33.7) | 34 (39.1) | 63 (36.4) |
| >2 | 26 (30.2) | 23 (26.4) | 49 (28.3) |
| **Number of prior non-biologic DMARDs** | | | |
| n | 86 | 87 | 173 |
| Mean | 2.31 | 2.07 | 2.19 |
| SD | 1.784 | 1.076 | 1.472 |
| Median | 2.00 | 2.00 | 2.00 |
| Min | 1.0 | 1.0 | 1.0 |
| Max | 11.0 | 5.0 | 11.0 |
| **Number of prior anti-TNF therapy - n(%)** | | | |
| 1 | 72 (83.7) | 70 (80.5) | 142 (82.1) |
| 2 | 10 (11.6) | 16 (18.4) | 26 (15.0) |
| 3 | 4 (4.7) | 1 (1.1) | 5 (2.9) |
| **Functional status (ACR 1991) - n(%)** | | | |
| Class I | 6 (7.0) | 6 (6.9) | 12 (6.9) |
| Class II | 52 (60.5) | 55 (63.2) | 107 (61.8) |
| Class III | 28 (32.6) | 26 (29.9) | 54 (31.2) |

All patients received anti-TNFs and non-biologic DMARDs prior to entering the study. The most commonly reported prior RA-related medications (excluding anti- TNFs) were selective immunosuppressants (23.1%) and glucocorticoids (19.1%). Etanercept was the most frequently used (34.1%) prior TNF-α inhibitor, followed by adalimumab (23.1%) and infliximab (15.6%). There were no relevant differences between the treatment groups in the type or frequency of use of prior (discontinued) RA-related medications.

There were no relevant differences between the two treatment groups in terms of non RA related medications and significant non-drug therapies used (and discontinued) prior to start of study drug (Riximyo 10.5% and MabThera 10.3%).

One patient in the MabThera group was accidentally un-blinded by a study nurse via the IRT system on Day 32. The accidental un-blinding was recorded as a protocol deviation and the patient discontinued from the study. The patient was not excluded from any analysis set.

**Table 7 - Baseline disease characteristics by treatment (Full Analysis Set)**

| Variable<br>Category / Statistics | GP2013<br>N=86 | MabThera®<br>N=87 | Total<br>N=173 |
|---|---|---|---|
| **C-reactive protein (CRP) (mg/L)** | | | |
| N | 86 | 87 | 173 |
| Mean | 17.58 | 19.50 | 18.54 |
| SD | 19.481 | 20.880 | 20.161 |
| Median | 11.80 | 13.90 | 12.50 |
| Min | 0.3 | 0.3 | 0.3 |
| Max | 110.6 | 109.4 | 110.6 |
| **Erythrocyte sedimentation rate (ESR) (mm/h)** | | | |
| n | 86 | 87 | 173 |
| Mean | 49.79 | 46.38 | 48.08 |
| SD | 18.309 | 18.369 | 18.365 |
| Median | 45.50 | 42.00 | 43.00 |
| Min | 15.0 | 12.0 | 12.0 |
| Max | 105.0 | 100.0 | 105.0 |
| **Rheumatoid factor (RF) (kIU/L)** | | | |
| n | 86 | 87 | 173 |
| Mean | 146.95 | 145.50 | 146.22 |
| SD | 178.176 | 152.346 | 165.209 |
| Median | 74.50 | 106.20 | 88.60 |
| Min | 10.1 | 8.0 | 8.0 |
| Max | 879.9 | 679.4 | 879.9 |
| **Anti-CCP antibodies (ACPA) (U/mL)** | | | |
| n | 86 | 86 | 172 |
| Mean | 329.00 | 286.29 | 307.65 |
| SD | 189.649 | 196.952 | 193.955 |
| Median | 413.00 | 309.50 | 365.00 |
| Min | 4.0 | 4.0 | 4.0 |
| Max | 500.0 | 500.0 | 500.0 |
| **Dose of methotrexate (at baseline; mg/week)** | | | |
| n | 82 | 82 | 164 |
| Mean | 14.59 | 14.72 | 14.66 |
| SD | 4.618 | 5.200 | 4.903 |
| Median | 15.00 | 15.00 | 15.00 |
| Min | 6.0 | 0.0 | 0.0 |
| Max | 25.0 | 25.0 | 25.0 |

The mean DAS28 (CRP) scores at baseline were 5.81 (SD=0.916) and 5.85 (SD=0.880), in the Riximyo and MabThera groups, respectively. The proportions of patients with positive anti-CCP antibodies (ACPA) and/or rheumatoid factor (RF) were similar, approximately 98% in both treatment arms. The mean steroid and methotrexate (MTX) doses taken were nearly identical between the treatment arms at baseline.

**Primary objective (GP13-201 Study Part I)**

The primary PK endpoint was AUC(0-inf) in serum samples, collected over 24 weeks. The ratio of the geometric means (Riximyo/MabThera) of AUC(0-inf) of serum concentration up to Week 24 was 1.064 and the 90% CI [0.968, 1.169] which was within the standard bioequivalence limits.

**Table 8 - AUC(0-inf) of serum concentration-time profile: Comparison between Riximyo and MabThera using ANOVA - GP13-201 Study Part I (PAS)**

| | | | | | Treatment Comparison | |
|---|---|---|---|---|---|---|
| PK Parameter (unit) | Treatment | n | Adjusted Geometric mean | Comparison | Geometric mean ratio | 90% CI of mean ratio |
| $AUC_{(0\text{-inf})}$ (day*mcg/mL) | GP2013 | 75 | 6738.51 | GP2013/ MabThera | 1.064 | [0.968, 1.169] |
| | MabThera | 70 | 6334.41 | | | |

n = number of patients with non-missing values

ANCOVA = Analysis of covariance; $AUC_{(0\text{-Inf})}$ = Area under the serum concentration-time curve from time zero to infinity; CI = Confidence interval; PAS = PK Analysis Set; PK=Pharmacokinetics

Ratio of geometric means and 90% confidence interval were estimated by an analysis of variance (ANOVA) on log-transformed PK parameter with treatment as the factor and gender (male/female) as a cofactor (while described in the CSR as an ANCOVA, the model did not account for any continuous independent variables). Results were then back-transformed to the original scale.

To conclude bioequivalence the 90% CI must be entirely within the standard bioequivalence limits of [0.8, 1.25].

PK concentrations below the limit of quantification (0.8 mcg/mL) were treated as zero for the calculation of pharmacokinetic parameters.

No imputation of missing values was performed.

A sensitivity analysis including body surface area as an additional covariate provided similar results. The ratio of the geometric means (Riximyo/MabThera) was 1.054.

The corresponding 90% CI (0.965, 1.151) was within the standard bioequivalence limits.

Following the first treatment course of Riximyo and MabThera, the overall exposure, AUC(0-inf), was comparable between the Riximyo and MabThera treatment arms and the mean serum concentration-time profiles over 24 weeks were nearly superimposable.

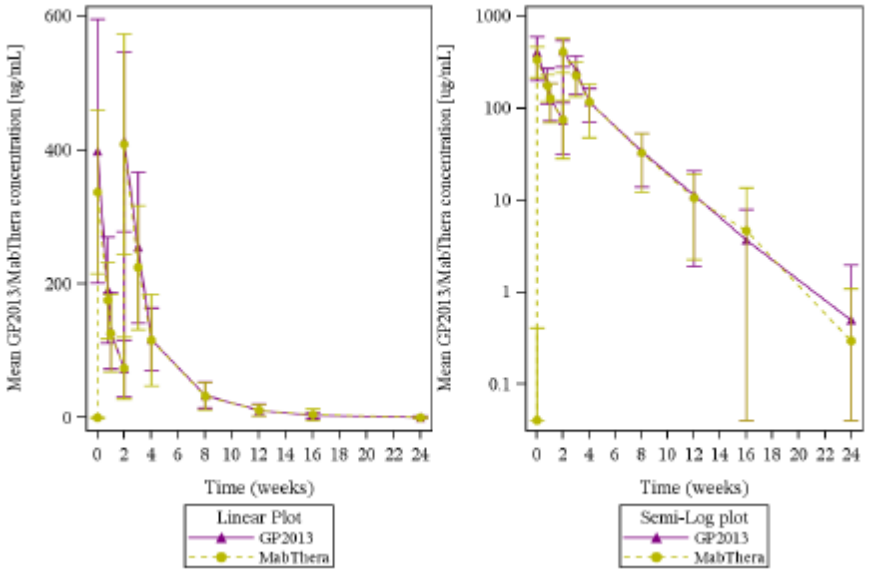



**Figure 6 - Arithmetic mean (SD) serum PK concentration-time profile over 24 weeks by treatment (PK Analysis Set)**

Summary statistics for primary PK parameter (AUC(0-inf)) by treatment are provided in Table 9.

**Table 9 - Summary of primary PK parameter by treatment - GP13-201 Study Part I (PAS)**

| Parameter | Statistics | GP2013 N= 86 | MabThera N= 86 |
|---|---|---|---|
| $AUC_{(0\text{-}inf)}$ (day*mcg/mL) | n | 75 | 70 |
| | Mean (SD) | 8005.04 (2653.757) | 7563.06 (3000.580) |
| | CV% mean | 33.15 | 39.67 |
| | Geometric mean | 7582.73 | 7046.23 |
| | CV% geometric mean | 34.25 | 39.54 |
| | Median | 7633.41 | 7441.26 |
| | Minimum - Maximum | 3973.1 - 13648.2 | 2054.7 - 20614.9 |

A number of patients were excluded from the analyses: for $AUC_{0\text{-}inf}$ (GP2013: n=11/86 (12.8%), MabThera: 16/87 (18.4%)) and for $AUEC_{0\text{-}14d}$ (GP2013: n=14/86 (16.3%), MabThera: 11/87 (12.6%)). The most common reason of exclusion of patients was positive ADA prior to or up to Week 24 and missing data noted to the extent that the parameter could not be derived. A number of patients were excluded from the analyses for $C_{max}1$ (GP2013: n=7/86 (8.1%), MabThera: 9/87 (10.3%)). The most common reason for exclusion of patients from the $C_{max}1$ analysis was that the post-infusion sample was not taken within 15 minutes of end of infusion, positive ADA at pretreatment and infusion interruption greater than 1 hr during the first infusion.

**Secondary PK results (GP13-201 Study Part I)**

Key Secondary endpoint Cmax1

The key secondary PK endpoint was a comparison of the maximum serum concentrations of Riximyo and MabThera after the 1st infusion (Cmax1). Bioequivalence was defined and analysed similar to the primary endpoint (AUC(0-inf)). The ratio of the geometric means (Riximyo/MabThera) was 1.133 and the corresponding 90% CI was [1.017, 1.262] with its upper limit slightly outside the standard bioequivalence limits [0.8, 1.25] (Table 10). Cmax2 was within the standard bioequivalence limits [0.8, 1.25].

**Table 10 - Serum Cmax (first infusion): Comparison between Riximyo and MabThera using ANOVA - GP13-201 Study Part I (PK Analysis Set)**

| | | | | | Treatment comparison | |
|---|---|---|---|---|---|---|
| PK parameter (unit) | Treatment | n | Adjusted Geometric mean | Comparison | Geometric mean ratio | 90% CI of mean ratio |
| $C_{max}1$ (mcg/mL) | GP2013 | 79 | 341.67 | GP2013/MabThera | 1.133 | [1.017, 1.262] |
| | MabThera | 77 | 301.62 | | | |

n = number of patients with non-missing values
ANCOVA = Analysis of covariance; $C_{max}1$ = The maximum serum concentration of rituximab after the first infusion in the first treatment course; CI = Confidence interval; PK = Pharmacokinetics
Ratio of geometric means and 90% confidence interval were estimated by an analysis of variance (ANOVA) on log-transformed PK parameter with treatment as the factor and gender (male/female) as a cofactor (while described in the CSR as an ANCOVA, the model did not account for any continuous independent variables). Results were then back-transformed to the original scale.
To conclude bioequivalence the 90% CI must be entirely within the standard bioequivalence limits of [0.8,1.25].
PK concentrations below the limit of quantification (0.8 mcg/mL) were treated as zero for the calculation of pharmacokinetic parameters.
No imputation of missing values was performed.

When studying study drug administration and compliance, the two treatment arms behaved similarly (e.g. regarding number of infusions, duration, volume of infusion.) regarding interruptions, more patients in both treatment arms experienced infusion interruptions during the first infusion (total of 26 (15.0%) patients) as compared to the second infusion (total of 12 (7.1%) patients). When comparing both treatment arms, there were more infusion interruptions in the MabThera arm (17.2% versus 12.9% for the first infusion of the first course) and 9.1% versus 4.7% for the second infusion of the first course, respectively. Similar observation was made for the second course.

Other secondary endpoints

The bioequivalence criteria were also met for all secondary AUC parameters (AUC(0-14d), AUC(0-12w), and AUC(0-24w) and Tmax (for both infusions, i.e. Tmax1 and Tmax2) as shown in Table 11.

**Table 11 - Additional PK parameters (AUCs, Cmax and Tmax): Comparison between Riximyo and MabThera using ANOVA - GP13-201 Study Part I (PAS)**

| | | | | Treatment Comparison | | |
|---|---|---|---|---|---|---|
| PK parameter (unit) | Treatment | n | Adjusted Geometric mean | Comparison | Geometric mean ratio | 90% CI of mean ratio |
| $AUC_{(0-14d)}$ (day* mcg/mL) | GP2013 | 78 | 1955.45 | GP2013/ MabThera | 1.106 | [1.010, 1.210] |
| | MabThera | 74 | 1768.78 | | | |
| $AUC_{(0-12w)}$ (day* mcg/mL) | GP2013 | 76 | 6575.23 | GP2013/ MabThera | 1.091 | [0.988, 1.205] |
| | MabThera | 72 | 6024.81 | | | |
| $AUC_{(0-24w)}$ (day* mcg/mL) | GP2013 | 73 | 6696.36 | GP2013/ MabThera | 1.087 | [0.980, 1.206] |
| | MabThera | 72 | 6159.42 | | | |
| $C_{max}2$ ($2^{nd}$ inf) (mcg/mL) | GP2013 | 76 | 386.22 | GP2013/ MabThera | 1.036 | [0.944, 1.138] |
| | MabThera | 75 | 372.63 | | | |
| $T_{max}1$ ($1^{st}$ inf) (h) | GP2013 | 79 | 4.42 | GP2013/ MabThera | -0.083 | [-0.167, -0.017] |
| | MabThera | 77 | 4.33 | | | |
| $T_{max}2$ ($2^{nd}$ inf) (h) | GP2013 | 76 | 3.43 | GP2013/ MabThera | 0.000 | [-0.083, 0.150] |
| | MabThera | 75 | 3.45 | | | |

n = number of patients with non-missing values

***PK/PD - Pivotal clinical efficacy and safety study in patients with FL (study GP13-301)***

This was a randomised, double-blind, active-controlled, multicenter, parallel group study to compare the efficacy, safety, PK and PD of Riximyo/MabThera in combination with cyclophosphamide, vincristine, prednisone (CVP), followed by Riximyo/MabThera maintenance therapy in patients with previously untreated, advanced stage FL. The study comprised four periods: Screening (up to 28 days prior to randomization), Combination Treatment (8 cycles; approximately 6 months), Maintenance Treatment (2 years) and Follow up (3 years from the date of randomization) (see Figure 7 below).

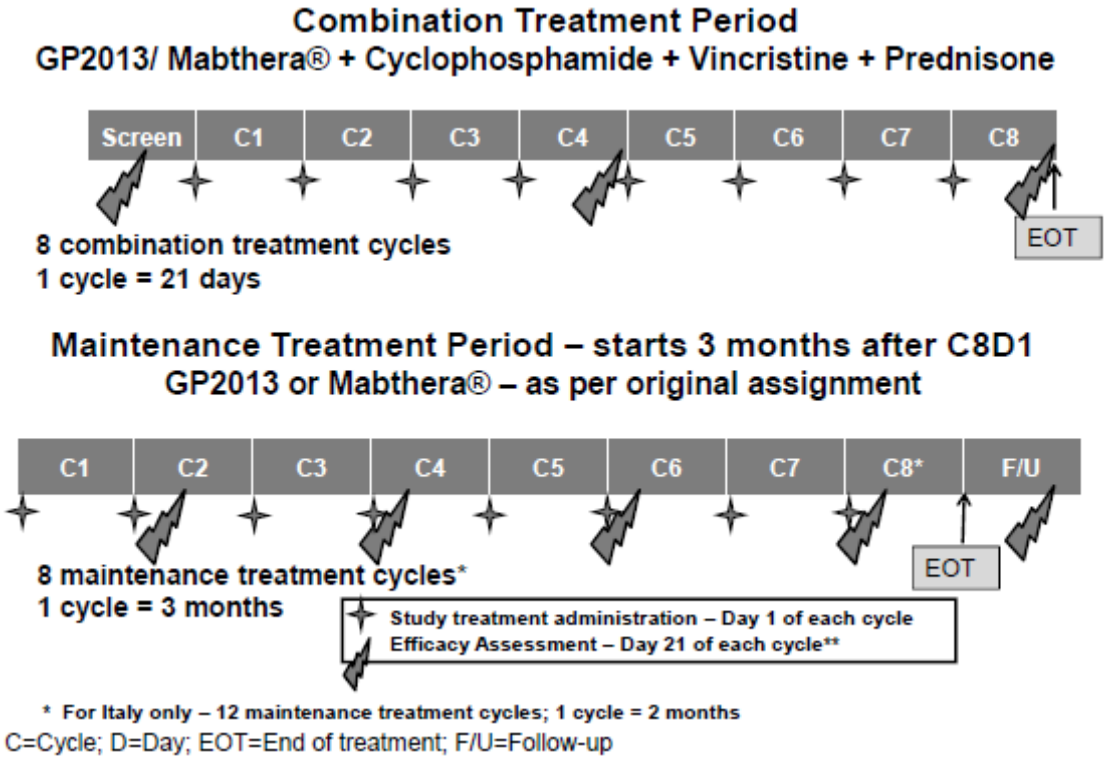



**Figure 7 - treatment scheme in study GP13-301**

After fulfilling the eligibility criteria evaluated during the screening period, the patients were randomised in a 1:1 ratio to receive 8 cycles of either Riximyo with CVP or MabThera with CVP in the combination treatment phase of the study (Table 12).

**Table 12 - Combination treatment arms - study GP13-301**

| Arm 1 – Investigational Treatment Arm | Arm 2 - Control Arm |
|---|---|
| **GP2013** (375 mg/m² i.v. on Day 1)<br>**Cyclophosphamide** (750 mg/m² i.v. on Day 1)[1]<br>**Vincristine** (1.4 mg/m² (max dose 2 mg) i.v. on Day 1)[1]<br>**Prednisone**[2] (100 mg p.o. on Days 1-5) | **MabThera** (375 mg/m² i.v. on Day 1)<br>**Cyclophosphamide** (750 mg/m² i.v. on Day 1)[1]<br>**Vincristine** (1.4 mg/m² (max dose 2 mg) i.v. on Day 1)[1]<br>**Prednisone**[2] (100 mg p.o. on Days 1-5) |

i.v.= intravenous; p.o. = orally; max = maximum

[1] Cyclophosphamide and vincristine may be given on Day 2 if logistically not feasible on Day 1.
[2] Equal dose (100 mg) of prednisolone can be used instead of prednisone in a study country where prednisone is not commercially available.

Randomisation into the two treatment arms (Riximyo-CVP or MabThera-CVP) was stratified by Follicular Lymphoma International Prognostic Index (FLIPI) risk group (Solal-Celigny et al 2004) for low/intermediate risk (FLIPI score 0-2) vs. high risk (FLIPI score 3-5), geographic region (Asia Pacific, Latin America, Japan and Europe) and by participating cohort for PK data collection (Cohort 2: extensive PK sampling; Cohort 1 exclusive of Cohort 2: sparse PK sampling; rest of patients without PK sampling). An overview of PK/PD cohorts is diagrammatically presented in Figure 8.

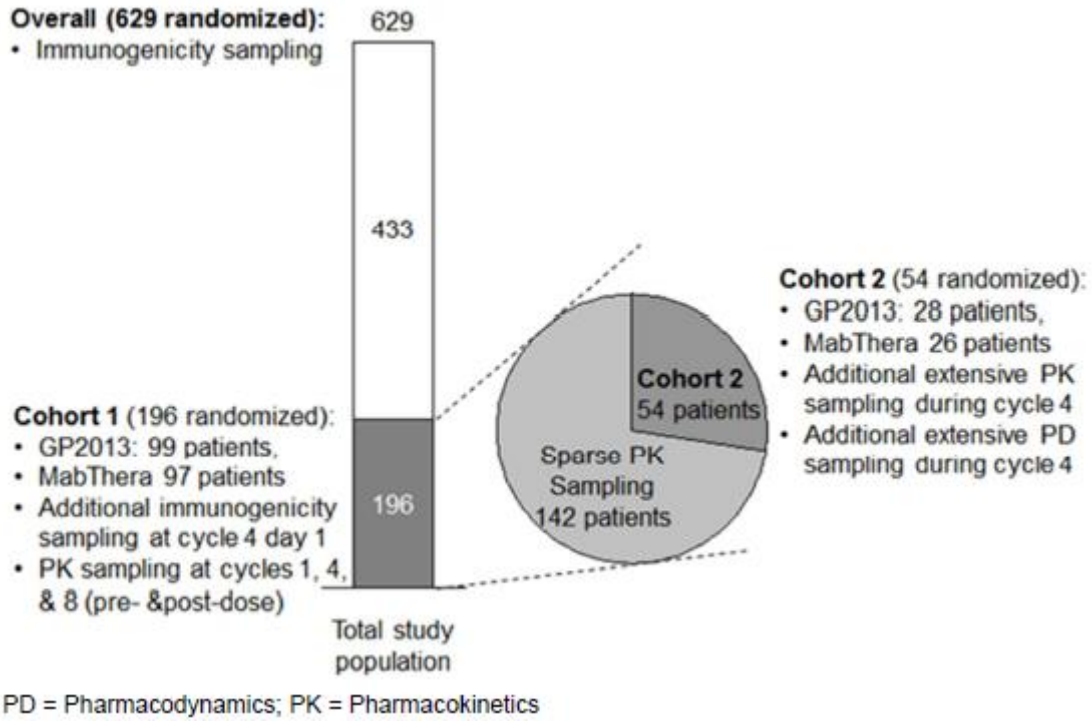



**Figure 8 - Overview of PK/PD cohorts in GP13-301 study**

196 patients were allocated to Cohort 1, in which sparse PK sampling, Ctrough and Cmax concentrations were taken for Cycles 1, 4 and 8. A further subgroup of Cohort 1 of 54 patients (approximately 20 patients per treatment arm), underwent more extensive PK sampling during Cycle 4 and pharmacodynamic sampling during Cycle 1 (Cohort 2).

The analysis sets used for the analyses of data locked on 30-Sep-2015 are summarised in Table 13.

**Table 13 - Analysis sets by treatment (Randomized set)**

| Analysis set | GP2013 N=314 n (%) | MabThera N=315 n (%) |
|---|---|---|
| Full analysis set (FAS) | 312 (99.4) | 315 ( 100) |
| Per protocol set (PP) | 311 (99.0) | 313 (99.4) |
| Safety set (SS) | 312 (99.4) | 315 ( 100) |
| Maintenance set | 231 (73.6) | 231 (73.3) |
| Pharmacokinetic analysis set 1 (PAS+A1)[1] | 119 (37.9) | 120 (38.1) |
| Pharmacokinetic analysis set 2 (PAS+A2)[1] | 27 ( 8.6) | 22 ( 7.0) |
| Pharmacodynamic analysis set (PDAS) | 24 ( 7.6) | 24 ( 7.6) |
| Immunogenicity analysis set | 268 (85.4) | 283 (89.8) |

[1] The two PK analysis set names with (+A1) and (+A2) reflect the inclusion of patients with confirmed positive immunogenicity in both sets.

Two PK analysis sets were defined for this analysis:

- The PAS+A1 (N=239) consisted of all patients in Cohort 1 (including Cohort 2 patients), who received at least one (partial or complete) dose of investigational treatment (Riximyo or MabThera) and had at least one evaluable PK sample collected and analysed. The PAS+A1 was used to present the descriptive statistics for Cmax and Ctrough of Riximyo and MabThera during Cycles 1, 4 and 8. Observed values of Cmax (end of infusion, EOI) and Ctrough (pre-

dose) were reported. Particularly, Cmax and Ctrough at steady state (Cycle 4) were assessed as secondary objectives.

- The PAS+A2 (N=49) consisted of all patients in Cohort 2, who received the investigational treatment (Riximyo or MabThera) and provided at least one evaluable PK sample after the Cycle 4 dose. A non-compartmental PK analysis of serum concentration time profile of Riximyo and MabThera was conducted based on PAS+A2 to obtain the AUC0-tau (AUC0-21days) and AUCall during Cycle 4 (near steady state). This subgroup also underwent PD sampling during Cycle 1.

**Results**

**Baseline characteristics**

Overall, baseline demographic and background characteristics were well balanced for the Riximyo and MabThera treatment arms and reflected the intended target population for the study.

The demographics were similar between the treatment arms in terms of age, gender, race or body surface area (BSA). The mean age of all patients was 56.9 years ranging between 23 to 84 years (57.5 years in Riximyo and 56.4 years in MabThera) and 46.1% of patients were ≥ 60 years of age (47.8% in Riximyo and 44.4% MabThera). More than half (58% in Riximyo and 53.7% MabThera) of patients in the FAS were female and approximately two-third (68.6% in Riximyo and 65.7% MabThera) of the total patients were Caucasian. The majority of patients (57.4% in Riximyo and 55.6% MabThera) had an Eastern Cooperative Oncology Group (ECOG) status of 0.

**Secondary objective (GP13-301 Study), PAS + A1**

The geometric mean and (CV% geometric mean) of the secondary endpoint Cmax at Cycle 4 Day 1 was 333.59 mcg/mL (41.09%) and 331.93 mcg/mL (35.32%) for the Riximyo and MabThera arms, respectively (Table 14). In addition to Cmax in Cycle 4, Cmax in Cycles 1 and 8 were also evaluated.

The geometric means ratio of Cmax at Cycle 4 Day 1 (Riximyo /MabThera) was 1.00 and the corresponding 90% CI was (0.925, 1.09). Based on the results, the Cmax at Cycle 4 Day 1 (near steady state) was similar between the Riximyo and MabThera arms. Also Cmax at Cycle 1 Day 1 and Cycle 8 Day 1 were similar between the Riximyo and MabThera arms.

**Table 14 - Summary of rituximab Cmax (mcg/mL), by treatment (Cohort 1) – study GP13-301 (PAS+A1)**

| Sampling time point | Statistics | GP2013 N=119 | MabThera N=120 |
|---|---|---|---|
| Cycle 4 assessment | | | |
| Day 1 (Cycle 4) | n | 108 | 111 |
| | Mean (SD) | 356.03 (121.612) | 350.99 (116.797) |
| | CV% mean | 34.158 | 33.276 |
| | Geometric mean | 333.59 | 331.93 |
| | CV% geometric mean | 41.09 | 35.32 |
| | Median | 349.7 | 331.3 |
| | Minimum - Maximum | 37.7-955.1 | 115.4-762.6 |
| Assessment at other cycles | | | |
| Day 1 (Cycle 1) | n | 105 | 104 |
| | Mean (SD) | 271.60 (95.799) | 281.18 (111.443) |
| | CV% mean | 35.272 | 39.634 |
| | Geometric mean | 252.28 | 258.16 |
| | CV% geometric mean | 44.65 | 46.87 |
| | Median | 267.1 | 267.6 |
| | Minimum - Maximum | 30.9-631.8 | 50.5-698.2 |
| Day 1 (Cycle 8) | n | 96 | 96 |
| | Mean (SD) | 391.11 (111.561) | 391.30 (125.511) |
| | CV% mean | 28.525 | 32.075 |
| | Geometric mean | 375.93 | 370.13 |
| | CV% geometric mean | 29.25 | 37.25 |
| | Median | 380.0 | 375.2 |
| | Minimum - Maximum | 136.4-811.8 | 55.5-918.9 |

$C_{max}$ = Maximum (peak) observed serum concentration of rituximab; CV% = Coefficient of variation (%) = sd/mean*100; PAS+A1 = Pharmacokinetic analysis set 1; SD = Standard deviation

CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Lower limit of quantification 28.9 mcg/mL

$C_{max}$ represents the measured rituximab concentration at the end of infusion at Cycles 1, 4 and 8

The secondary endpoint, mean Ctrough levels at Cycle 4 Day 1 evaluated in Cohort 1 was 66.42 mcg/mL (CV% 71.7 %) and 82.13 mcg/mL (CV% 74.9 %) for the Riximyoand MabThera arms, respectively. The Ctrough levels are similar in Cycle 4 Day 1 (around steady state) and Cycle 8 Day 1 and between Riximyoand MabThera and the data ranges in both arms largely overlap. The CV% was high (greater than 70% in Cycle 4) and this was due to the fact that many patients have Ctrough levels below the limit of detection and were reported as 0.

**Table 15 - Summary of rituximab Ctrough (mcg/mL), by treatment (Cohort 1) – study GP13-301 (PAS+A1)**

| Sampling time point | Statistics | GP2013 N=119 | MabThera N=120 | All Patients N=239 |
|---|---|---|---|---|
| Cycle 4 assessment | | | | |
| Day 1 (Cycle 4) | n | 104 | 110 | 214 |
| | k | 81 | 88 | 169 |
| | Mean (SD) | 66.42 (47.593) | 82.13 (61.526) | 74.50 (55.628) |
| | CV% mean | 71.659 | 74.909 | 74.673 |
| | Median | 67.0 | 81.0 | 74.6 |
| | [Min; Max] | [0.0; 177.9] | [0.0; 282.7] | [0.0; 282.7] |
| | [Q1; Q3] | [35.7; 97.6] | [45.0; 113.1] | [40.0; 105.5] |
| Assessment at other cycles | | | | |
| Day 1 (Cycle 1) | n | 111 | 110 | 221 |
| | k | 0 | 0 | 0 |
| | Mean (SD) | 0.00 (0.000) | 0.00 (0.000) | 0.00 (0.000) |
| | CV% mean | | | |
| | Median | 0.0 | 0.0 | 0.0 |
| | [Min; Max] | [0.0; 0.0] | [0.0; 0.0] | [0.0; 0.0] |
| | [Q1; Q3] | [0.0; 0.0] | [0.0; 0.0] | [0.0; 0.0] |
| Day 1 (Cycle 8) | n | 98 | 94 | 192 |
| | k | 93 | 85 | 178 |
| | Mean (SD) | 123.10 (59.048) | 127.19 (76.346) | 125.10 (67.919) |
| | CV% mean | 47.969 | 60.024 | 54.291 |
| | Median | 118.4 | 119.6 | 119.0 |
| | [Min; Max] | [0.0; 306.0] | [0.0; 444.9] | [0.0; 444.9] |
| | [Q1; Q3] | [90.2; 151.2] | [94.9; 155.2] | [90.9; 152.7] |

k = number of non-zero counts.
CV% = coefficient of variation (%) = sd/mean*100.
Lower limit of quantification 28.9 mcg/mL.
Ctrough represents the measured rituximab concentration prior to infusion at cycles 1, 4, and 8.

**GP13-301 Study: Secondary objective; PAS + A2**

The geometric mean (CV% geometric mean) for AUC(0-21d) during Cycle 4 evaluated in Cohort 2 was 3210 mcg*day/mL (27.5%) and 3340 mcg*day/mL (34.9%) for the Riximyo and MabThera treatment arms, respectively. Since many patients had rituximab concentrations below LLOQ at later time points of the Cycle 4 PK profile (e.g., 360 h after EOI or pre-dose Cycle 5), their AUC(0-21d) could not be accurately determined. In such cases, area under the curve from the time of dosing to the time of the last observation, regardless of whether the last concentration was measureable or not (AUCall) was used for exposure evaluation. The geometric mean (CV% geometric mean) for AUCall during Cycle 4 evaluated in Cohort 2 was 2510 mcg*day/mL (55.1%) and 2310 mcg*day/mL (109.1%) for the Riximyo and MabThera treatment arms, respectively. Based on the results, the AUC(0-21d) and AUCall are similar between the Riximyo and MabThera arms.

**Table 16 - Summary of AUC(0-21d) (mcg*day/mL) and AUCall (mcg*day/mL) for Cycle 4 (Cohort 2) - study GP13-301 (PAS+A2)**

| Parameter | Statistics | GP2013 N=27 | MabThera N=22 |
|---|---|---|---|
| $AUC_{(0-21d)}$ | n | 20 | 17 |
| | Mean (SD) | 3320 (872) | 3500 (1020) |
| | CV% mean | 26.3 | 29.1 |
| | Geometric mean | 3210 | 3340 |
| | CV% geometric mean | 27.5 | 34.9 |
| | Median | 3220 | 3690 |
| | Minimum - Maximum | 2150-4600 | 1360-4870 |
| $AUC_{all}$ | n | 24 | 22 |
| | Mean (SD) | 2820 (1250) | 2950 (1510) |
| | CV% mean | 44.3 | 51.2 |
| | Geometric mean | 2510 | 2310 |
| | CV% geometric mean | 55.1 | 109.1 |
| | Median | 2700 | 3220 |
| | Minimum - Maximum | 854-4590 | 155-4970 |

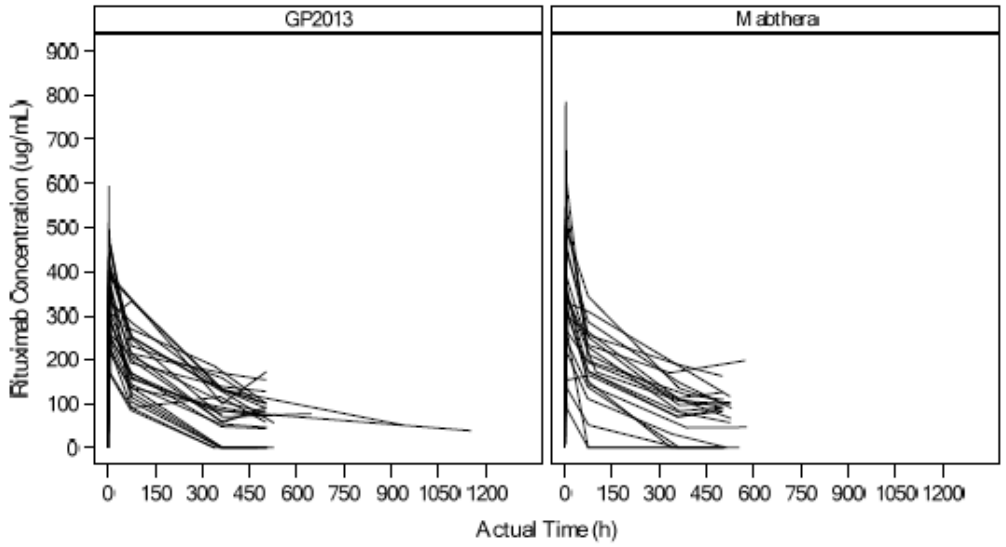



**Figure 9 - Individual concentration-time profiles for rituximab by treatment (Cohort 2) (PAS+A2)**

***Special populations***

**Table 17 - PK data in patients > 65 years old**

| | Age 65 – 74 (Older subjects number / total number) | | Age 75 – 84 (Older subjects number / total number) | | Age 85+ (Older subjects number / total number) | |
|---|---|---|---|---|---|---|
| | **Riximyo** | **Originator** | **Riximyo** | **Originator** | **Riximyo** | **Originator** |
| **PK Trials** | | | | | | |
| **GP13-101** | 1/6 | -- | -- | -- | -- | -- |
| **GP13-201** | 22/133 | 35/179 | 6/133 | 3/179 | -- | -- |

## 2.4.3. Pharmacodynamics

***Mechanism of action***

No clinical pharmacodynamic studies on the mechanism of action have been submitted.

***Primary and Secondary pharmacology***

**B-cell depletion as a marker for the effect of rituximab**

*Analytical methods*

Peripheral B-cell counts were measured after immunostaining by flow cytometry assay. As CD19+ B-cell depletion is considered a surrogate for CD20+ B-cell depletion, CD19+ analysis on B-cells has been validated as an exploratory biomarker of Riximyo/MabThera activity by Quintiles and Eurofins.

PD results; Key secondary PD endpoint: B-cell depletion – AUEC(0-14d) (GP13-201 Study Part I)

In addition to evaluating PK bioequivalence, the GP13-201 study also evaluated equivalence in terms of depletion of peripheral B-cells in response to Riximyo or MabThera defined as "area under the effect-time curves" (AUECs) of the percent change of the blood B-cell count relative to baseline up to the second infusion (i.e. Day 15). Other supportive PD endpoints were also evaluated as described below.

In order to conclude equivalence, the 95% CI of ratio of the geometric means (Riximyo/MabThera) had to be within the pre-specified equivalence limits of [0.8, 1.25].

The ratio of the geometric means (Riximyo/MabThera) was 1.019 and the corresponding 95% CI [0.997, 1.042] was within the pre-specified equivalence limits. Therefore, the secondary endpoint for equivalence was met.

**Table 18 - AUEC(0-14d) of percent B-cells relative to baseline: Comparison between Riximyo and MabThera using ANOVA (GP13-201 Study Part I) (PAS)**

| | | | | | Treatment Comparison | |
|---|---|---|---|---|---|---|
| PD Parameter (unit) | Treatment | n | Adjusted Geometric mean | Comparison | Geometric mean ratio | 95% CI of mean ratio |
| $AUEC_{(0-14d)}$ (%*day) | GP2013 | 72 | 1223.71 | GP2013/ MabThera | 1.019 | [0.997, 1.042] |
| | MabThera | 75 | 1200.49 | | | |

n = number of patients with non-missing values

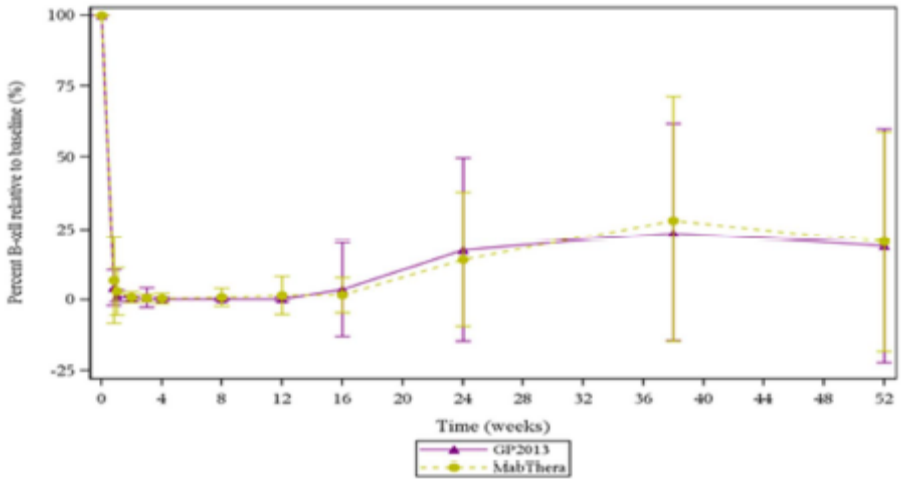
ANCOVA = Analysis of covariance; $AUEC_{(0-14d)}$ = Area under the effect-time curve from time 0 to Day 14; CI = Confidence interval; PAS = Pharmacokinetics (PK) Analysis Set; PD=Pharmacodynamics. Ratio of geometric means and 95% confidence interval were estimated by analysis of variance (ANOVA) on log-transformed PD parameters with treatment as the factor (while described in the CSR as an ANCOVA, the model did not account for any continuous independent variables). Results were then back-transformed to the original scale.

B-cell counts below the limit of quantification (<3 cells/mcL) were treated as zero for the calculation of AUEC.

No imputation of missing values was performed.

Additionally, the study evaluated the percentage of peripheral blood CD20+ B-cell levels relative to baseline following Riximyo or MabThera infusion at Days 15, Week 12, 16, and 24 and proportion of

patients in whom the peripheral blood CD20+ B-cell counts decreased below the detection limit at Days 1 (before first infusion), 4, 8 and 15 (before second infusion). The mean percentage of B-cell counts relative to baseline over time was also similar between the two treatments.




PAS = Pharmacokinetics (PK) Analysis Set; SD = Standard deviation

**Figure 10 - Arithmetic mean (SD) of percent B-cell relative to baseline over 52 weeks by treatment - (GP13-201 Study Part I) (PAS)**

Overall, the proportion of patients with B-cell counts below the lower limit of quantification (LLOQ) was comparable between Riximyo and MabThera on Days 4, 8 and 15. More than 50% patients by Day 8 and more than 70% patients by Day 1 5 were below the LLOQ in both treatment groups.

**Table 19 - Summary of absolute peripheral blood B-cells below limit of quantification by treatment - (GP13-201 Study Part I) (PAS)**

| Variable<br>Time point | GP2013<br>N= 86<br>n/N' (%) | MabThera<br>N= 86<br>n/N' (%) |
|---|---|---|
| B-cell count below limit of quantification (<3 cells/mcL) | | |
| Day 1 (before first infusion) | 0/ 82 (0.0) | 0/ 77 (0.0) |
| Day 4 | 23/ 79 (29.1) | 25/ 75 (33.3) |
| Day 8 | 45/ 78 (57.7) | 44/ 77 (57.1) |
| Day 15 (before second infusion) | 61/ 77 (79.2) | 56/ 79 (70.9) |

N' is the total number of patients with an available assessment at the visit
PAS = Pharmacokinetics (PK) Analysis Set

**Peripheral CD20+ B-cells percentage relative to baseline (study GP13-301)**

In addition to evaluating efficacy of Riximyo compared to MabThera in FL patients, the study evaluated peripheral CD20+ B-cell depletion in terms of AUEC(0-21d) of percent change in blood CD20+ B-cell count relative to baseline following the treatment with Riximyo-CVP and MabThera-CVP. This study was not powered for PD analysis and all PD data were presented using descriptive statistics.

Pharmacodynamics (PD) analyses were conducted using Pharmacodynamic Analysis Set (PDAS).

The PDAS consisted of 48 patients, 24 in the Riximyo and MabThera arms, respectively. The PDAS included patients in Cohort 2 who received Cycle 1 of investigational drug and had at least one post-baseline pharmacodynamic sample collected and analysed.

The Pharmacodynamic Analysis Set (PDAS) was used to analyze AUEC(0-21d) of all patients who received the investigational treatment (Riximyo or MabThera) during Cycle 1 in Cohort 2. Blood samples for this PD assessment were taken at screening and at the following time points during Cycle 1: pre-dose, EOI, 24 hours after EOI, 72 after EOI, and prior to Cycle 2. The baseline was defined as the mean of peripheral CD20+ B-cell counts at screening and predose of Cycle 1. For each patient, the percentage relative to baseline for peripheral CD20+ B-cell counts was calculated. The PD profile in terms of peripheral CD20+ B-cells percentage relative to baseline was similar between Riximyo and MabThera.

**Table 20 - Summary of peripheral CD20+ B-cells percentage relative to baseline, by treatment - study GP13-301 (PDAS)**

| Sampling time point | Statistics | GP2013 N=24 | MabThera N=24 |
|---|---|---|---|
| 0 h (post EOI - Cycle 1 Day 1) | n | 18 | 18 |
| | k | 12 | 11 |
| | Mean (SD) | 10.39 (21.503) | 6.78 (10.639) |
| | CV% mean | 206.933 | 156.886 |
| | Median | 0.8 | 2.2 |
| | Minimum-Maximum | 0.0-74.0 | 0.0-36.1 |
| 24 h (post EOI - Cycle 1 Day 2) | n | 18 | 19 |
| | k | 11 | 13 |
| | Mean (SD) | 8.13 (18.307) | 9.24 (15.589) |
| | CV% mean | 225.151 | 168.622 |
| | Median | 0.5 | 1.7 |
| | Minimum-Maximum | 0.0-67.5 | 0.0-52.9 |
| 72 h (post EOI - Cycle 1 Day 4) | n | 21 | 16 |
| | k | 11 | 10 |
| | Mean (SD) | 10.87 (24.869) | 5.58 (9.542) |
| | CV% mean | 228.761 | 170.867 |
| | Median | 0.1 | 1.4 |
| | Minimum-Maximum | 0.0-91.5 | 0.0-33.3 |
| Pre-dose (Cycle 2 Day 1) | n | 22 | 19 |
| | k | 11 | 7 |
| | Mean (SD) | 6.24 (14.007) | 6.64 (11.781) |
| | CV% mean | 224.551 | 177.539 |
| | Median | 0.0 | 0.0 |
| | Minimum-Maximum | 0.0-60.1 | 0.0-35.9 |

k = number of non-zero counts

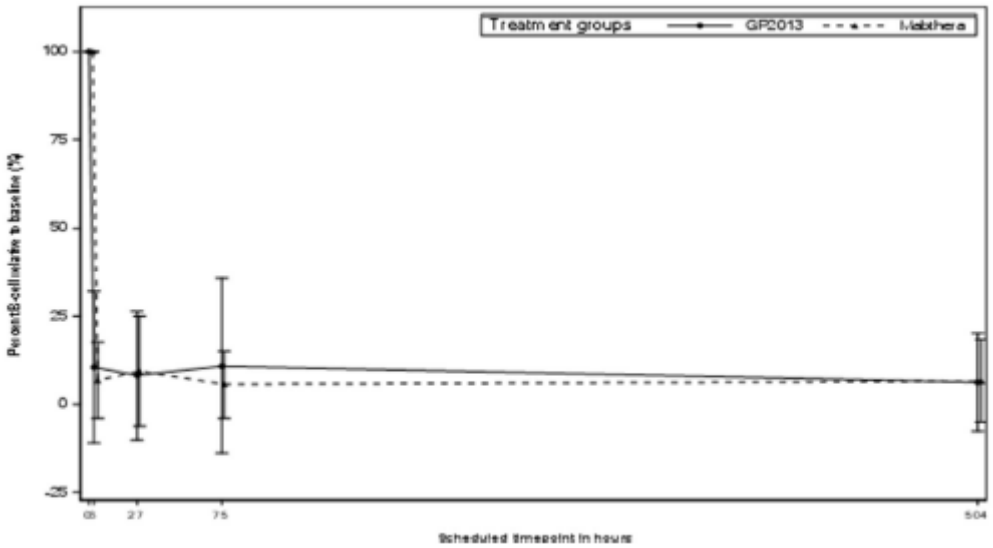
CV% = coefficient of variation; EOI = End of infusion; PDAS = Pharmacodynamic Analysis Set; SD = Standard deviation

CV% = sd/mean*100

Baseline value is defined as the average of the two pre-dose measurements.

When only one pre-dose value is available, it will be used as the baseline value.

Note: nominal time is used for the summary of data at each timepoint




PDAS = Pharmacodynamic Analysis Set; SD=Standard deviation

**Figure 11 - Arithmetic mean (SD) plot of percentage relative to baseline for peripheral CD20+ B-cells counts vs times, by treatment (Cohort 2) - study GP13-301 (PDAS)**

AUEC(0-21d) for peripheral CD20+ B-cell counts in Cycle 1 was a secondary endpoint, which was calculated using the percentage relative to baseline data for peripheral CD20+ B-cell counts. The mean AUEC(0-21d) during Cycle 1 evaluated in Cohort 2 was 1830 %*day (CV% 18.7%) and 1920 %*day (CV% 12.0%) for the Riximyo and MabThera arms, respectively.The geometric means ratio of AUEC(0-21d) (%*day) of peripheral B-cells (Cohort 2) (Riximyo /MabThera) was 0.939, and the corresponding 90% CI was [0.845; 1.04]). The summary results show that the AUEC(0-21d) in Cycle 1 is similar between the two treatment arms.

**Table 21 - Summary of AUEC(0-21d) (%*day) and Tlast (day) of peripheral CD20+ B cells (Cohort 2) - study GP13-301 (PDAS)**

| Parameter | Statistics | GP2013 N=24 | MabThera N=24 |
|---|---|---|---|
| $AUEC_{(0-21d)}$ | n | 19 | 18 |
| | Mean (SD) | 1830 (343) | 1920 (231) |
| | CV% mean | 18.7 | 12.0 |
| | Geometric mean | 1790 | 1910 |
| | CV% geometric mean | 23.5 | 13.3 |
| | Median | 1980 | 2020 |
| | Minimum-Maximum | 948-2070 | 1370-2130 |
| $T_{last}$ | n | 19 | 18 |
| | Mean (SD) | 20.6 (0.928) | 20.7 (1.02) |
| | CV% mean | 4.5 | 4.9 |
| | Geometric mean | 20.5 | 20.7 |
| | CV% geometric mean | 4.6 | 5.1 |
| | Median | 20.9 | 20.9 |
| | Minimum-Maximum | 17.9-22.7 | 17.9-21.9 |

$AUEC_{(0-21d)}$ = area under the effect-time curve from time 0 to Day 21; CV% = coefficient of variation (%); PDAS = Pharmacodynamic Analysis Set; SD = Standard deviation; $T_{last}$ = Time of last non-zero concentration

CV% = sd/mean*100

CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

***Immunogenicity***

No special studies were conducted with immunogenicity assessment as primary objective under Riximyo clinical development program; however, GP13-201 study in patients with RA, GP13-301 study in patients with FL and GP13-101 study in Japanese patients with indolent NHL contributed to the immunogenicity data for immunology and oncology set-up.

*Bioanalytical methods for immunogenicity assessment:*

The immunogenicity evaluation of rituximab as determined by the formation of antibodies against rituximab was made by a 3-step procedure comprising a validated screening and confirmatory as well as a titer assay based on an ELISA (used for RA study GP13-201) or bridging electrochemiluminescence assay (ECL) format (used for FL studies GP13-101 and GP13-301) and a validated neutralising antibody (NAb) assay. For the ADA screening, confirmatory and titer assays, anti-rituximab antibodies were used as positive control. For the NAb assay, a neutralising anti-rituximab antibody was used.

*Immunogenicity in RA patients (GP13-201 Study Part I)*

A total of 173 patients (86 in Riximyo and 87 in MabThera arms) were evaluated for immunogenicity.

According to the protocol, samples to assess the presence of anti-drug antibodies (ADA) were collected at visits 3 (predose), 8 (14 days post dose), and 11 to 14 (96, 154, 252, 350 days post dose) and in case of retreatment (pre dose) and at the 26 week retreatment follow up:

At randomization (pre-treatment), ADAs were detected in 2 (1.2%) patients in MabThera arm and these 2 patients were excluded from further ADA summary. However, none of these 2 patients had ADAs detected at later time points. Interestingly, ADAs to rituximab were also detected in 3.6% of placebo-treated patients with active RA in the SERENE study (Emery et al 2010). Overall, post-treatment ADA was detected in 9 out of 82 (11.0%) patients in the Riximyo and 18 out of 84 (21.4%) patients in the MabThera arm.

Samples with confirmed positive ADAs were further assessed for the neutralizing capacity of the antibodies using a cell based assay (NAb assay). A total of four patients exhibited NAbs, 3 out of 82 (3.7%) patients in the Riximyo arm and 1 out of 84 (1.2%) patient in the MabThera arm. Among them, two patients, one in the Riximyo arm and one in the MabThera arm showed ADA titer > 100 mcg/mL. The highest ADA concentration (>2000 mcg/mL) in patients with NAb was detected for the positive determined patient in the MabThera arm.

*Immunogenicity in FL patients (study GP13-301)*

In this study, immunogenicity (ADA) was assessed for all patients at screening (or pre-dose or both), End of treatment (EOT) Combination Phase, and EOT Maintenance Phase. For Cohort 1 patients, an additional immunogenicity assessment was performed at pre-dose Cycle 4 Day 1. Patients with pre-existing immunogenicity were excluded from this assessment.

Overall, five patients with pre-existing ADAs at screening, were excluded from this assessment. Four of these patients (three in Riximyo arm and one in MabThera arm) were consistently ADA negative at later visits whereas one patient in the Riximyo group had confirmed non-neutralising ADA positive result at the end of the maintenance phase.

A total of 551 (87.6%) patients were included in the immunogenicity analysis, 268 (85.4%) patients in the Riximyo and 283 (89.8%) patients in the MabThera arm. Overall, the number of patients with detectable post-dose ADAs was low in the study (n/N=8/551 (1.5%)), with no significant differences between Riximyo (n/N=5/268 (1.9%)) and the MabThera (n/N=3/283 (1.1%)) arms. This is comparable with data provided for NHL patients in the MabThera SmPC: 1.1% of patients with DLBCL developed human anti-chimeric antibodies. Based on the limited PK data in ADA positive patients, there is no indication that ADA is having an impact on PK exposure.

Overall, NAbs were detected in 2 out of 268 (0.7%) patients in the Riximyo group and 2 out of 283 (0.7%) patients in the MabThera group. Among them, one in the Riximyo group was detected at the end of Maintenance Treatment Phase. All other NAb positive incidences were detected during the combination phase. An assessment of safety parameters found that all four patients had no AEs of infusion-related reactions. One patient in MabThera group died due to cardiac arrest and had several SAEs of which two SAEs (neutropenia) were considered to be related to study drug. This patient also had grade 3 chills after the first infusion. Overall, all four incidences of NAb showed no link with any immunogenicity related SAEs or diminished efficacy.

## 2.4.4. Discussion on clinical pharmacology

The analytical methods used are appropriate and well-described. In general, the pre-specified criteria for the different validation parameters are in line with the Guideline on bioanalytical method validation and were fulfilled.

From the pharmacokinetics point of view, the PK pivotal Study GP13-201-Part 1 and supportive study GP13-301 are considered sufficient to demonstrate biosimilarity between the test and reference product. Supportive Study GP13-101 is less relevant as the rituximab product used is Rituxan licensed in Japan- considering no bridge between the EU Mabthera and Rituxan (Japan) has been established. The number and type of studies submitted are in line with EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1).

The biosimilar comparability limit were met for the primary PK parameter AUC(0-inf) from RA patients in study GP13-201 Part I. Uncertainties about the exclusion of ADA positive patients from PK evaluation and the calculation of adjusted mean values were discussed, however there was no relevant difference observed in the PK exposure of ADA positive RA patients compared to patients who did not develop ADAs in study GP13-201. Considering that the (geometric) mean and median of the half-life of the two products are very similar, a statistically significant difference in AUC values by ADA status was unlikely.

In study GP13-201 $C_{max1}$ slightly exceeded the upper limit (i.e. 126%), this was due to the high variability caused by longer duration and more escalation steps during the 1st infusion in comparison to the 2nd infusion. It is agreed that for a drug product delivered via infusion, the peak systemic concentrations represent the end-of-infusion concentrations which are highly dependent on infusion rate and are therefore not adequate as a measure for bioavailability. Cmax2 was within the standard bioequivalence limits [0.8, 1.25]. Therefore, the criterion of bioequivalence was met.

Due to the sparse sampling of PK data in study GP13-301 in FL patients, the value of these data for the decision on PK similarity is limited and only supportive. The descriptive PK results do not fully support PK similarity of Ctrough at predose cycle 4 (mean Ctrough 66.4 vs. 82.1 mcg/mL for Riximyo and MabThera, resp.) with Riximyo exposure being around 10% lower than in the MabThera group. On the other hand, comparison of pre-dose cycle 8 Ctrough values (123 vs. 127 µg/mL for Riximyo and

MabThera, respectively) supports similarity between the groups. Frequency of BLQ samples in both treatment arms was low in both ADA positive and ADA negative patients and comparable between the treatment groups. This indicated that Ctrough results from cohort 1 are not biased by BLQ treatment.

The comparison of AUC(0-21d) in Cohort2 (subgroup with full profile) was also influenced by the fact that many patients (around 25%) had rituximab concentrations below LLOQ at later time points of the Cycle 4 PK profile (e.g., 360 h after EOI or pre-dose Cycle 5) so that their AUC(0-21d) could not be accurately determined. However, AUC comparison in the remaining patients (n=20 and 17) in cohort 2 rather supports similarity and does not indicate a large difference in bioavailability of Riximyo and MabThera during steady state in the presence of co-medication. Since the difference between AUCall (area under the curve from the time of dosing to the time of the last observation, regardless of whether the last concentration was measureable or not) and AUC(0-21d) was the same in both groups, observation and handling of BLQ samples appeared to have no relevant impact on the supportive evidence for biosimilarity.

PK data from the rheumatoid arthritis and follicular lymphoma patients are being extrapolated to the other oncology indications (i.e. chronic lymphocytic leukaemia) and auto-immune indications (i.e. granulomatosis with polyangiitis and microscopic polyangiitis). In all indications, the clearance of rituximab occurs through two pathways: the non-specific IgG clearance pathways and the target mediated drug disposition (TMDD) pathway. The non-specific IgG clearance pathways are reported to be mediated by binding to the neonatal Fc receptor (FcRn) and to various Fc receptors (FcγRs). Riximyo and MabThera, being similar in structure, bind to FcRn and various FcγRs with similar affinity. The TMDD pathway for rituximab is mediated by binding to the CD20 receptor on target cells. It is known that the extent of TMDD in various populations is correlated to the CD20+ B-cell levels (or tumour load in haematologic oncology indications), which differ within and between populations (e.g. CD20+ B-cell NHLs << CLL). Despite the expected difference in CD20+ B-cell levels and extent of TMDD in different disease indications, the same clearance mechanisms (non-specific and TMDD) is expected. In addition, the comparable in vitro binding properties of Riximyo combined with the human comparability data in B-cell depletion from both the autoimmune (RA) and oncology (FL) indications, provide sufficient evidence that the clearance of Riximyo is expected to be comparable to that of MabThera in all indications that are approved for MabThera. Therefore, an extrapolation of the PK data from rheumatoid arthritis and follicular lymphoma patients to the other oncology and auto-immune indications of MabThera can be considered acceptable.

The discriminative power of the PD parameter AUEC(0-14d) of B-cell depletion (based on 3 data points) is considered low, since B-cell depletion was almost complete from day 3 to week 12 in both arms of study GP13-201. The similar time courses of B-cell recovery after 16 weeks can be considered as supportive for similarity, since the time interval of B-cell recovery is considered to be quite sensitive for detecting differences. On the other hand, potential differences might be more indicative for other (patient) factors than for PK differences. In contrast to the PK analysis, ADA positive patients were included in PD evaluation of study GP13-201. The individual time courses of B cell depletion by ADA status showed that inclusion of ADA positive patients did not have a significant impact on the evaluation of the time course of B cell recovery. In study GP13-301, B-cell depletion was complete in all samples over the whole treatment cycle, thus, the discriminative power of the parameter AUEC(0-21d) for detecting differences is also low.

As far as known, there is no strong correlation between the extent of B-cell reduction and the extent of the clinical response in RA. For NHL, the correlation is even less clear, since circulating B-cells may not directly reflect tumour mass, and this response cannot be considered as an appropriate surrogate of the clinical response. Nevertheless, the comparative B-cell depletion data are considered relevant 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; these mechanisms of action are applicable to all indications.

As part of immunogenicity assessment the following aspects were considered, according to EMA's Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins: i) rate of ADAs; ii) hyper-acute / acute reactions; iii) delayed reactions and iv) autoimmunity (cross-reactivity to an endogenous counterpart) (See Clinical safety).

Two different assay formats were used for the determination of immunogenicity (anti-drug antibodies, ADA) in the sera of the two pivotal studies (affinity capture elution ELISA method for the RA patient serum samples and the ECL assay for the FL serum measurements) and 2 approaches for the detection of neutralizing anti-rituximab antibodies (NAb assay) were applied: In RA study GP13-201, a cell-based CDC assay format was chosen, whereas in the FL study, due to very strong matrix interference in FL serum, the assay format had to be changed to a competitive ligand binding assay format.

Both immunogenicity screening assays are considered appropriate to detect ADAs, however, the assay in FL serum is considered more reliable than the RA assay in terms of sensitivity and drug tolerance. Both assay formats are designed to measure Riximyo-specific ADAs rather than MabThera-specific ADAs. No data were provided on the use of the originator substance rituximab as capture and bridging antigen which could demonstrate antigenic equivalence of Riximyo and MabThera for binding of ADAs in the assays. The chosen design may overestimate ADA incidence of Riximyo vs. MabThera rather than vice versa, it therefore does not give a competitive edge for the biosimilar product. From a comparison of drug concentration present in the immunogenicity samples, it can be concluded that the majority (75%) of NAb incidence results can be considered as conclusive.

There are only few data on the incidence of ADA after intravenous application of MabThera in RA patients from other clinical studies for comparison: Similar (slightly lower) incidences of treatment-emergent ADA (13,5 % and 17.6 %) were observed in recent biosimilar PK trials for the RA patient group receiving MabThera (Cohen et al. 2016 and Yoo et al. 2013). The longer observation period in the Riximyo study (including the time period of B cell recovery) compared to the literature data is considered as supportive for a proper immunogenicity assessment and might be a reason for observation of higher incidences. It is agreed that comparison between studies in literature may be due to different assays used. At any rate, it is likely that the difference of -10% could be a chance finding and ultimately it is not of concern since immunogenicity –if anything—is lower than that of the reference product which is in accordance with the overarching guidelines (CHMP/437/04 Rev 1; EMEA/CHMP/BMWP/42832/2005 Rev1).

Immunogenicity results revealed the ADA incidence being 2-fold lower in RA patients treated with Riximyo compared to MabThera (11.0 % vs. 21.4 %). The statistical significance and potential reasons of this finding was questioned. The incidences lie in the range of treatment-emergent ADA incidences (13.5 % and 17.6 %) observed in recent trials in RA patients receiving MabThera (Cohen et al. 2016 and Yoo et al. 2013). In the oncology setting a lower immunogenicity of Riximyo (2.1%) and MabThera (0.9%) was observed; however, significance of this result is limited. The observed number of patients with ADA (including NAb) in trial GP13-301 was very low which can probably attributed to the immunosuppressive effect of the concomitant chemotherapy. Therefore, this population is not the most sensitive population for detecting a difference in immunogenicity. ADA incidence for MabThera in this study was similar to the 1.1 % observed diffuse large B cell lymphoma (DLBCL) patients receiving MabThera 375 mg/m2 plus standard CHOP chemotherapy every 3 weeks for eight cycles (see MabThera SmPC).

## 2.4.5. Conclusions on clinical pharmacology

Comparison of PK parameters and the time courses of B-cell depletion as PD biomarker in both studies shows biosimilarity of Riximyo to Mabthera, which is supported by the similar time courses of B-cell recovery after 16 weeks (and by ADA status).

An extrapolation of the PK/PD data from rheumatoid arthritis and follicular lymphoma patients to the other oncology and auto-immune indications of MabThera is acceptable due to the same clearance mechanisms (non-specific and target-mediated), similar *in vitro* binding properties of Riximyo and comparable human data in B-cell depletion from both the autoimmune (RA) and oncology (NHL) indications.

# *2.5. Clinical efficacy*

## 2.5.1. Dose response studies

Dose response studies were not submitted (see discussion on clinical efficacy).

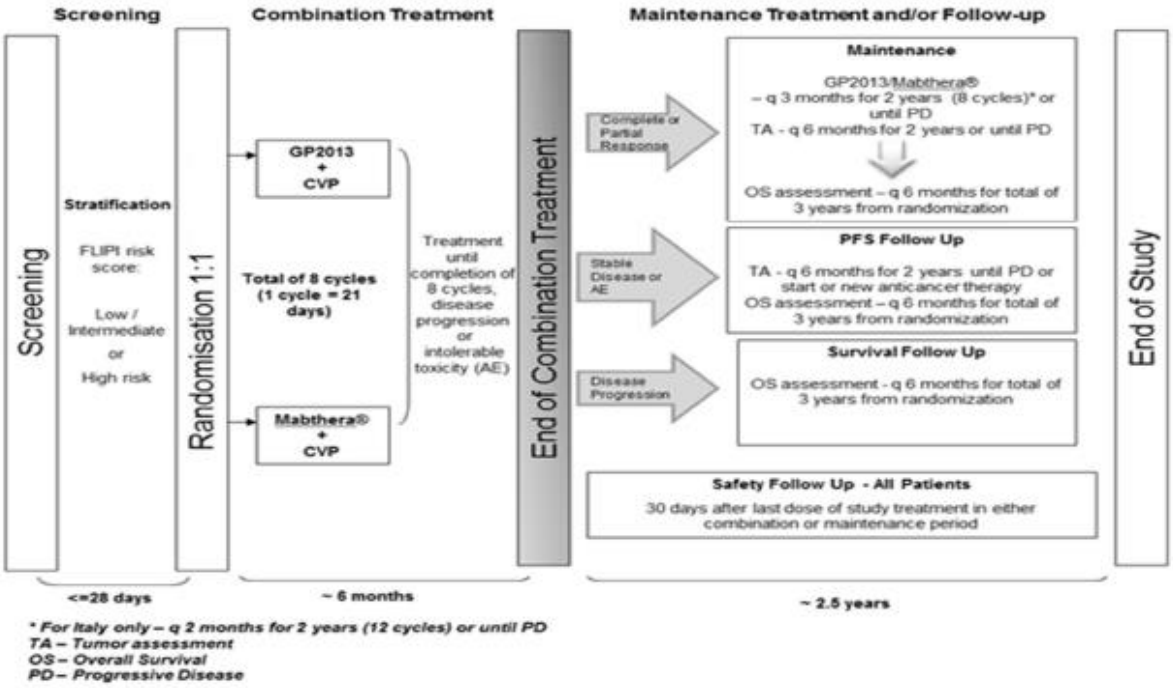
## 2.5.2. Main study

### Study GP13-301 - Pivotal clinical efficacy and safety study in patients with FL

#### Methods

Study GP13-301, conducted in patients with previously untreated, advanced stage FL is a randomised, active-controlled, double-blind, multi-center, parallel group confirmatory study to compare the efficacy, safety, PK, and pharmacodynamics of Riximyo plus CVP vs MabThera plus CVP in patients with previously untreated, advanced stage FL.

Patients who achieved a CR or PR at the end of the combination treatment period were eligible to receive single-agent Riximyo/MabThera maintenance treatment, according to original treatment assignment, for a period of two years. Patients for whom progression of disease was documented at any time during either the combination or maintenance treatment periods, discontinued study treatment, but continued to be followed for survival every 6 months for a total period of a maximum of three years from the date of randomisation.




Note: during maintenance period, in Italy only, Riximyo/MabThera every 2 months for 2 years (12 cycles) or until disease progression
AE=Adverse event; CVP= Cyclophosphamide, vincristine, prednisone; FLIPI=Follicular Lymphoma International Prognostic Index; PFS=Progression free
survival; q=every "x" months or years
Methods

**Figure 12 - Overall GP13-301 study design**

**Study participants**

The study population consisted of adult (≥ 18 years old) patients with previously untreated, advanced stage (Ann Arbor stage III/IV) FL of WHO histological grades 1 -3a. FL histology, WHO histological grade, and CD20-positivity were confirmed by central pathological testing prior to patient randomization.

Man Inclusion criteria

Patients eligible for inclusion in this study had to meet all of the following criteria:

1. Patient with previously untreated advanced stage, CD20-positive FL:
    a. Ann Arbor classification stage III/IV;
    b. WHO histologic grade 1, 2 or 3a, as confirmed by central pathological testing; and
    c. Require therapy for FL as per local guidelines or in the opinion of the treating physician.
2. Patient age ≥ 18 years. For India only as per Protocol Amendment 5: patients aged 18 to 75 years, inclusive
3. Patient with at least one measurable lesion (accurately measureable in at least 2 perpendicular dimensions);
    a. at least 1 measurable nodal lesion > 20 mm in the long axis; OR
    b. at least 1 measurable extranodal lesion with both long and short axes ≥ 10 mm.

Main Exclusion criteria

Patients eligible for this study must not have met any of the following criteria:

1. Patient with grade 3b (aggressive) FL or any histology other than FL grade 1, 2, or 3a.
2. Patient with histological evidence of transformation to high grade or diffuse large B-cell lymphoma.
3. Patient who has previously received any prior therapy for lymphoma, e.g., cytostatic or cytotoxic agents, antibodies, anti-lymphoma vaccination, experimental treatments and radiotherapy, except who received involved field radiation 4 weeks prior to Cycle 1 Day 1, of up to two lesions that will not be used to evaluate disease progression.
4. Evidence of significant leukemic disease, defined as >10 x 109 /L circulating CD20+ lymphoma cells.
5. Patient with clinical evidence of central nervous system involvement by lymphoma or any evidence of spinal cord compression by lymphoma.
6. Patient with evidence of any uncontrolled, active infection (viral, bacterial, including tuberculosis or fungal).
7. Patient receiving chronic (>3 months high dose (>20 mg of prednisone or > pproximately 3 mg of dexamethasone per day or equivalent doses of other steroid medications) of systemic corticosteroids.
8. Patient with any malignancy within 5 years prior to date of randomization, with the exception of adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma, or non-melanomatous skin cancer.
9. Patient with a known hypersensitivity to any of the study treatment ingredients, e.g., to recombinant human antibodies.
10. Patient with concurrent serious illnesses, uncontrolled medical conditions, or other medical history including clinically relevant abnormal laboratory results, which in the investigator's opinion would interfere with a patient's participation in the study, or with the interpretation of study results:
    a. uncontrolled neurological disease (e.g., recurrent seizures despite existing anticonvulsant therapy);
    b. neuropathy ≥ grade 1, neuromuscular disease;
    c. severe disturbance of liver function;
    d. severe constipation;
    e. cystitis or other ongoing infections;
    f. disturbance of micturition;
    g. severe chronic obstructive pulmonary disease with clinically manifest hypoxemia;
    h. uncontrolled hypertension (defined as systolic blood pressure (BP) > 160 mm Hg, or diastolic BP > 100 mm Hg);
    i. history of stroke or cerebral ischemia (within 6 months prior to screening );
    j. history of myocardial infarction or other clinically significant myocardial disease (within 6 months prior to screening or unstable angina (≥ New York Heart Association Grade II);
    k. known infection with human immunodeficiency virus (HIV) or any other severe immune-compromised state according to patient history (if required by local regulations or clinical practice guidelines, patient may be tested during the screening period to confirm HIV status);
    l. evidence of ongoing drug or alcohol abuse within the last 6 months before screening;
11. Patient has had major surgery, open biopsy or trauma within 4 weeks prior to date of screening (lymph node biopsy is not regarded as major surgery), or expects the need for major surgery during the course of study treatment.
12. Female patient who is nursing (lactating/breast-feeding), pregnant or planning a pregnancy within 12 months after the last infusion of study drug; where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
13. Patient has received therapy with any other investigational medicinal product within the last 30 days or 5 times the half-life, whichever is longer, prior to screening.
14. Patient plans to receive live vaccines during the study or has received live vaccines 4 weeks prior to date of screening. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.
15. Patient is using growth factors or transfusions to meet study eligibility requirements during Screening period. (The use of growth factors and transfusions during screening is permissible,

if there is suspicion of bone marrow involvement by lymphoma and patient is deemed not to be growth factor-dependent or transfusion-dependent).

**Treatments**

Study treatment (drug) includes any of the drugs as follows: Riximyo, MabThera, CVP, or combination of these drugs in either of the two treatment arms administered to the patient as part of the required study procedures.

**Table 22 - Combination Treatment Period – Dosing Schedule by Treatment**

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|
| Blinded study drug[1] | Intravenous infusion | 375 mg/m² | Day 1 of each 21 day cycle (for 8 cycles) |
| Prednisone[2,3,4] | Oral | 100 mg | Day 1-5 of each 21 day cycle (for 8 cycles) |
| Cyclophosphamide[2] | Intravenous bolus or infusion | 750 mg/m² | Day 1 of each 21 day cycle (for 8 cycles) |
| Vincristine[2] | Intravenous infusion | 1.4 mg/m² (max 2 mg) | Day 1 of each 21 day cycle (for 8 cycles) |

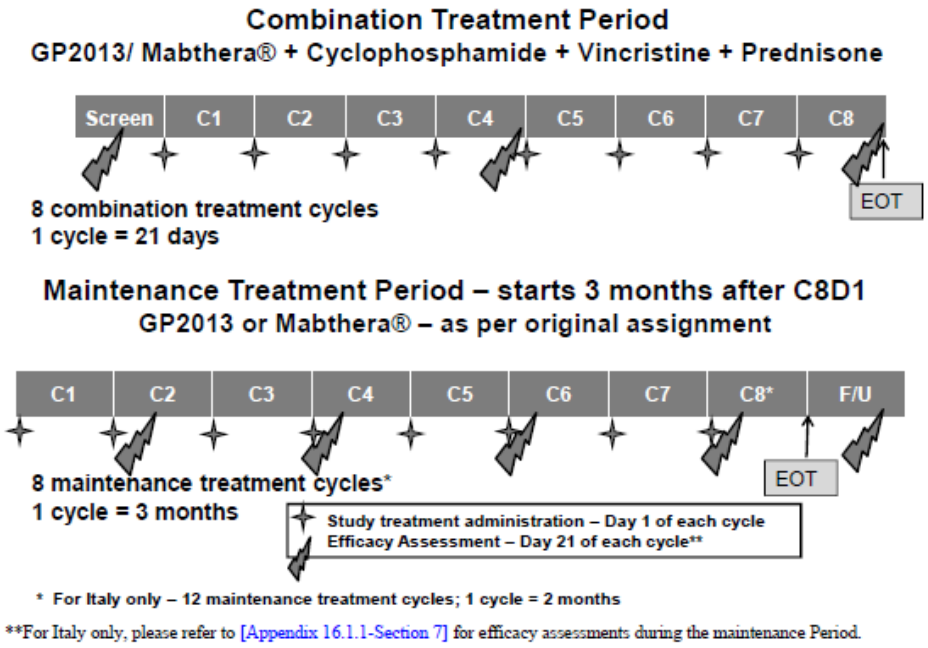



**Figure 13 - Study design – combination and maintenance periods**

Infusion procedures for Riximyo and MabThera

The following recommended pre-medications may have been given 30 minutes prior to the start of infusion for all combination treatment cycles paracetamol (500 mg p.o.); H1 antihistamine (p.o. or i.v.); prednisone (100 mg p.o.).

**Objectives**

Primary objective:

To demonstrate comparability of the overall response rate (ORR) in patients with previously untreated, advanced stage FL who receive Riximyo-CVP combination treatment to patients who receive MabThera-CVP combination treatment.

Other Efficacy objectives:

- To evaluate complete response (CR) rate
- To evaluate partial response (PR) rate
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)

Safety objectives:

- To describe safety of Riximyo in comparison to MabThera either as a single agent or in combination with CVP
- To evaluate the incidence of immunogenicity (anti-drug antibody [ADA] formation) against Riximyo and MabThera

Pharmacokinetic (PK)/Pharmacodynamic objectives:

- To evaluate the PK of Riximyo and MabThera
- To evaluate a Pharmacodynamic marker following the treatment with Riximyo-CVP and MabThera-CVP
-

**Outcomes/endpoints**

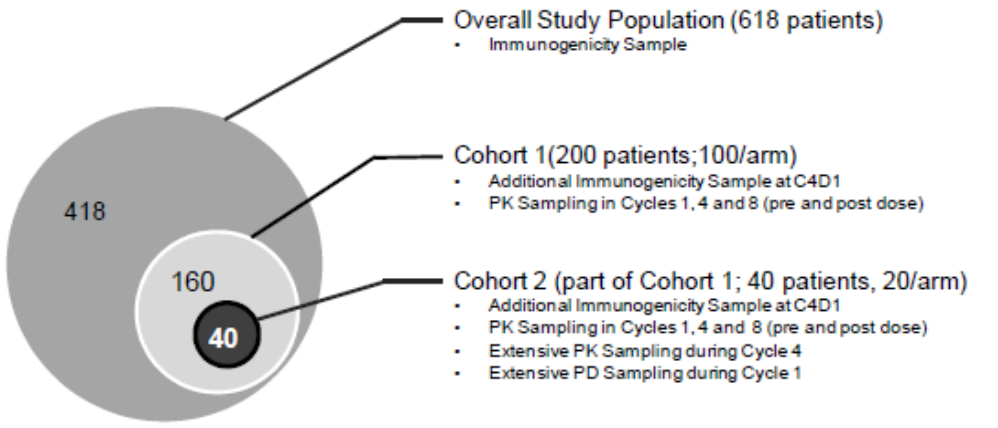
Efficacy endpoints included ORR, CR, PR, PFS, and OS. Efficacy was evaluated using Modified Response Criteria for Malignant Lymphoma based on contrast-enhanced Computerized tomography (CT) or Magnetic Resonance Imaging (MRI) and bone marrow evaluations. B-symptoms were also evaluated at the same time points as tumour assessments.

**Sample size**

Anticipating an expected overall response rate of 81% for both treatment arms and a pre-specified equivalence margin of 12%, it was calculated that a total of 556 patients (288 per arm) were required to assess equivalence of Riximyo to the reference drug at a two one-sided significance level of 2.5% with 90% power. In order to allow for 10% of drop-outs and major protocol violations, a total of 618 patients were planned to be randomized; 629 patients were actually randomized into the study.

The equivalence margin (δ) was based on historical data of a phase III study in patients with previously untreated advanced FL (Ann Arbor classification stages III to IV), where the patients received either CVP plus MabThera (n=162) or CVP (n=159) (Marcus 2005). The observed ORR in the study was 81% for the MabThera-CVP arm and 57% for CVP arm, the observed add-on effect of CVP plus MabThera on ORR was 24% (95%-CI: 14% to 34%). The equivalence margin of 12% was determined considering the variability of the point estimate of the add-on effect (24%) by taking a value lower than the lower bound of the 95% CI for MabThera-CVP vs. CVP obtained from the historical data.

An approximate cohort of 100 patients per treatment arm (Cohort 1, who consented to the trial) underwent PK sampling. A further subgroup of approximately 20 patients per arm (Cohort 2, i.e., 40 of the patients in Cohort 1), also were to undergo extensive PK sampling during Cycle 4 and pharmacodynamic sampling during Cycle 1. Immunogenicity (ADA) formation) samples were collected from all patients.




The study is composed of four periods: Screening, Combination Treatment, Maintenance Treatment, and Follow-up (Figure 9-2 and Figure 9-3).

**Figure 14 - Planned PK/Pharmacodynamic cohort design**

**Randomisation**

Subjects were randomised (via IRT) in an 1:1 ratio to receive either Riximyo-CVP or MabThera-CVP in a 1:1. Randomisation was stratified by FLIPI risk group (FLIPI score 0-2 vs. FLIPI score 3-5), geographic region (Asia Pacific, Latin America, and Europe) and by participating cohort for PK data collection (Cohort 2: extensive PK sampling; Cohort 1 exclusive of Cohort 2: sparse PK sampling; rest of patients without PK sampling).

**Blinding (masking)**

Patients, investigator site staff, persons performing the assessments, and data analysts in this study remained blinded to the identity of the treatment from the time of randomisation until database lock (DBL). As the appearance of the test and reference product was not identical, the preparation of the study medication was performed by dedicated unblinded site staff not involved in the further conduct of the study. Unblinding was to occur only in the case of patient emergencies, for regulatory reporting purposes, and at the conclusion of the study. Unblinding occurred when the primary DBL was reached (i.e. when all randomized patients have completed the combination treatment period).

**Statistical methods**

In general data were summarised by statistical characteristics (categorical data: absolute and relative frequencies; continuous data: mean, standard deviation, median, minimum, and maximum) stratified by treatment group and visit (where applicable).

Efficacy analyses

The primary efficacy endpoint was ORR during the combination phase as based on Central Blinded Review of radiological response. The primary analysis of ORR was based on the per-protocol set (PPS). Equivalence was to be concluded in case the 95% CI for the difference of proportions in ORR between both treatment groups fell completely into the pre-defined equivalence range (-12%, 12%). Normal approximation to the binomial distribution was used to generate the 95% CI. In addition a logistic regression model with the exploratory variables FLIPI score and treatment was used to derive an estimate and associated 90% CI of the odds ratio of treatment difference (Riximyo versus MabThera) adjusting for FLIPI score.

To support the primary analysis the following analyses were planned:

- analysis of CRB-ORR on the PPS excluding patients whose best overall response was unknown or missing
- CRB-ORR performed on FAS
- sub-group analyses of ORR on both PPS and FAS by age and FLIPI score risk group
- ORR based on investigator review for the PPS and FAS

For the primary endpoint, subjects with missing endpoint information were considered non-responder.

Time-to-event analyses were based on the Kaplan-Meier approach. For OS and PFS the median time (including its 90%-CI) was estimated for each treatment arm. In addition, the 25% and 75% percentiles were also provided for each treatment arm. Using the Kaplan-Meier methodology, the PFS and survival probabilities at 6, 12, 24, 30, and 36 months including their 90%-CIs were estimated. The hazard ratio between treatment arms was estimated from a Cox regression model with treatment as covariate and FLIPI score as stratification factor. The associated 90% CI was also generated.

Safety analyses

Safety analyses were mainly based on the frequency of AEs and on the number of patients with laboratory values that fell outside the pre-determined ranges. Other safety data (e.g. vital signs, ECG) were summarized similarly.

PK analyses

Descriptive statistics stratified by treatment were presented for Cmax and Ctrough (pre-dose) during Cycles 1, 4, and 8 for Cohort 1patients. Furthermore, for Cycle 4 Day 1 Cmax, two-sided 90% CIs for the mean difference of Riximyo (test) versus MabThera (reference) on the logscale were calculated and the back-transformed point estimate as well as the 90% CI for the ratio of geometric means were also provided (for descriptive purposes only).

PD-analyses

Summary statistics stratified for treatment and visit were presented for B-cell counts, absolute changes and percentage relative to baseline in CD19+ B-cell values. The depletion of peripheral B-cells was measured as the area under the effect-time curve (AUEC(0-21d)) of the percent peripheral B cell count relative to baseline up to the second infusion (i.e., Day 21 or Cycle 2 Day1). For AUEC0-21d, two-sided 90% CIs for the mean difference of Riximyo versus MabThera (test - reference) on the log-scale was calculated and the backtransformed point estimate as well as the 90% CI for the ratio of geometric means was provided (for descriptive purposes only).

### *Results*

### *Participant flow*

The planned number of randomised patients for this analysis was 618.

However, 629 were actually randomised (314 patients to the Riximyo arm and 315 patients to the MabThera arm; two Riximyo patients were mis-randomised and were discontinued before being treated).

**Table 23 - Patients' disposition in the Combination Treatment Phase (Study GP13-301)**

| Disposition<br>Reason | GP2013<br>N=314<br>n (%) | MabThera<br>N=315<br>n (%) | All patients<br>N=629<br>n (%) |
|---|---|---|---|
| Patients randomized | | | |
| Untreated | 2 (0.6) | 0 | 2 (0.3) |
| Treated | 312 (99.4) | 315 (100) | 627 (99.7) |
| Primary reason for end of combination treatment[1]: | | | |
| Treatment duration completed as per protocol | 274 (87.3) | 274 (87.0) | 548 (87.1) |
| Adverse Event(s) | 7 (2.2) | 10 (3.2) | 17 (2.7) |
| Subject withdrew consent | 5 (1.6) | 4 (1.3) | 9 (1.4) |
| Administrative problems | 2 (0.6) | 1 (0.3) | 3 (0.5) |
| Death | 5 (1.6) | 7 (2.2) | 12 (1.9) |
| Disease progression | 10 (3.2) | 10 (3.2) | 20 (3.2) |
| Protocol deviation | 6 (1.9) | 2 (0.6) | 8 (1.3) |
| Physician's decision | 5 (1.6) | 7 (2.2) | 12 (1.9) |

As of 10-Jul-2015 data cut-off date, 73.6% (n=231) of patients in the Riximyo arm and 73.3% (n=231) of patients in the MabThera arm entered the Maintenance Phase and received at least one dose of the maintenance treatment. A total of 303 patients were still receiving study treatment in the Maintenance Phase, 142 patients (61.5%) in the Riximyo arm and 161 patients (69.7%) in the MabThera arm. In the Maintenance Phase of the study, the primary reason for EOT (38.5% in Riximyo arm and 30.3% in MabThera arm) was disease progression (16.0% Riximyo; 10.8% MabThera) and "Treatment duration completed as per protocol" (15.2% Riximyo; 13.4% MabThera).

**Recruitment**

Study initiation date: 01-Dec-2011 (first patient screened)

Study completion date: 09-Jul-2015 (last patient last visit in the combination treatment period)

Study center(s): 174 centers screened patients and 159 centers randomized patients from centers in 26 countries.

Follow-Up period: 2.5 years (max. 3 years)

**Conduct of the study**

The study protocol was amended 5 times, the original protocol and all amendments are provided:

Amendment 1 (27-Feb-2012): the key purpose of this protocol amendment was to update and clearly define the attributes of the study inclusion and exclusion criteria, revise the recommended dose modification per current clinical practice, and change the primary ORR analysis from local to Central Blinded Review of radiological response.

Amendment 2 (17-Jan-2013) was a country specific amendment for Italy to change the schedule of treatment in the maintenance phase of the study from every 3 months to every 2 months as requested by Italian health authority.

Amendment 3 (21-Jan-2013) with the primary purpose to allow lymph node biopsy samples collected within 5 months of screening to establish and confirm the diagnosis of follicular lymphoma to confirm patient eligibility. Furthermore, the population PK of Riximyo and MabThera was removed in the amendment as this analysis was not deemed necessary to compare the PK of Riximyo and MabThera.

Amendment 4 (26-Sep-2013), was a global amendment with the primary reason to add a planned interim analysis (based on specific health authority feedback) to support the regulatory filing of Riximyo with EMA and potentially other health authorities.

Amendment 5 (10-Nov-2014). This amendment was based on Health Authority feedback received in February 2014, which lead to the removal of the planned interim analysis added in protocol amendment version 4.0. As of 20-Oct-2014, 561 patients were enrolled in the study.

**Baseline data**

**Table 24 - Demographics and baseline characteristics - study GP13-301 (FAS)**

| Demographics and baseline characteristics | GP2013 N=312 | MabThera N=315 | All patients N=627 |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 57.5 (11.86) | 56.4 (11.72) | 56.9 (11.79) |
| Median | 58.5 | 57.0 | 58.0 |
| Min-Max | 23 – 84 | 24 – 84 | 23 – 84 |
| Age category (years) – n (%) | | | |
| < 60 | 163 (52.2) | 175 (55.6) | 338 (53.9) |
| ≥ 60 | 149 (47.8) | 140 (44.4) | 289 (46.1) |
| Gender – n (%) | | | |
| Female | 181 (58.0) | 169 (53.7) | 350 (55.8) |
| Male | 131 (42.0) | 146 (46.3) | 277 (44.2) |
| Race -n (%) | | | |
| Caucasian | 214 (68.6) | 207 (65.7) | 421 (67.1) |
| Asian | 71 (22.8) | 85 (27.0) | 156 (24.9) |
| Black | 6 (1.9) | 3 (1.0) | 9 (1.4) |
| Native American | 2 (0.6) | 5 (1.6) | 7 (1.1) |
| Other | 19 (6.1) | 15 (4.8) | 34 (5.4) |
| Body surface area ($m^2$) | | | |
| Mean (SD) | 1.8 (0.23) | 1.8 (0.21) | 1.8 (0.22) |
| Median | 1.8 | 1.8 | 1.8 |
| Min-Max | 1.1 – 2.5 | 1.2 – 2.3 | 1.1 – 2.5 |
| ECOG performance status - n (%) | | | |
| 0 - No restrictions | 179 (57.4) | 175 (55.6) | 354 (56.5) |
| 1 - Only light work | 125 (40.1) | 123 (39.0) | 248 (39.6) |
| 2 - Only self-care | 5 (1.6) | 13 (4.1) | 18 (2.9) |
| Missing | 3 (1.0) | 4 (1.3) | 7 (1.1) |

ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; Max=Maximum; Min=Minimum; SD = Standard deviation
Source: [Module 5.3.5.1 GP13-301-Table 11-2]

**Table 25 - Disease history and baseline characteristics by treatment (FAS)**

| Patient and disease Characteristics at baseline | GP2013 N=312 | MabThera N=315 | All patients N=627 |
|---|---|---|---|
| Time from initial diagnosis to study randomization (months) | | | |
| n | 305 | 307 | 612 |
| Mean (SD) | 3.9 (11.95) | 3.3 (6.73) | 3.6 (9.69) |
| Median | 1.8 | 1.8 | 1.8 |
| Min-Max | 0.4 – 183.9 | 0.6 – 69.3 | 0.4 – 183.9 |
| Histologic grade - n(%) | | | |
| Grade 1 | 161 (51.6) | 162 (51.4) | 323 (51.5) |
| Grade 2 | 126 (40.4) | 128 (40.6) | 254 (40.5) |
| Grade 3a | 24 (7.7) | 24 (7.6) | 48 (7.7) |
| Other | 1 (0.3)[1] | 0 (0.0) | 1 (0.2) |
| Missing | 0 (0.0) | 1 (0.3) | 1 (0.2) |
| Ann Arbor Staging System Status- n(%) | | | |
| Stage III | 143 (45.8) | 135 (42.9) | 278 (44.3) |
| Stage IV | 169 (54.2) | 180 (57.1) | 349 (55.7) |
| FLIPI Risk Group – n(%) | | | |
| Low risk (0 or 1 factors) | 30 (9.6) | 35 (11.1) | 65 (10.4) |
| Intermediate risk (2 factors) | 106 (34.0) | 103 (32.7) | 209 (33.3) |
| High risk (3 or more factors) | 176 (56.4) | 177 (56.2) | 353 (56.3) |
| No systemic B-symptoms - n(%) | | | |
| Yes | 220 (70.5) | 219 (69.5) | 439 (70.0) |
| No | 92 (29.5) | 96 (30.5) | 188 (30.0) |
| Presence of at least one specific B symptom - n(%) | | | |
| Yes | 92 (29.5) | 96 (30.5) | 188 (30.0) |
| No | 220 (70.5) | 219 (69.5) | 439 (70.0) |
| Single extranodal site - n(%) | | | |
| Yes | 97 (31.1) | 101 (32.1) | 198 (31.6) |
| No | 215 (68.9) | 214 (67.9) | 429 (68.4) |
| Presence of bulky disease - n(%) | | | |
| Yes | 44 (14.1) | 56 (17.8) | 100 (15.9) |
| No | 268 (85.9) | 259 (82.2) | 527 (84.1) |
| Splenic involvement - n(%) | | | |
| Yes | 46 (14.7) | 42 (13.3) | 88 (14.0) |
| No | 266 (85.3) | 273 (86.7) | 539 (86.0) |

[1] Two tumor samples from this patient had been collected prior to randomization, of which one was histological grade 2.
Histology grade is based on central laboratory reading.
Missing here means no central confirmation available.
The source for FLIPI score is the relevant CRF page.
Source: Table 14.1-2.3

**Numbers analysed**

The study was conducted in 26 countries and 159 centers randomised patients.

The planned number of randomised patients for this analysis was 618, however, 629 were actually randomised (314 patients to the Riximyo arm and 315 patients to the MabThera arm; two Riximyo patients were mis-randomised and were discontinued before being treated).

**Table 26 - Patient disposition by treatment – Combination phase (Randomized set)**

| Disposition Reason | GP2013 N=314 n (%) | MabThera N=315 n (%) | All patients N=629 n (%) |
|---|---|---|---|
| Patients randomized | | | |
| Untreated | 2 (0.6) | 0 | 2 (0.3) |
| Treated | 312 (99.4) | 315 (100) | 627 (99.7) |
| Primary reason for end of combination treatment[1]: | | | |
| Treatment duration completed as per protocol | 274 (87.3) | 274 (87.0) | 548 (87.1) |
| Adverse Event(s) | 7 (2.2) | 10 (3.2) | 17 (2.7) |
| Subject withdrew consent | 5 (1.6) | 4 (1.3) | 9 (1.4) |
| Administrative problems | 2 (0.6) | 1 (0.3) | 3 (0.5) |
| Death | 5 (1.6) | 7 (2.2) | 12 (1.9) |
| Disease progression | 10 (3.2) | 10 (3.2) | 20 (3.2) |
| Protocol deviation | 6 (1.9) | 2 (0.6) | 8 (1.3) |
| Physician's decision | 5 (1.6) | 7 (2.2) | 12 (1.9) |

[1] End of treatment refers to discontinuation combination study treatment.
All percentages are based on randomized patients.
Source: Table 14.1-1.1

Data sets analyzed

**Table 27 - Analysis sets by treatment (Randomized set)**

| Analysis set | GP2013 N=314 n(%) | MabThera N=315 n(%) | All patients N=629 n(%) |
|---|---|---|---|
| Full analysis set (FAS) | 312 (99.4) | 315 ( 100) | 627 (99.7) |
| Per protocol set (PP) | 311 (99.0) | 313 (99.4) | 624 (99.2) |
| Safety set | 312 (99.4) | 315 (100) | 627 (99.7) |
| Maintenance set | 231 (73.6) | 231 (73.3) | 462 (73.4) |
| Pharmacokinetic analysis set 1 (PAS+A1) | 119 (37.9) | 120 (38.1) | 239 (38.0) |
| Pharmacokinetic analysis set 2 (PAS+A2) | 27 (8.6) | 22 (7.0) | 49 (7.8) |
| Pharmacodynamic analysis set (PDAS) | 24 (7.6) | 24 (7.6) | 48 (7.6) |
| Immunogenicity analysis set | 268 (85.4) | 283 (89.8) | 551 (87.6) |

Source: Table 14.1-2.1

A total of 279 patients had at least one protocol deviation and these were balanced between the treatment arms: 137 patients (43.9%) in the Riximyo arm and 142 patients (45.1%) in the MabThera arm. These deviations were not believed to have introduced a bias in the efficacy or safety data comparisons between the two treatment arms.

**Outcomes and estimation**

Primary efficacy results

The ORR, based on the Modified Response Criteria for Malignant Lymphoma using central blinded review of the radiological response and liver/spleen enlargement assessments from the patients in the

PPS, was 87.1% in the Riximyo arm and 87.5% in the MabThera arm and the difference in ORRs was -0.40% (95% CI [-5.94%, 5.14%]; 90% CI [-5.10%, 4.30%]). Equivalence was concluded as the entire 95% CI for the difference in ORR between the two treatments was within the pre-specified equivalence margin of ±12%.

Of the 624 patients in the PPS 35 patients (5.6%; 19 Riximyo patients, 16 MabThera patients) had missing/unknown best overall response (BOR) based on central blinded review. When these patients were excluded from analysis, Overall response rate (CR or PR) was similar 0.55 (-4.03, 5.14) thus confirming previous findings. Also, OR for FAS was similar with a difference of -0.44, (95% CI: 4.03, 5.14).

**Table 28 - Primary efficacy analysis of overall response rate based on central blinded review (PPS)**

| | GP2013 N=311 | | MabThera N=313 | | GP2013 – MabThera | | |
|---|---|---|---|---|---|---|---|
| | n (%) | [90% CI][1] | n (%) | [90% CI][1] | Diff | [95% CI][2] | [90% CI][2] |
| Overall response rate (CR or PR) | 271 (87.1) | (83.59,90.15) | 274 (87.5) | (84.04,90.49) | -0.40 | (-5.94, 5.14) | (-5.10, 4.30) |

[1] The 90% CIs of ORR are exact intervals derived using the Clopper-Pearson formula.
[2] The 95% and 90% CIs for differences in proportions are based on normal approximation to the binomial distribution.
Source: Table 14.2-1.1

**Table 29 - Overall response rate based on central blinded review of tumour assessment by treatment (FAS)**

| | GP2013 N=312 | | MabThera N=315 | | | | |
|---|---|---|---|---|---|---|---|
| | n(%) | [90% CI][1] | n(%) | [90% CI][1] | Difference | [95% CI][2] | [90% CI][2] |
| Overall response rate (CR or PR) | 272 (87.2) | (83.64,90.18) | 276 (87.6) | (84.14,90.56) | -0.44 | (-5.95, 5.07) | (-5.12, 4.24) |

[1] The 90% CIs are exact intervals derived using the Clopper-Pearson formula.
[2] The 95% CI and 90% CI for differences in ORR is based on normal approximation to the normal distribution.
Source: Table 14.2-1.2

**Subgroup analyses of ORR were performed as supportive analyses to the primary analysis:**

Subgroup analyses of ORR by FLIPI score and age (< 60 years vs. ≥ 60 years; PPS, FAS). Analyses according to age demonstrated similarity. However, the two arms were numerically different for ORR randomized by FLIPI strata, favoring MabThera (91.2% vs. 82.8% in Riximyo) in the subset of patients with a FLIPI score 0-2 (low-intermediate risk), and favoring Riximyo (90.4% vs. 84.7%) in the subset of patients with a FLIPI score 3-5 (high risk).

Secondary efficacy results

***Best overall response (BOR)***

In general, the proportions of patients with BORs for the four categories were similar for the two treatment arms. The proportion of patients with BOR as 'unknown' was summarised by reason for the combination phase in the PPS and the FAS. In general, the reasons for an unknown response were balanced between the two treatment groups.

**Table 30 - Best overall response based on central blinded review (PPS)**

| Best overall response | GP2013 N=311 n (%) | [90% CI] | MabThera N=313 n (%) | [90% CI] |
|---|---|---|---|---|
| Complete Response (CR) | 46 (14.8) | (11.6, 18.5) | 42 (13.4) | (10.4, 17.0) |
| Partial Response (PR) | 225 (72.3) | (67.9, 76.5) | 232 (74.1) | (69.7, 78.2) |
| Stable Disease (SD) | 20 (6.4) | (4.3, 9.2) | 20 (6.4) | (4.3, 9.1) |
| Progressive Disease (PD) | 1 (0.3) | (0.0, 1.5) | 3 (1.0) | (0.3, 2.5) |
| Unknown (UNK) | 10 (3.2) | | 6 (1.9) | |
| Missing | 9 (2.9) | | 10 (3.2) | |

The CIs are exact intervals derived using the Clopper-Pearson formula.
Source: Table 14.2-1.3

**Table 31 - Best overall response based on investigator versus central blinded review (PPS)**

This table displays the number of patients who had a given BOR as per investigator (rows) and as per central (columns), regardless of treatment arm.

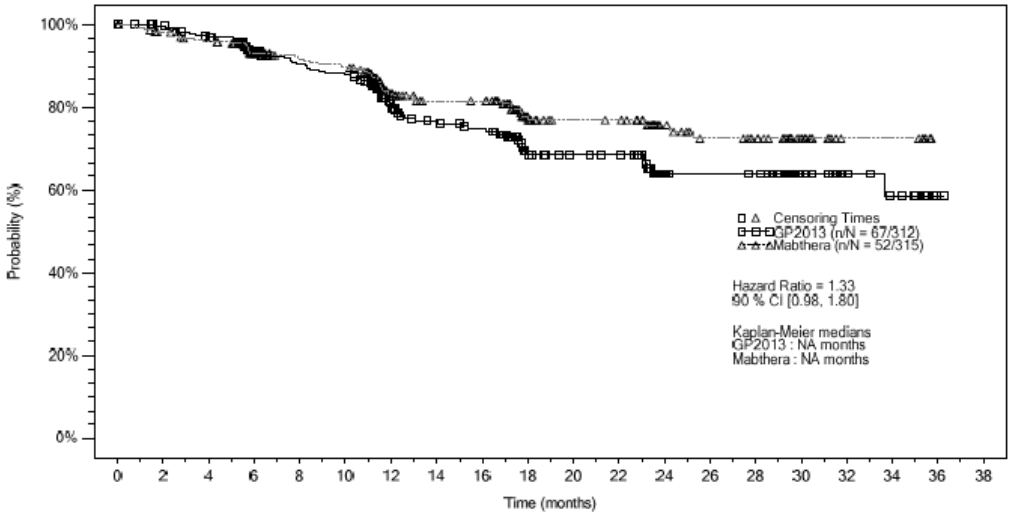
| | Investigator BOR Results[1] | | Central radiology review BOR results[1] CR (n=88) n (%) | PR (n=457) n (%) | SD (n=40) n (%) | PD (n=4) n (%) | UNK (n=16) n (%) | Missing (n=19) n (%) |
|---|---|---|---|---|---|---|---|---|
| GP2013 / MabThera (N=624) | CR (N=114) | [2] | 52 (45.6) | 58 (50.9) | 1 (0.9) | 1 (0.9) | 1 (0.9) | 1 (0.9) |
| | | [3] | 52 (59.1) | 58 (12.7) | 1 (2.5) | 1 (25.0) | 1 (6.3) | 1 (5.3) |
| | PR (N=442) | [2] | 35 (7.9) | 381 (86.2) | 20 (4.5) | 2 (0.5) | 4 (0.9) | 0 |
| | | [3] | 35 (39.8) | 381 (83.4) | 20 (50.0) | 2 (50.0) | 4 (25.0) | 0 |
| | SD (N=30) | [2] | 1 (3.3) | 14 (46.7) | 15 (50.0) | 0 | 0 | 0 |
| | | [3] | 1 (1.1) | 14 (3.1) | 15 (37.5) | 0 | 0 | 0 |
| | PD (N=9) | [2] | 0 | 1 (11.1) | 3 (33.3) | 1 (11.1) | 3 (33.3) | 1 (11.1) |
| | | [3] | 0 | 1 (0.2) | 3 (7.5) | 1 (25.0) | 3 (18.8) | 1 (5.3) |
| | Unknown (N=29) | [2] | 0 | 3 (10.3) | 1 (3.4) | 0 | 8 (27.6) | 17 (58.6) |
| | | [3] | 0 | 3 (0.7) | 1 (2.5) | 0 | 8 (50.0) | 17 (89.5) |

N: The total number of patients in investigator radiological reviews.
n: Number of patients who are at the corresponding Category. Missing: patient who never has a central blinded review.
[1] Best Overall Response (BOR) for both response based on central radiology review of tumor assessment and based on investigator assessment of tumor.
[2] Row percent rates are calculated as the number of patients in the corresponding cell (e.g., CR/CR) divided by the total number of patients corresponding to that particular row as per investigator assessment (e.g., all patients with investigator BOR result = CR).
[3] Column percent rates are calculated as the number of patients in the corresponding cell (e.g., CR/CR) divided by the total number of patients corresponding to that particular column as per central radiology review (e.g., all patients with radiology review BOR result = CR)
Source: Table 14.2-1.12

**PFS**

PFS was based on investigator assessment only.

The median PFS was not reached for either of the two treatment groups. As of the time of data cutoff (10-Jul-2015), respectively 21.5% [n=67] and 16.5% [n=52] of patients in Riximyo and MabThera treatment arms progressed or died, with 62.5% [n=195] and 71.7% [n=226] patients censored without event and having adequate follow-up, respectively. The hazard ratio (HR) estimate and its associated 90% CI are obtained by fitting Cox regression model with treatment allocation as covariate and FLIPI score as stratification factor. The PFS HR (Riximyo/MabThera) was 1.33 (90% CI: [0.98, 1.80]), based on the investigator assessment.




No. of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GP2013 | 312 | 298 | 285 | 217 | 196 | 190 | 135 | 119 | 113 | 79 | 71 | 69 | 39 | 37 | 36 | 22 | 14 | 10 | 1 | 0 |
| Mabthera | 315 | 301 | 291 | 220 | 204 | 200 | 143 | 128 | 127 | 85 | 74 | 73 | 49 | 41 | 37 | 20 | 8 | 8 | 0 | 0 |

**Figure 15 - Kaplan-Meier plot of PFS by treatment based on investigator assessment (FAS)**

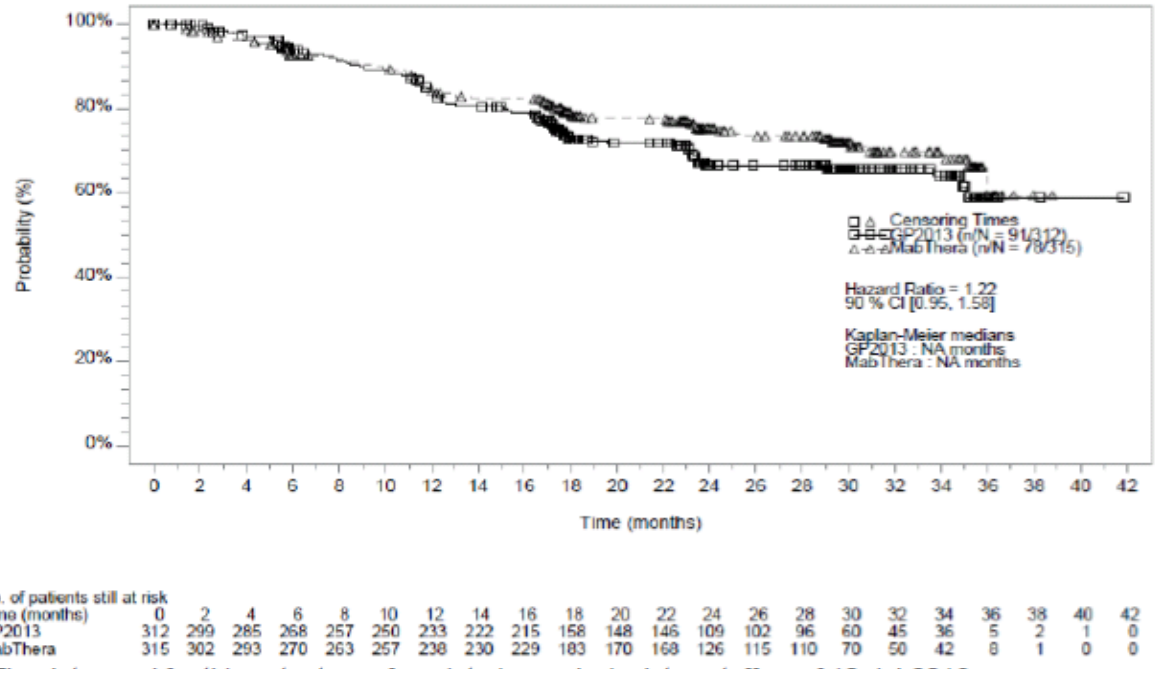
### Ancillary analyses

The PFS analysis was repeated with refined criteria for PFS events and censoring.

**PFS – Set 1** is defined using the following modified censoring rules: If patient has no event, the date is set as date of last adequate tumour assessment; If there is no adequate assessment, then the date is set as randomisation date; An adequate assessment is defined as an assessment with known overall response (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]). As of database cut-off, 10-Jul-2016, 91 of 312 (29.2%) patients in the Riximyo and 78 of 315 (24.8%) patients in the MabThera treatment arms had a PFS event using the set 1 definition. The result of the sensitivity analysis of PFS following the set 1 rules with a hazard ratio of 1.22 (with 90% CI: [0.95, 1.58]).

**Table 32 - Sensitivity analysis of PFS based on investigator assessment: KM and cox-regression method with modified censoring rules – Set 1 (FAS)**

| | Event/ N (%) | Median time in months (90% CI) | Cox Model [1] Hazard Ratio | 90% CI |
|---|---|---|---|---|
| All Patients | | | | |
| GP2013 | 91/312 (29.2) | NE | 1.22 | [0.95, 1.58] |
| MabThera | 78/315 (24.8) | NE | | |




No. of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GP2013 | 312 | 299 | 285 | 268 | 257 | 250 | 233 | 222 | 215 | 158 | 148 | 146 | 109 | 102 | 96 | 60 | 45 | 36 | 5 | 2 | 1 | 0 |
| MabThera | 315 | 302 | 293 | 270 | 263 | 257 | 238 | 230 | 229 | 183 | 170 | 168 | 126 | 115 | 110 | 70 | 50 | 42 | 8 | 1 | 0 | 0 |

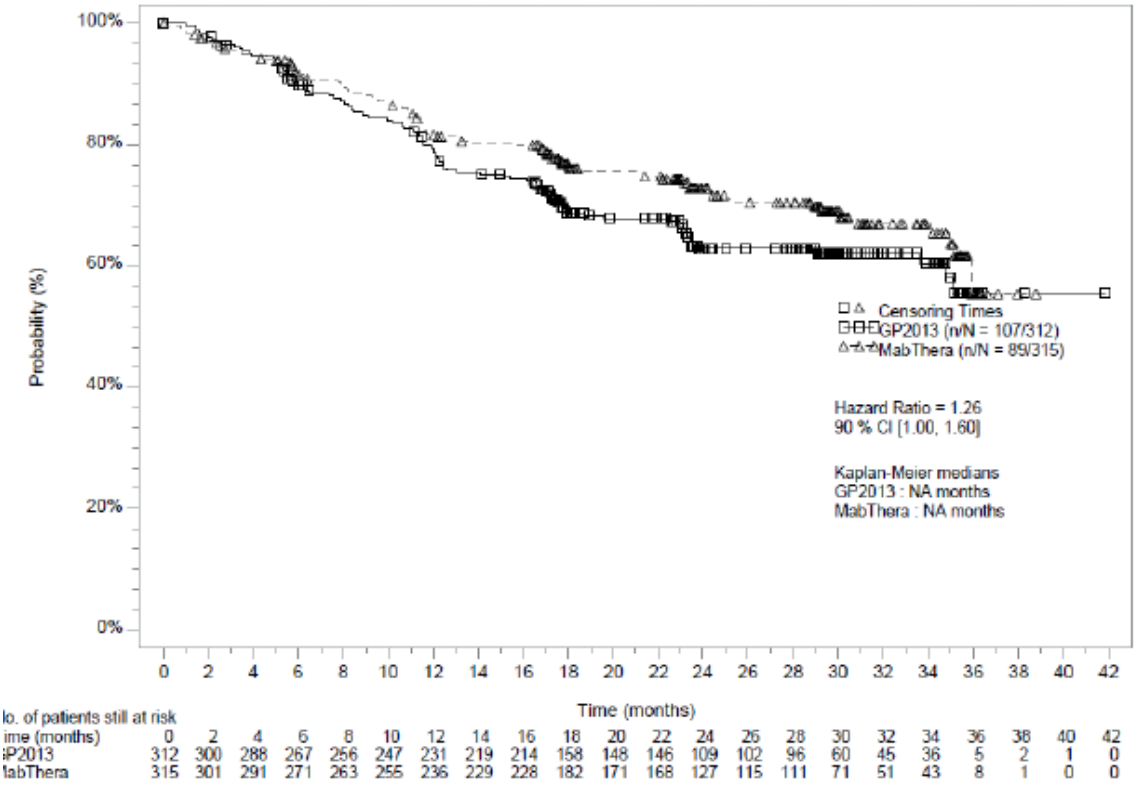
**Figure 16 - K-M plot of PFS by treatment (by investigator – modified censoring rules – Set 1 (FAS)**

**PFS – Set 2**

PFS for set 2 is defined as the time from the date of randomisation to date of event which is defined as the first observation of disease progression (documented or without documentation of evidence of disease progression based on the investigator response), death, or start of another cancer therapy, using the following modified censoring rules: If patient has no event, the date is set as date of last adequate tumour assessment; If there is no adequate assessment (with known overall response CR, PR, SD or PD), then the date is set as randomisation date.

**Table 33 - analysis of PFS based on investigator assessment: KM and cox-regression – Set 2 (FAS)**

| | Event/ N (%) | Median time in months (90% CI) | Cox Model [1] Hazard Ratio | 90% CI |
|---|---|---|---|---|
| All Patients | | | | |
| GP2013 | 107/312 (34.3) | NE | 1.26 | [1.00, 1.60] |
| MabThera | 89/315 (28.3) | NE | | |




The data used for this output was from interim analysis data cutoff as of 10-Jul-2016.

**Figure 17 - 21: K-M plot of PFS by treatment (by investigator – Set 2 (FAS)**

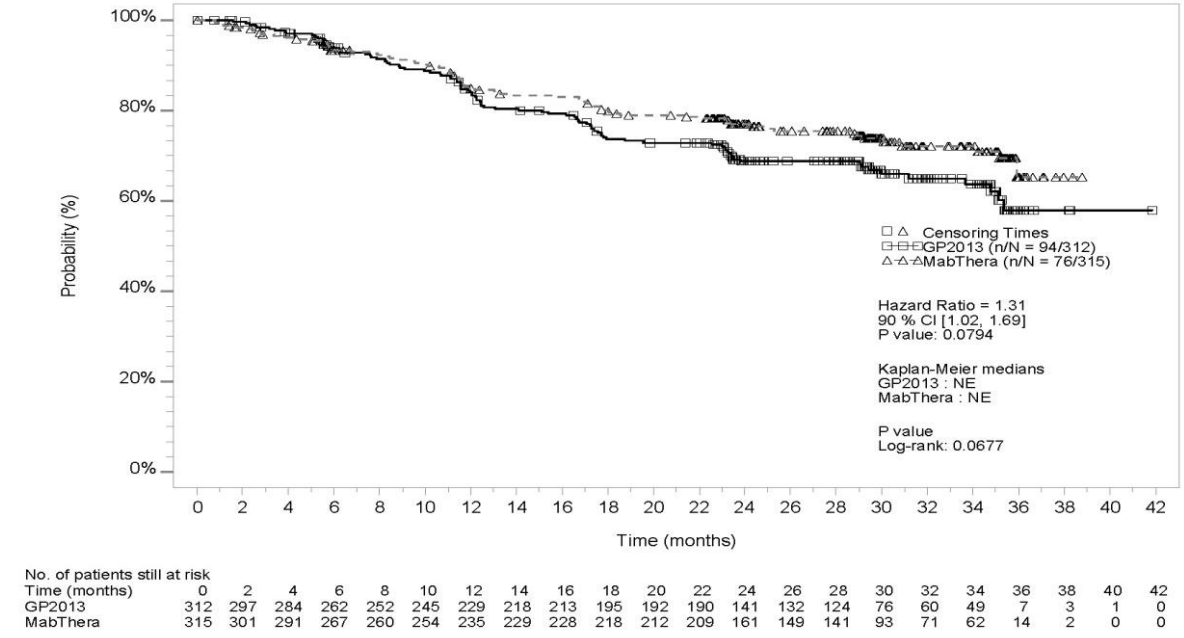



**Figure 18 - Kaplan-Meier plot of PFS by treatment based on investigator assessment (FAS) – data cut off December 2016**

**GAP analysis for PFS**

In order to assess the robustness of the random censoring mechanism for PFS, for censored patients, the gap between data cutoff date and last tumour assessment was assessed.

The median gap time for PFS follow-up as compared to cut-off date in patients who were still followed-up for efficacy between the Riximyo and MabThera groups was 3.2 months and 3.0 months, respectively. A minority of patients had a gap of more than one year between the data cutoff date and their last tumour assessment; 8.2% [n=20] and 5.7% [n=15] of censored patients in Riximyo and MabThera groups, respectively.

For all patients, 30.3% and 25.4% of patients had less than 6 months and 6 to 12 months PFS follow-up, respectively; these percentages were similar between the treatment groups. Considering that the majority of PFS events occurred during the Maintenance Phase, these figures are suggestive of immaturity of PFS data and should be taken into account when interpreting PFS results.

**OS**

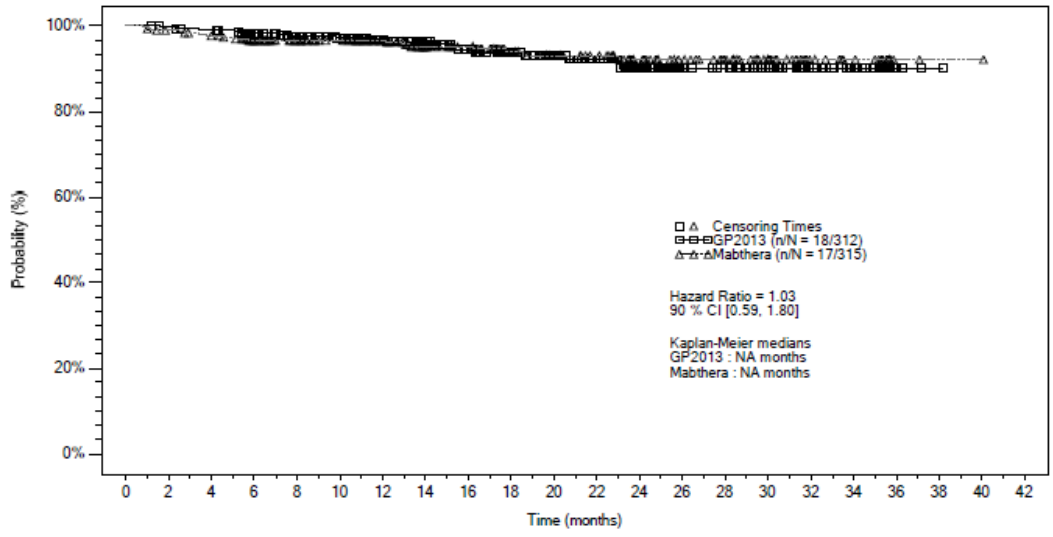
At the time of data cutoff (10-July 2015), the number of deaths (18 events in the Riximyo group vs. 17 events in the MabThera group) were similar between the two treatment arms.

**Table 34 - Analysis of OS using Kaplan-Meier and Cox regression (FAS)**

| | | | Cox Model | |
|---|---|---|---|---|
| | Event / N(%) | Median time in months (90% CI) | Hazard Ratio[1] | 90% CI |
| All Patients | | | | |
| GP2013 | 18/312 (5.8) | NE | 1.03 | (0.59, 1.80) |
| MabThera | 17/315 (5.4) | NE | | |

[1] The hazard ratio (HR) estimate and its associated 90% CI are obtained by fitting Cox regression model with treatment allocation as covariate and FLIPI score as stratification factor. This study is not powered for any hypothesis testing, hence, the HR and its associated 90% CI are presented for descriptive purpose.

The median OS has not yet been reached for either treatment group based on the currently available data. The analysis of OS using the Cox regression method showed that the HR was 1.03 (90% CI: 0.59, 1.80).




No. of patients still at risk

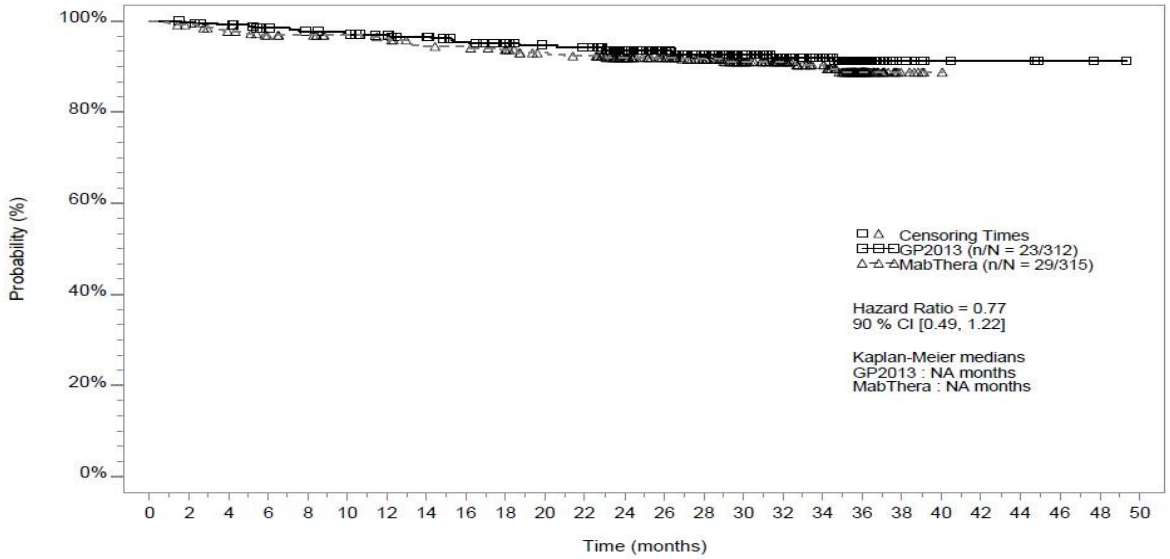
| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GP2013 | 312 | 309 | 305 | 279 | 250 | 238 | 204 | 173 | 154 | 134 | 112 | 97 | 74 | 55 | 51 | 41 | 29 | 20 | 5 | 1 | 0 | 0 |
| Mabthera | 315 | 309 | 302 | 279 | 251 | 230 | 201 | 169 | 159 | 131 | 107 | 96 | 77 | 64 | 54 | 37 | 20 | 14 | 2 | 1 | 1 | 0 |

Source: Figure 14.2-1.2 Kaplan-Meier plot of OS by treatment (FAS)

**Figure 19 - Kaplan-Meier plot of OS by treatment (FAS)**

The analysis of overall survival using the Kaplan-Meier and Cox-regression method for the PPS was consistent with the findings for the FAS.

The reasons for censoring patients were also similar between the two treatment groups.




No. of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GP2013 | 312 | 310 | 306 | 299 | 295 | 292 | 286 | 280 | 272 | 268 | 260 | 258 | 227 | 202 | 185 | 163 | 133 | 119 | 54 | 11 | 5 | 4 | 4 | 2 | 1 | 0 |
| MabThera | 315 | 310 | 303 | 295 | 293 | 288 | 285 | 277 | 276 | 272 | 261 | 258 | 235 | 214 | 195 | 166 | 141 | 116 | 57 | 6 | 1 | 0 | 0 | 0 | 0 | 0 |

**Figure 20 - Kaplan-Meier plot of OS by treatment (FAS)- data cut off 31-12- 2016**

**Table 35 - Summary of reasons for censoring patients for PFS and overall survival analysis by treatment (FAS – data cut off July 2015)**

| Study analysis endpoint(s) | Reason of censoring | GP2013 N=312 n (%) | MabThera N=315 n (%) | Total N=627 n (%) |
|---|---|---|---|---|
| OS | Number of patients censored | 294 (94.2) | 298 (94.6) | 592 (94.4) |
| | Reason of censoring | | | |
| | Alive[1] | 291 (93.3) | 294 (93.3) | 585 (93.3) |
| | Lost to follow-up[2] | 3 (1.0) | 4 (1.3) | 7 (1.1) |
| PFS | Number of patients censored | 245 (78.5) | 263 (83.5) | 508 (81.0) |
| | Reason of censoring | | | |
| | Ongoing without event[1] | 195 (62.5) | 226 (71.7) | 421 (67.1) |
| | Initiation of new anticancer therapy | 15 (4.8) | 8 (2.5) | 23 (3.7) |
| | Adequate assessment no longer available[3] | 35 (11.2) | 29 (9.2) | 64 (10.2) |

[1] Patients without event and had adequate follow-up as of data cut-off date of 10-Jul-2015.
[2] Recorded on the End of treatment CRF, Study evaluation completion CRF or defined as not adequately followed as of the cut-off
[3] Patients censored without adequate evaluations for a specified period prior to data cut-off or without adequate baseline assessments.

**Summary of main study**

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 benefit risk assessment (see later sections).

**Table 36 - Summary of efficacy for trial GP13-301**

| **Title:**<br><br>A randomised, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of Riximyo plus cyclophosphamide, vincristine, prednisone vs. MabThera plus cyclophosphamide, vincristine, prednisone, followed by Riximyo or MabThera maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma | | |
|---|---|---|
| Study identifier | GP13-301 (CIGG013A2301J) | |
| Design | Parallel group design | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 8 cycles (~ 6 months)<br>not applicable<br>not applicable |
| Hypothesis | Equivalence | |
| Treatments groups | Riximyo | Combination Phase:<br>Riximyo: 375 mg/m2 + CVP every 21 days for 8 cycles;<br>number randomized = 314 (2 misrandomized) |

| | | | |
|---|---|---|---|
| | Mabthera | | Combination Phase:<br>MabThera: 375 mg/m2 + CVP every 21 days for 8 cycles;<br>number randomized = 231 |
| Endpoints and definitions | Primary endpoint | ORR | ORR defined as the proportion of patients whose best overall disease response (BOR) either CR or PR during the combination treatment period (according Central Blinded Review of radiological response). |
| | Secondary | PFS | Time from randomisation to either PD or death |
| | Secondary | OS | Time from randomisation to death |
| Database lock | data cutoff (10-Jul-2015) | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Per Protocol Population<br>At the end of the combination phase | | | |
| Descriptive statistics and estimate variability | Treatment group | Riximyo | MabThera | |
| | Number of subject | 311 | 313 | |
| | ORR | 271/311 (87.1%) | 274/313 (87.5%) | |
| | 90%-CI | (83.59%, 90.15%) | (84.04%, 90.49%) | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | Riximyo - Mabthera |
| | | Difference in incidences | -0.40% |
| | | 95%-CI | (-5.94, 5.14) |
| | | Equivalence margin | (-12%, 12%) |
| Notes | Equivalence has been shown. The primary analyses results are supported by the outcome of various sensitivity analyses: e.g. same analysis excluding patients with missing values: difference in ORR -0.55 (95%-CI: -4.03, 5.14); FAS analysis: difference -0.44 (95%-CI:-5.95%, 5.07%). | | |

| **Analysis description** | **Secondary analysis** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Full Analysis Set<br>Start of treatment until date of data cutoff | | | |
| Descriptive statistics and estimate variability | Treatment group | Riximyo | MabThera | |
| | Number of subject | 312 | 315 | |
| | PFS (median months) | NE | NE | |
| | OS (median months) | NE | NE | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | PFS | Comparison groups | Riximyo - Mabthera |
| | | HR1 | 1.33 |
| | | 90%-CI | (0.98, 1.80) |
| Effect estimate per comparison | OS | Comparison groups | Riximyo - Mabthera |
| | | HR1 | 1.03 |
| | | 90%-CI | (0.59, 1.80) |

**Analysis performed across trials (pooled analyses and meta-analysis)**

N/A

**Clinical studies in special populations**

**Table 37 - Clinical efficacy in patients aged ≥65 years old**

| | **Age 65 – 74 (Older subjects number / total number)** | | **Age 75 – 84 (Older subjects number / total number)** | | **Age 85+ (Older subjects number / total number)** | |
|---|---|---|---|---|---|---|
| | **Riximyo** | **Originator*** | **Riximyo** | **Originator*** | **Riximyo** | **Originator*** |
| **Controlled Trials** | | | | | | |
| **GP13-201** | 22/133 | 35/179 | 6/133 | 3/179 | -- | -- |
| **GP13-301** | 63/314 | 65/315 | 23/314 | 15/315 | -- | -- |
| **Non Controlled Trials** | | | | | | |
| **GP13-101** | 1/6 | -- | -- | -- | -- | -- |

*Originator is for GP13-201 study MabThera (data from Part I Week 52) and Rituxan (data from Part II Week 24) combined; for GP13-301 study originator is MabThera.

***Supportive study GP13-201***

Supportive efficacy data were obtained from study GP13-201, the pivotal PK/PD study conducted in adult patients with active RA (3rd line treatment- see also Clinical pharmacology section)

The study consisted of a screening period (running from Visit 1 up to but not including Visit 3), an optional washout period between Visit 1 and Visit 2 for anti-TNF or DMARD, a baseline visit (Visit 2) to reassess the RA status and associated laboratory testing in order to confirm eligibility of the patient and to perform a complete disease activity assessment. Visit 3 (Day 1) consisted of randomisation and first study drug administration.

On Week 24 after the first infusion, patients who were considered responders (defined as having a decrease in Disease Activity Score (DAS28) and if they had at least residual active disease (DAS28 ≥ 2.6) were re-treated with a second course of treatment (either 1000 mg i.v. Riximyo or MabThera on two separate occasions, 2 weeks apart) up to Week 52 at the discretion of the investigator. Patients who received this second course of treatment had a safety, efficacy and PD assessment performed 26 weeks after the first infusion of the second course of study medication.

The primary objective was to assess the PK bioequivalence between Riximyo and MabThera in combination with MTX. Secondary objectives also included several efficacy parameters:

- Change from baseline in DAS28 (CRP) at Week 24 (key secondary efficacy endpoint)
- Averaged change from baseline in DAS28 (CRP) between Weeks 4 and 24
- DAS28 by visit
- Change from baseline in DAS28 across study drug batches
- ACR20 response analysis
- Difference in ACR-N scores at Week 24
- ACR20, ACR50, ACR70 response analysis
- EULAR response based on DAS28 (CRP)
- Disease activity according to DAS28
- Disease activity according to SDAI/CDAI
- Quality of Life
- Rheumatoid factor (RF) and Anti-CCP antibodies (ACPA)

*Efficacy Results Study GP13-201*

A total of, 173 patients were randomised, of which 86 patients received Riximyo and 87 patients received MabThera. The majority of randomised patients (82.1%) completed up to 52 weeks. About 65% of the subjects were re-treated in period following Week 24. In total 6 patients were excluded from the per-protocol set, because of major protocol violations (not meeting inclusion criteria, receiving wrong study drug and missing CRP measurements).

Baseline demographics and disease severity were comparable for the Riximyo and MabThera treatment groups, and reflected the intended target population. The majority of patients were female (86.1%) and Caucasian (80.9%). The mean age of all patients was 53.7 years and 20.8% of patients were ≥65 years of age. The mean duration of RA was 10.07 years (range: 1.0 to 34.0 years). All patients had previously been treated with 1-3 anti-TNFs or other biologic DMARDs, in line with the protocol inclusion criteria. The mean DAS28 (CRP) scores at baseline were 5.81 (SD=0.92) and 5.85 (SD=0.88), in the Riximyo and MabThera groups, respectively, indicating moderate-severe disease activity.

In both treatment groups, the DAS28 scores improved significantly form baseline (see Figure 21 below). The mean changes from baseline were comparable between Riximyo and MabThera. The upper limit of the 95% CI of the difference between both groups was 0.462, below the pre-defined non-inferiority criterion of 0.6.

**Table 38 - Averaged change from baseline in DAS28 (CRP) at Week 24 (PP Analysis Set)**

| Treatment group | LS Mean (standard error) | LS Mean difference (standard error) | 95% CI of difference |
|---|---|---|---|
| GP2013 (N= 85) | -2.16 (0.142) | 0.07 (0.201) | (-0.328, 0.462) |
| MabThera® (N= 82) | -2.23 (0.143) | | |

LS=least squares, CI=confidence interval

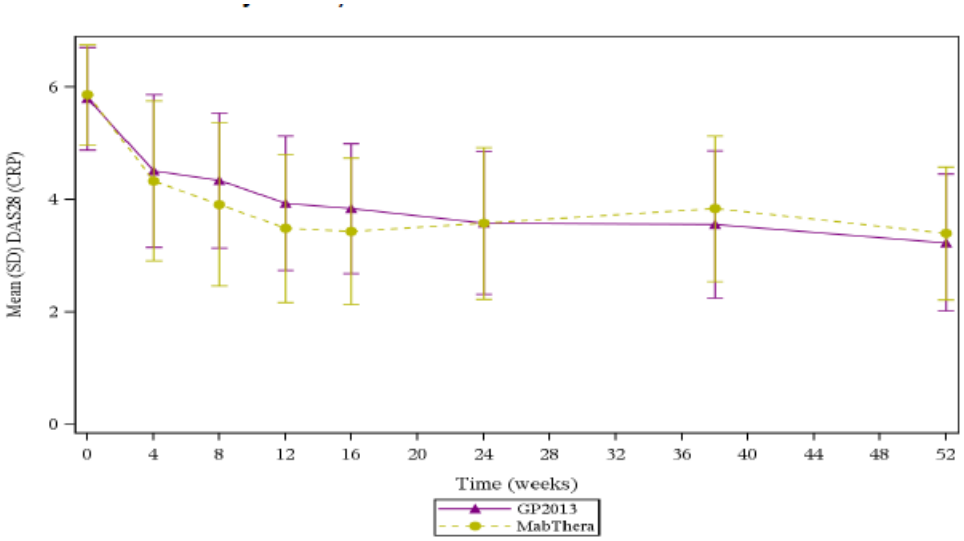



**Figure 21 - Mean (SD) DAS28-CRP scores, Study GP13-201**

The ACR20 (CRP) response rates at Week 24 were 71.8% and 72.4% in the Riximyo and MabThera group, respectively. The lower limit of the 95% CI for the difference in response rates was -14.74%, above the pre-defined equivalence margin of -15.0%.

**Table 39 - ACR20 responder rates, Week 24, Study GP13-201**

| Treatment group | Total | ACR20 (CRP) responders n (%) | Response rate difference (%) / (standard error) | 95% CI of difference |
|---|---|---|---|---|
| GP2013 (N= 85) | 78 | 56 (71.8) | -0.57 (7.23) | (-14.74, 13.60) |
| MabThera® (N= 82) | 76 | 55 (72.4) | | |

1. n: the number of ACR20 responders.
2. Total is the number of subjects with a valid ACR20 assessment at Week 24 and is the denominator used for ACR20 (CRP) responders.
3. To conclude non-inferiority the lower 95% CI should be greater than -15.0%.

Retreatment (i.e. a second treatment course), occurred in about 65% of the participants (59 in Riximyo arm, and 60 in the MabThera arm), after on average 232.8 (SD62.1) days and 241.5 (SD64.4) days, respectively. Beyond B-cells levels and ADA (anti-drug-antibody), no clinical outcomes were reported after retreatment.

**Table 40 - Summary of Study GP13-201 efficacy in RA**

| | | |
|---|---|---|
| **Title**: A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of Riximyo and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies. | | |
| Study identifier | GP13-201 | |
| Design | This is a 52-week multicenter, randomized, double-blind, study designed to assess the pharmacokinetics, pharmacodynamics, safety and efficacy of Riximyo and MabThera® in patients with RA refractory or intolerant to one or up to three anti-TNF therapies.<br>Study Part I design: Patients received their first course of treatment (study drug infusion on two separate occasions, two weeks apart) and were followed for 52 weeks. After Week 24, responders (defined as having a decrease in DAS28 derived either with ESR or CRP of > 1.2 from baseline) could be re-treated with study medication at the discretion of the investigator, if they had at least residual active disease (DAS28 ≥ 2.6). | |
| | Duration of main phase: | 52 weeks |

| | | | |
|---|---|---|---|
| | Duration of Run-in phase: | None | |
| | Duration of Extension phase: | None | |
| Hypothesis | **Equivalence:**<br>**Primary objective:** Bioequivalence between Riximyo and MabThera (PK)<br>**Secondary objective:**<br>• Non-inferiority of Riximyo to MabThera with respect to:<br>  • Change from baseline in DAS28 (CRP) disease activity score at Week 24 (using a mixed model for repeated measures). The upper bound of the 95% confidence limit for the mean difference between Riximyo and MabThera was to be equal or less than 0.6 in order to conclude equivalence.<br>  • ACR20 (CRP) response rate at Week 24 (estimated based on pooled standard error and chi-square statistics). The lower bound of the 95% confident limit was to be greater than -15% in order to conclude equivalence. | | |
| Treatments groups | Riximyo | | Riximyo: Two 1000 mg iv infusions, on Day 1 and Day 15, add-on to methotrexate<br>Number of patients randomized: 86 |
| | MabThera | | MabThera: Two 1000 mg iv infusions, on Day 1 and Day 15, add-on to methotrexate<br>Number of patients randomized: 87 |
| | Efficacy secondary endpoints:<br>Equivalence of Riximyo to MabThera with respect to change from baseline in DAS28 (CRP) at Week 24 | DAS28 (CRP) at Week 24 | Change from baseline in DAS28 (CRP) at Week 24. A two-sided 95% CI for the mean difference between Riximyo and MabThera® was derived and compared to the pre-specified equivalence margin of 0.6. |
| | Equivalence of Riximyo to MabThera with respect to ACR20 (CRP) response rate at Week 24: Comparison between Riximyo and MabThera | ACR20 (CRP) at Week 24 | Percentage of ACR20 responders at Week 24 |
| Database lock | 11-Dec-2014 | | |

| | | | |
|---|---|---|---|
| Results and Analysis | | | |
| | Secondary endpoint<br>Change from baseline in DAS28 (CRP) at Week 24 (PPS) | Comparison groups | Riximyo vs. MabThera |
| | | LSM difference | 0.07 |
| | | SE<br>95% CI of mean difference | 0.201<br>[-0.328, 0.462] |
| | | P-value | Not evaluated |
| | Secondary endpoint<br>ACR20 (CRP) at Week 24 (PPS) | Comparison groups | Riximyo vs. MabThera |
| | | Response rate difference (%) | -0.57 |

| | | | |
|---|---|---|---|
| | | SE<br>95% CI of mean difference | 7.23<br>[-14.74, 13.60] |
| | | P-value | Not evaluated |
| Analysis description | Analysis of key secondary variables:<br>For the key secondary efficacy endpoint change from baseline in DAS28 at Week 24 (using CRP for the calculation), a mixed model for repeated measures was used, to estimate both mean change from baseline at Week 24 and the averaged change between Week 4 and 24. Two-sided 95% Cl for the mean difference between Riximyo and MabThera were derived and compared to the pre-specified margin of 0.6. The upper limit of the CI was required to be equal to or less than 0.6 in order to claim equivalence.<br><br>Analysis of other secondary variables:<br>A two-sided 95% CI for the difference in both the ACR20 (CRP) response rates at Week 24 was estimated based on the pooled standard error and chi-square statistic. The lower bound of the confidence limit must be greater than -0.15 or -15.0% in order to conclude equivalence. | | |

## 2.5.3. Discussion on clinical efficacy

***Design and conduct of clinical studies***

Dose response studies are not required for biosimilar products. For the justification of the dose, a reference is made to the dossier of the originator.

In the pivotal study GP13-301, the choice of the study population of patients with advanced stage Follicular lymphoma to demonstrate therapeutic equivalence is supported as this is the most common of the approved oncology indications of MabThera. Moreover, the additive treatment effect to a background therapy of CVP is expected to be reasonable large in this population based on historical data, indicating that FL is a sensitive model to detect differences between the biosimilar and originator product.

The parallel, two-arm, randomised study was adequately designed. The ORR, determined by central reading, is considered a relevant primary endpoint for this indication. The equivalence margin of +/- 12% is considered acceptable from a clinical perspective. This margin is below the 95% CI of the treatment effect of the main study of the reference product in this indication. In the placebo-controlled study of the originator, the ORR was 81% for the MabThera-CVP arm and 57% for CVP + placebo arm, with a treatment effect of 24% (95% CI: 14%, 34%). Moreover, the choice of 12% margin is also supported by the indirect confidence interval approach, which was calculated to be 13.4% by the Applicant, in accordance the EMA Guidance Choice of Non-inferiority Margin. The missing data imputation of the ORR measures by considering missing data as non-responders, is considered appropriate.

Efficacy was a secondary endpoint in Study GP13-201 in RA patients, which was powered and designed to establish bio-equivalence of PK as primary objective. As the study was not powered to establish non-inferiority (or equivalence) of efficacy, the data on therapeutic endpoints should be considered as supportive.

In RA, the regular maintenance dosing schedule is every 24 weeks (6 months). Treatment continuation with a second course of the study drugs after 24 weeks and the timing of a second course was to be individually decided by the prescriber, based on the level of residual disease activity. Therefore, the

data sampling from the second part of the study was more variable, hampering firm conclusions regarding long-term efficacy after Week 24. The decision making regarding re-treatment was in line with the posology of MabThera and SAWP recommendations.

The choice of mean change from baseline of DAS28 as 'key' secondary endpoints, instead of ACR20 responder rate as originally proposed in the Scientific Advice in 2011, is supported, as continuous endpoints may be more sensitive to evaluate therapeutic equivalence than dichotomous ones. The NI margin of 0.6 points is agreed, as it is based on clinical grounds, i.e. a change of DAS28 score of 0.6 is considered a minimal clinically relevant change. For another secondary endpoint, ACR20, the NI margin was set at +/- 15%. The cut-off of 15% was based on meta-analysis of other RA studies showing a difference of ACR20 of 31% (95% CI 25%, 38%) between rituximab and MTX. The 15% equivalence limit is approximately half of this effect size, and is below the lower limit of the 95% CI. The 15% margin is considered relatively high from a clinical perspective. However, it is acceptable in this context. No imputation of missing data was applied for the efficacy outcomes, and the analyses were performed in the Per-Protocol set. Considering the exploratory character of the study regarding the clinical efficacy endpoints and that the study was not powered for establishing equivalence of efficacy in RA, this is accepted.

A high frequency of minor protocol deviations was reported for both studies; most frequently reported minor protocol deviations being "PK sample out of visit window or missing" (96.5%), "scheduled visits out of the defined time window" (59.5%), "blood pressure measurement not performed per protocol" (18.5%), and "premedication not administered per protocol" (16.8%). It is not expected that critical findings of GCP Inspection of one site would have largely influenced the study outcomes, given the small number of subject involved, and that three other sites were considered GCP-compliant.

***Efficacy data and additional analyses***

GP13-301 (pivotal efficacy trial)

The demographics were largely similar between the treatment arms in terms of age, gender, race, or other demographic parameters. Patients treated with Riximyo were slightly more likely older, more female, Caucasian (and not Asian), with better ECOG but only with minor differences. Regarding disease history there is a slight increase of patients with bulky or stage 4 disease in the Mabthera treated group.

The ORR was 87.1% in the Riximyo arm and 87.5% in the MabThera arm and the difference in ORRs was -0.40% (95% CI [-5.94%, 5.14%]; 90% CI [-5.10%, 4.30%]). Equivalence was concluded as the entire 95% CIs for the difference in ORR between the two treatments was within the pre-specified equivalence margin of ±12%. Thus, the primary endpoint was met. This was further supported by pre-defined sensitivity analyses.

Subgroup analyses according to age demonstrated similarity. However, the two arms were numerically different for ORR randomized by FLIPI strata, favoring MabThera (91.2% vs. 82.8% in Riximyo) in the subset of patients with a FLIPI score 0-2 (low-intermediate risk), and favoring Riximyo (90.4% vs. 84.7%) in the subset of patients with a FLIPI score 3-5 (high risk). However, an analysis of PFS and OS according to FLIPI score did not reveal major differences with regards to outcome between the treatment arms.

In general, the proportions of patients with best overall response (BOR) for the four categories (CR, PR, SD and PD) were similar. The results of the sensitivity analysis repeated using the FAS were consistent with those seen in the PPS.

Notably, the rate of Complete Remission (about 14%) was significant lower in Study 301 than reported before for other trials (Marcus: 30%, Federico: 67%). This might be explained by differences in the study populations. Patients in the Study GP13-301 had a higher risk at baseline (FLIPI 3 score -5 in 56% of patients), than in the historical trials (22-38%) The CR rate was assessed and confirmed by central review, which was not the case with public available CR rates from historical trials where only CR rates from local reading are available. Thus, the CR outcomes of Study GP13-301 met more stringent criteria; however, the CR rates were balanced between both treatment arms of Study GP13-301, and the overall response (ORR) is high and similar. Assay sensitivity could still be assumed despite the relative low CR rates, as the overall ORR is in the same range as reported before, and response might be even lower in populations at higher risks –providing a potential larger treatment effect.

When comparing best overall response based on investigator versus central blinded review it was observed that for 114 patients who had a CR as per investigator, the central review confirmed only 52 as a CR and 58 as a PR with a few results being determined as SD, PD and unknown. However, this discrepancy is not viewed as important since (a) primary analyses were conducted under central review, (b) the discrepancy is only one stage category and (c) even with this difference the primary endpoint is ORR which is the sum of both CR + PR. However, such discrepant findings may impact on the PFS analysis, which was conducted as secondary analysis and by investigator review only (see further below).

PFS was based on investigator assessment. The median PFS was not reached for either of the two treatment groups. As of the time of data cutoff (10-Jul-2015), respectively 21.5% [n=67] and 16.5% [n=52] of patients in Riximyo and MabThera treatment arms progressed or died, with 62.5% [n=195] and 71.7% [n=226] patients censored without event and having adequate follow-up, respectively. The majority of these patients were still ongoing after the Combination Treatment Phase so their eventual PFS outcomes in the study may still potentially alter the PFS curve of either treatment arm beyond 6 months.

The PFS HR (Riximyo/MabThera) was 1.33 (90% CI: [0.98, 1.80]), based on the investigator assessment indicating that PFS may deviate between assignments in the treatment maintenance phase, not in favour of Riximyo (data cut-off 10-Jul-2015). It has to be taken into consideration that the study is not adequately powered to demonstrate equivalence of PFS. With the PFS update of 10-Jul-2016 the hazard ratio is 1.25 (with 90% CI: [0.96, 1.61]) thus decreasing with an increase in number of events over time. The median follow-up time was 18.15 months for the Riximyo group and 22.80 months for the MabThera group. The median PFS could not yet be estimated for either treatment group based on the currently available data. Considering that the majority of PFS events occurred during the Maintenance Phase, these figures are still suggestive of immaturity of PFS data. Sensitivity analyses were performed on the PFS in the ongoing monotherapy maintenance treatment phase. The landmark analyses, selecting patients who were at risk of progression at the time of entrance of the maintenance phase –i.e. those patients without progression in the first combination-therapy study phase-, showed similar outcomes as the ITT FAS analyses. Refined criteria for PFS events and censoring did not lead to different conclusions. When exploring differences of time-interference for either treatment, using Kaplan-Meier estimates up to the time point of the last event occurred, a statistically significant difference in PFS was observed after 24 months between Riximyo and MabThera, but no statistically significant differences were noted at other time-points. However, Month 24 is only covering a third of the enrolled study population, and the data were too immature for final conclusions on differences in time-interference. In the updated submission (data cut off: 31-Dec-2016) the number of PFS events was still low and the rate of censoring high. The divergence between the two KM curves has not decreased with these updated data. The PFS HR (Riximyo/MabThera) was 1.31

(90% CI [1.02, 1.69]), in the same range as observed with the first PFS analysis (data cut off: 10-Jul-2016) thus in line with the PFS findings from the 1st PFS interim analysis. The follow-up time is still too short to allow for an estimation of median PFS.

The divergence is considered due to patient heterogeneity or random data variation rather than a real treatment effect; the study was not powered to demonstrate similarity (nor to detect a difference) in PFS between the products, and that the PFS results should be interpreted with caution. Moreover, the potential PFS difference is not reflected by an effect in CR rates at various time points (month 15, 27, 33 and at end of study). CR has been shown to correlate with OS (even as surrogate marker when measured at week 30) whereas PFS has not. [Shi Q, Flowers CR, Hiddemann W et al (2017); Thirty-months complete response as a surrogate end point in first-line follicular lymphoma therapy: An individual patient-level analysis of multiple randomized trials. J Clin Oncol 35(5): 552-560]. Furthermore, the interpretability of the PFS results is hampered by the study design (PFS assessment at only 6 month time interval, and no planned assessment for disease progression beyond 3 years follow up), the immaturity of the data, the high level of censoring (70% of the patients with main reason for censoring "adequate assessment no longer available", ~50% of censored patients), and median follow up time of less than 2 years.

As of July 2015, the number of deaths (18 events [5.8%] in the Riximyo group vs. 17 events [5.4%] in the MabThera group) were similar between the two treatment arms. The median OS has not yet been reached for either treatment group based on the currently available data. The analysis of OS using the Cox regression method showed that the HR was 1.03 (90% CI: 0.59, 1.80) at July 2015 and with the data update from 15-Jul-2016 the HR for OS changed to 0.78 and to 0.77 (90% CI: [0.49, 1.22]) at data cut off: 31-Dec-2016. The analysis of overall survival using the Kaplan-Meier and Cox-regression method for the PPS was consistent with the findings for the FAS. The currently observed data are still premature and cannot meaningfully contribute to the biosimilarity assessment. Updated PFS and OS data are to be expected with the next planned update (see RMP).

GP13-201 (efficacy data in RA)

The key secondary efficacy endpoint was change from baseline in DAS28 (CRP) at Week 24. The least square (LS) mean difference between Riximyo and MabThera in the change from baseline in DAS28 (CRP) at Week 24 was 0.07 (95% CI -0.328, 0.462). The upper limit of the corresponding 95% CI was 0.462, which is below the pre-defined non-inferiority margin of 0.6. Thus, the criterion for non-inferiority was met.

The mean difference between Riximyo and MabThera in the averaged change from baseline in DAS28 (CRP) between Weeks 4 and 24 was 0.33 (95% CI 0.029, 0.639). The upper limit of the corresponding 95% CI was 0.639, slightly above the pre-defined non-inferiority margin of 0.6; indicating a marginal difference compared to MabThera. However, the results do not indicate clinically relevant differences between both treatment groups. Analysis of DAS 28 per visit by treatment group suggests similarity. Mean DAS28 (CRP) was numerically lower for the MabThera treatment arm compared to Riximyo until Week 24. After Week 24, a reverse trend was observed up to Week 52. Both treatment arms, however, exhibit a large degree of variation at all timepoints as shown by the wide SD markers. Post-hoc analysis showed no clear trend for DAS28 with regards to Cmax, suggesting that the observed variability in Cmax had no influence on efficacy in either of the treatment arms.

The mean profiles for both Riximyo batches lie at the upper end, meaning less mean change of DAS 28 from baseline, consistent with the observation in the primary analysis of DAS28 (change from week 4 to 24) and more pronounced in the average change from week 4 to 24. However, both Riximyo batches lie within the range of mean profiles for different MabThera batches. For all batches, there is a degree of variability in the mean change from baseline in DAS28 (CRP) profiles.

The ACR20 (CRP) response rates at Week 24 were similar for the two treatment groups (71.8% and 72.4% in the Riximyo and MabThera groups, respectively). The lower bound of the 95% CI for the difference in response rates was -14.74%, above the pre-defined non-inferiority margin of -15.0%. Further analyses for ACR20 (CRP) were conducted (averaged ACR20 (CRP) responder estimate between Week 4 and 24; averaged ACR20 (CRP) at week 24). All analyses show that MabThera and Riximyo are similar regarding ACR20 rates with when applying equivalence margins of ±15%.

The difference between ACR20 (CRP) scores at different time points -except for weeks 16 and 38-, with a confidence interval contained within +/- equivalence margins, were discussed but were not viewed as clinically meaningful. In addition, slight differences were observed up to and including week 16 (ACR50, ACR70) or up to and including week 24 (SDAI/CDAI). The differences in efficacy scores/values between Riximyo and Mabthera among weeks 4 to 24 are decreasing with the data update (cut-off 10-Jul-2015) and were not supported by the comparisons to the US product Rituxan to which bridging of data has been made.

In overall, results from the ACR20 response analysis at week 24 and averaged ACR20 responders between week 4 and week 24 showed that Riximyo and MabThera are similar regarding ACR20 rates with when applying equivalence margins of ±15%.in study GP13-201 the criterion for non-inferiority in terms of the key secondary efficacy endpoint change from baseline in DAS28 (CRP) at Week 24- was met.

Demonstrating equivalence of efficacy in both a model of the haematology-oncology and for the RA indication, the most common of the immunology indications, supports the extrapolation to the non-studied oncology and immunology indications, together with the evidence from functional assays and PK-PD studies.

## 2.5.4. Conclusions on the clinical efficacy

Efficacy and biosimilarity to Mabthera has been demonstrated in an adequately designed randomised study, 627 patients with follicular non-Hodgkin lymphoma (FL) as regards ORR (supported by sensitivity analyses in the FAS population) and BOR. Efficacy and biosimilarity to Mabthera has been shown in a supportive study in patients with RA.

The efficacy outcomes of the confirmatory study in FL and the exploratory study in RA support extrapolation to the other non-studied oncology and immunology indications.

## 2.6. Clinical safety

**Table 41 - Safety data set**

| Study | Definition | Number of patients in SAF[1] |
|---|---|---|
| GP13-201 (Part I) | The **Safety Analysis Set** consisted of all patients who received study drug at least once. Patients were analyzed according to treatment received. | **N=173 (100%)**<br>GP2013=86 (100%)<br>MabThera=87 (100%) |
| GP13-301 (data until cut-off 10-Jul- 2015) | The **Safety Set** population consisted of a subset of the patients in the Full Analysis Set who actually received at least one (partial or complete) dose of investigational treatment (MabThera or GP2013) and had at least one post-baseline safety evaluation (e.g., lab, vital signs, AEs)[2]. All safety analyses that included safety information limited to the Combination Phase were based on the Safety Set. | **N=627 (99.7%)**<br>GP2013=312 (99.4%)<br>MabThera=315 (100%) |
| | The **Maintenance Set** consisted of all patients who agreed to participate in the Maintenance Phase of the study and received at least one dose of investigational treatment (MabThera or GP2013) in the Maintenance Phase. | **N=462 (73.4%)**<br>GP2013=231 (73.6%)<br>MabThera=231 (73.3%) |
| GP13-101 | The **Safety Set** was identical to Full Analysis Set which included all patients who received at least one dose of GP2013 | **N=6 (100%)**<br>GP2013=6 (100%) |

AE=adverse event; CVP= Cyclophosphamide, vincristine, prednisone; N=number of patients in respective SAF; SAF=safety analysis set

[1] Percentages are based on the number of randomized patients in each category

[2] Patients were analyzed according to the investigational treatment they actually received, i.e., if a patient was randomized into the MabThera-CVP treatment arm, but received GP2013-CVP treatment, they were analyzed as part of the GP2013-CVP treatment arm. If a patient received two different investigational treatments during the study, the treatment they received more than 50% of the time, using the cumulative dose in the Combination Phase, was considered the actual investigational treatment received. If it was exactly 50% of the cumulative dose, the patient was assigned to the randomized investigational treatment arm.

***Patient exposure***

A total of 404 patients (86 RA patients and 318 NHL patients; 87.1 Patients'Years (PY)) have been exposed to Riximyo in studies GP13-201, GP13-301 and GP13-101.

Prolonged treatment continuation of Riximyo up to a maximum 2.5 years was applied in 231 patients with Follicular Lymphoma. The maintenance treatment part of Study GP13-301 is still ongoing. At the cut-off date of data sampling, about 50% of the study population had received at least 4 cycles of Riximyo/MabThera. Total exposure to Riximyo was 476.4 PY at cut-off of 10 July 2015.

**Table 42 - Study drug administration and compliance, by treatment in patients with RA – GP13-201 (Safety Analysis Set)**

| Variable<br>Category / Statistic | GP2013<br>N=86 | MabThera<br>N=87 |
|---|---|---|
| **Number of infusions of the study drug – n (% )** | | |
| First infusion/first course | 86 (100) | 87 (100) |
| Second infusion/first course | 84 (97.7) | 85 (97.7) |
| First infusion/second course | 59 (68.6) | 60 (69.0) |
| Second infusion/second course | 59 (68.6) | 58 (66.7) |
| **Dose during first infusion/first course (mg)[1]** | | |
| n | 86 | 86 |
| Mean (SD) | 976.79 (190.586) | 972.41 (126.110) |
| Median (range) | 1000.00 (100.0 – 1268.3) | 995.83 (308.3 – 1308.3) |
| **Dose during second infusion/first course (mg)[1]** | | |
| n | 84 | 85 |
| Mean (SD) | 971.86 (137.138) | 982.42 (197.723) |
| Median (range) | 1000.00 (300.0 - 1413.3) | 1000.00 (291.7 - 2140.7)) |

**Table 43 - Exposure to investigational study treatment in patients with FL by cumulative dose, dose intensity, and relative dose intensity – GP13-301 Combination and Maintenance Phase (Safety Set)**

| | Combination Phase | | Maintenance Phase[1] | |
|---|---|---|---|---|
| | GP2013 | MabThera | GP2013 | MabThera |
| Exposure variable | N=312 | N=315 | N=231 | N=231 |
| **Cumulative dose (mg)[2]** | | | | |
| Mean (SD) | 4983.6 (1215.98) | 5002.9 (1224.72) | 2781.3 (1731.68) | 2912.8 (1770.51) |
| Median | 5171.6 | 5205.0 | 2261.3 | 2705.0 |
| 25th percentile | 4588.2 | 4699.0 | 1280.0 | 1350.0 |
| 75th percentile | 5670.0 | 5681.3 | 4252.5 | 4509.0 |
| Minimum | 312.6 | 49.9 | 468.8 | 208.0 |
| Maximum | 7426.0 | 6960.0 | 7162.0 | 6847.5 |
| **Actual dose intensity (mg/day)[3]** | | | | |
| Mean (SD) | 30.7 (4.80) | 30.8 (4.57) | 10.4 (12.70) | 14.0 (47.84) |
| Median | 30.7 | 31.0 | 8.3 | 8.4 |
| 25 percentile | 27.7 | 27.8 | 7.4 | 7.4 |
| 75th percentile | 33.8 | 33.5 | 9.6 | 10.1 |
| Minimum | 10.8 | 2.4 | 5.2 | 2.3 |
| Maximum | 43.0 | 51.0 | 152.2 | 652.5 |
| **Relative dose intensity[4]** | | | | |
| Mean (SD) | 0.99 (0.056) | 0.99 (0.065) | 1.00 (0.011) | 1.00 (0.044) |
| Median | 1.00 | 1.00 | 1.00 | 1.00 |
| 25th percentile | 1.00 | 1.00 | 1.00 | 1.00 |
| 75th percentile | 1.00 | 1.00 | 1.00 | 1.00 |
| Minimum | 0.36 | 0.07 | 0.83 | 0.34 |
| Maximum | 1.00 | 1.02 | 1.00 | 1.00 |

Pooling of safety data of these studies is not considered meaningful, considering the differences in rituximab standard treatment regimen between oncology and auto-immune indications, which is by far more intensive for NHL than for RA. Moreover, there are differences in background risks of the patients' populations and their concurrent therapies, which chemotherapy in NHL and methotrexate in RA. Therefore, the safety outcomes are discussed separately for each clinical study in this report.

***Adverse events***

GP13-201

The overall incidence of AEs was comparable for the two treatment groups (Riximyo: 56 patients, 65.1% vs. MabThera: 57 patients, 65.5%) with no clinically meaningful differences between the treatment groups for any SOC.

The most commonly affected primary SOC was infections and infestations (33.5% overall). This is in line with earlier studies with MabThera. The next 2 most commonly affected primary SOCs were musculoskeletal and connective tissue disorders (17.3% overall) and gastrointestinal disorders (16.2% overall).

The most common AEs overall included urinary tract infection, nasopharyngitis, (worsening of) rheumatoid arthritis, hypertension, upper respiratory tract infection, and bronchitis. Urinary tract infection occurred more often in the Riximyo group (10.5%) compared with the MabThera group (5.7%). None of the AEs of urinary tract infection in the Riximyo group were serious, all were mild in severity (except for one moderate), and all resolved. This was further addressed in the response to Q89. There were otherwise no clinically meaningful differences between the treatment groups for any of the most frequently occurring AEs.

**Table 44 - Summary of AE categories in patients with RA – GP13-201 (Safety Analysis Set)**

| Category | GP2013 N=86 n (%) | MabThera N=87 n (%) |
|---|---|---|
| Adverse events (AEs) | 56 (65.1) | 57 (65.5) |
| Suspected to be drug-related | 28 (32.6) | 29 (33.3) |
| Leading to premature discontinuation | 4 (4.7) | 7 (8.0) |
| Leading to dose adjustment or interruptions of study drug | 6 (7.0) | 11 (12.6) |
| Deaths | 1 (1.2) | 0 |
| Other non-fatal serious adverse event (SAEs) | 10 (11.6) | 14 (16.1) |
| Suspected to be drug-related | 3 (3.5) | 6 (6.9) |
| Not leading to premature discontinuation | 10 (11.6) | 12 (13.8) |
| Leading to premature discontinuation | 2 (2.3) | 4 (4.6) |
| Potential infusion related reactions | 32 (37.2) | 37 (42.5) |
| Infections and infestations AEs | 27 (31.4) | 31 (35.6) |

AE=adverse event; n=number of patients in respective category; N=number of patients in a treatmen group; RA=rheumatoid arthritis
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

AEs suspected to be related to study drug based on investigator assessment occurred equally between the two treatment groups (Riximyo 28 patients; 32.6%, MabThera 29 patients, 33.3%).

The most common suspected drug-related AEs were related to infections and infestations with comparable incidence between the two treatment groups (Riximyo 13 patients, 15.1%; MabThera 15 patients, 17.2%). The next most common AEs were related to Respiratory, thoracic and mediastinal disorders (Riximyo 2 patients, 2.3%; MabThera 7 patients, 8%), vascular disorders (Riximyo 4 patients, 4.7%; MabThera 4 patients, 4.6%), gastrointestinal disorders (Riximyo 2 patients, 2.3%; MabThera 6 patients, 6.9%) and general disorders and administrative site conditions (Riximyo seven patients, 8.1%; MabThera one patient, 1.1%).

The five most common AEs rated to have a relationship to study drug overall were urinary tract infection (4%), nasopharyngitis (3.5%), hypertension (2.9%), infusion related reaction (2.9%) and pruritus (2.9%). There was a higher rate of urinary tract infections for Riximyo in comparison to MabThera (10.5 versus 5.7%). In contrast, the overall rates of pruritus and infections were slightly higher for MabThera. For the latter this was attributed to a higher rate of respiratory tract infections (bronchitis: Riximyo 3.5%, MabThera 5.7%; upper respiratory tract infection: Riximyo 3.5%, MabThera 5.7%; cough: Riximyo 2.3%, MabThera 4.6%; respiratory tract infection: Riximyo none, MabThera 3.4%).

GP13-301

***Combination Phase***

The rate and severity of adverse events was considerable higher for FL versus RA patients. This is to be expected considering the more frequent rituximab treatment regimen of 8 dosing cycles within 6 months, as compared to a 24 weeks dosing regimen in RA, and the combination with CVP in FL treatment.

The overall incidence of AEs during the combination phase was similar in both treatment groups (Riximyo -CVP: 92.6%; MabThera-CVP 91.4%). The most commonly (>30% incidence in either treatment group) affected primary SOCs were gastrointestinal disorders (primarily constipation and nausea), nervous system disorders (primarily peripheral neuropathy, and paraesthesia) and infections and infestations (primarily urinary tract infection and upper respiratory tract infection).

Different than in the RA study, neutropenia, peripheral neuropathy/paraesthesia, fatigue and nausea/constipation or abdominal pain were frequently reported in the FL study population, with frequencies over 10%. In comparison, in the RA study only one case of neutropenia was reported (in the MabThera arm), and a low frequency of fatigue (2.4%), abdominal pain (1.7%) and paraesthesia (1.2%). These differences are probably due to CVP co-treatment or other co-medications (like opioids), and/or differences in the rituximab treatment schedule, or the disease itself.

The only AE reported with at least a 5% absolute difference and more frequently in the Riximyo group than in the MabThera group was peripheral neuropathy (15.1% vs. 9.5%, respectively). The only AE reported with at least a 5% absolute difference and occurring more frequently in the MabThera group compared to the Riximyo group was paraesthesia (14.3% vs. 8.3%), although it must be noted that peripheral neuropathy and paresthesia are essentially the same and taken together, the combined incidence rate of peripheral neuropathy and paraesthesia is similar between the treatment groups (i.e., Riximyo with 15.1% + 8.3% = 23.4% vs. MabThera with 9.5% + 14.3% = 23.8%).

The incidence of grade 3 and 4 AEs were similar between the two treatment groups (Riximyo grade 3 40.7%, grade 4 12.5%; MabThera grade 3 41.9%, grade 4 14.9%).

**Table 45 - Summary of AE categories in patients with FL – GP13-301 Combination Phase (Safety Set)**

| Category | GP2013-CVP N=312 n(%) | MabThera-CVP N=315 n(%) |
|---|---|---|
| Adverse events (AEs) | 289 (92.6) | 288 (91.4) |
| Suspected to be drug-related | 230 (73.7) | 223 (70.8) |
| Grade 3-4 AEs | 135 (43.3) | 145 (46.0) |
| Suspected to be drug-related | 89 (28.5) | 98 (31.1) |
| Deaths | 4 (1.3) | 7 (2.2) |
| Serious adverse events (SAEs) | 71 (22.8) | 63 (20.0) |
| Suspected to be drug-related | 32 (10.3) | 25 (7.9) |
| AEs leading to discontinuation[1] | 23 (7.4) | 22 (7.0) |
| Suspected to be drug-related | 14 (4.5) | 16 (5.1) |
| Potential infusion related reaction | 229 (73.4) | 222 (70.5) |
| Suspected to be drug-related | 154 (49.4) | 152 (48.3) |
| AEs requiring dose interruption and/or reduction[1] | 127 (40.7) | 140 (44.4) |
| AEs requiring additional therapy[2] | 261 (83.7) | 264 (83.8) |

In the Combination Phase, AEs considered as study drug-related were reported by 230 (73.7%) Riximyo and 223 (70.8%) MabThera patients. These events were primarily grade 1 (mild) or 2 (moderate). The most common AEs were neutropenia, constipation and infusion-related reactions.

**Maintenance Phase**

During the Maintenance Phase, AEs were reported by 63.2% in the Riximyo group and by 57.1% in the MabThera group. With the data update this percentage difference decreased from 6.1% to 1.6%. The most commonly affected (>15% incidence in either treatment group) primary SOCs were infections and infestations (primarily upper respiratory tract infection and urinary tract infection), musculoskeletal and connective tissue disorders (primarily arthralgia and back pain), gastrointestinal disorders (primarily diarrhea and vomiting), and general disorders and administration site conditions (primarily asthenia and pyrexia). Six AEs occurred with a frequency of >5% in either treatment group. While neutropenia and cough occurred more frequently in the Riximyo group, the other common AEs occurred more frequently in the MabThera group.

The incidence of grade 3 AEs were similar between the two treatment groups (Riximyo 13.9%; MabThera 13.0%), while there were more grade 4 AEs occurring in the Riximyo group (12 patients, 5.2%) compared to the MabThera group (4 patients, 1.7%). Neutropenia was the only AE that was reported to occur at a greater than 2% frequency (Riximyo, grade 3/4 in 17 patients [7.4%] MabThera, grade 3/4 in nine patients [3.9%]). However, this difference was not accompanied by a higher number of febrile neutropenia or infections (SOC infections and infestations - Riximyo: 32.7%; Mabthera: 36.5%, cut-off 10-Jul-2016).

**Table 46 - Summary of AE categories in patients with FL – GP13-301 Maintenance Phase (Maintenance Set)**

| Category | GP2013 N=231 n(%) | MabThera N=231 n(%) |
|---|---|---|
| Adverse events (AEs) | 146 (63.2) | 132 (57.1) |
| Suspected to be drug-related | 54 (23.4) | 38 (16.5) |
| Grade 3-4 AEs | 39 (16.9) | 32 (13.9) |
| Suspected to be drug-related | 16 (6.9) | 12 (5.2) |
| Deaths | 2 (0.9) | 2 (0.9) |
| Serious adverse events (SAEs) | 14 (6.1) | 10 (4.3) |
| Suspected to be drug-related | 6 (2.6) | 3 (1.3) |
| AEs leading to discontinuation | 8 (3.5) | 4 (1.7) |
| Potential infusion related reaction | 85 (36.8) | 88 (38.1) |
| Suspected to be drug-related | 25 (10.8) | 19 (8.2) |
| AEs requiring dose interruption and/or reduction | 17 (7.4) | 17 (7.4) |
| AEs requiring additional therapy[1] | 111 (48.1) | 104 (45.0) |

In the Maintenance Phase, AEs considered as study drug-related were reported by 54 (23.4%) Riximyo and 38 (16.5%) MabThera patients. These events were primarily grade 1 (mild) or 2 (moderate).

There were 16 (6.9%) Riximyo and 12 (5.2%) MabThera patients reporting drug-related grade 3/4 AEs.

***Serious adverse event/deaths/other significant events***

GP13-201

Overall, the number of patients with SAEs was comparable for the two treatment groups with no clinically meaningful difference between the treatment groups (Riximyo: 10 patients (11.6%) vs. MabThera: 14 patients (16.1%)). SAEs were reported most often in the infections and infestations SOC: 5 (5.8%) patients in the Riximyo group and 4 (4.6%) patients in the MabThera group.

SAEs judged by the investigator to have a relationship to study drug were reported overall in 3 (3.5%) patients in the Riximyo group and 6 (6.9%) patients in the MabThera group. The most common of these were reported in the infections and infestations SOC: 3 (3.5%) patients in the Riximyo group (abscess, groin abscess, Klebsiella sepsis, and soft tissue infection) and 2 (2.3%) patients in the MabThera group (atypical pneumonia and pneumonia haemophilus).

The proportions of patients with other non-fatal SAEs or who discontinued study treatment due to AEs were generally comparable for the two treatment groups.

One patient in the Riximyo group died during the study due to a treatment-emergent adverse event of multi-organ failure after an accidental overdose of MTX (daily dose instead of weekly intake). As this event occurred 18 weeks after the first course of treatment, causality seems unlikely.

GP13-301

***Combination Phase***

During the Combination Phase, the incidence of SAEs was similar between the Riximyo (71 patients, 22.8%) and MabThera (63 patients, 20.0%) groups.

In the SOC of blood and lymphatic disorders, SAEs were reported for 23 (7.4%) Riximyo and 17 (5.4%) MabThera patients. The SAE of infusion-related reaction occurred in three Riximyo patients and one MabThera patients. For infections and infestations, the number of patients with an SAE was equal (21 patients each, 6.7%) for both treatment groups.

The incidence of individual SAEs was <5% in either treatment group; the majority of reported SAEs occurred in one or two patients. The most common SAEs were febrile neutropenia (Riximyo 4.8%; MabThera 2.9%), pyrexia (Riximyo 1.3%; MabThera 2.2%), abdominal pain (Riximyo 1.3%; MabThera 1.9%), neutropenia (Riximyo 1.3%; MabThera 1.6%), and sepsis (Riximyo 0.6%; MabThera 1.6%).

The incidence of study drug-related SAEs was similar between the Riximyo (32 patients, 10.3%) and MabThera (25 patients, 7.9%) groups. The incidence of specific SAEs was <4% for either treatment group. The most common related SAE was febrile neutropenia (Riximyo 11 patients, 3.5%; MabThera 9 patients, 2.9%). Differences between treatment groups for specific SAEs were <1%.

***Maintenance Phase***

During the Maintenance Phase, the incidence of SAEs was low and slightly higher for Riximyo (14 patients, 6.1%) than for MabThera (10 patients, 4.3%). This difference also decreased with the data update from 10-Jul-2016 (20 [7.9%] for Riximyo and 18 [7.1%] for MabThera). The incidence of individual SAEs was <1% for both treatment groups. The types of SAEs reported were similar between the two treatment groups. The SOC with the highest reported number of SAEs was infections and infestations (7 patients Riximyo; 6 patients MabThera). The causes of SAE were very diverse, and no clear pattern emerged

- Deaths

Mortality rates were similar between both treatments throughout Study GP13-301. During the entire study for all phases combined (Combination, Maintenance, and Posttreatment), 35 (5.6%) patients died (18 [5.8%] in the Riximyo group and 17 [5.4%] in the MabThera group). The most common cause of death during the study was Non- Hodgkin's lymphoma in both treatment arms, eight (2.6%) in the Riximyo group and six (1.9%) in the MabThera group.

During the Maintenance Phase, 4 patients died (2 in the Riximyo group and 2 in the MabThera group. These cases were not considered related to rituximab treatment.

**Adverse events of special interest**

GP13-201

The overall incidence of AEs considered to be of special interest was comparable for the two treatment groups (24.4% vs. 25.3%) with no clinically meaningful differences between the treatment groups for any SOC. The two most commonly reported AEs of special interest were rheumatoid arthritis (Riximyo 4 patients, 4.7%; MabThera 5 patients, 5.7%) and hypertension (Riximyo 3 patients, 3.5%; MabThera 5 patients, 5.7%).

- Infusion-related reactions

The numbers of patients who reported at least one IRR at any time during the observation period overall was 32 (37.2%) patients in the Riximyo group and 37 (42.5%) patients in the MabThera group. The most common of these IRRs were hypertension (4.6% overall), back pain (4% overall), headache (4% overall), nausea (4% overall), and pruritus (4% overall).

The incidence of potential infusion related reactions with suspected causal relationship to the study drug was similar between both treatment groups (Riximyo: 18 patients, 20.9%; MabThera: 19 patients, 21.8%).

Infusion related reactions occurring on the day or the day after the infusion were considered to be potentially hyper-acute or acute infusion reactions. After the first infusion, such events occurred in a total of 24 (13.9%) patients (Riximyo: 10 patients, 11.6%; MabThera: 14 patients, 16.1%). After the second infusion, fewer events of potential infusion related reactions occurred on the day or the day after the infusion, i.e. in a total of 11 (6.4%) patients (Riximyo: 4 patients, 4.7%; MabThera: 7 patients, 8.0%). Despite the numerical differences, no clinically relevant differences were noted between the groups.

GP13-301

For study GP13-301, cytokine release syndrome and PML were defined as AEs of special interest in the clinical study protocol. No PML occurred during the study. During Combination Phase, cytokine release syndrome occurred in 2 (0.6%) patients during the Maintenance Phase.

- Infusion-related reactions

***Combination Phase***

During the Combination Phase of study GP13-301, the frequency of patients experiencing the AE "infusion related reaction" with suspected relationship to study drug was similar between both treatment groups (Riximyo: 13.1%, grade 3 or 4 1.0%; MabThera: 11.7%, grade 3 or 4 0.6%).

The frequency of patients experiencing the AE "infusion related reaction" requiring study drug dose adjustments or temporary interruptions during the Combination Phase was also similar in both treatment arms (Riximyo: 6.7%, grade 3 or 4 1.0%; MabThera: 7.0%, grade 3 or 4 0.6%).

One patient in each treatment arm discontinued the treatment due to the AE "infusion related reaction" during the Combination Phase. SAEs of infusion related reactions with suspected causal relationship to study drug were reported with a frequency of 1.0 % in patients treated with Riximyo and of 0.3% treated with MabThera during the Combination Phase.

***Maintenance Phase***

During the Maintenance Phase of GP13-301, the frequency of potential infusion related reactions with suspected causal relationship to study treatment was similar between the Riximyo (10.8%) and MabThera (8.2%) groups.

The most frequently reported AEs related to infusion related reactions (i.e. >1% of patients in either treatment group) were infusion related reaction (Riximyo: 1.3%; MabThera: 1.3%), cough (Riximyo: 2.2%; MabThera: none), thrombocytopenia (Riximyo: 0.4%; MabThera: 1.3%), and arthralgia (Riximyo: none; MabThera: 1.3%). Other infusion related reactions were reported by 1 or 2 patients in either treatment group, with a similar frequency and pattern.

**Serious adverse events and deaths**

GP13-201

Overall, the number of patients with SAEs was comparable for the two treatment groups with no clinically meaningful difference between the treatment groups (Riximyo: 10 patients (11.6%) vs. MabThera: 14 patients (16.1%)). SAEs were reported most often in the infections and infestations SOC: 5 (5.8%) patients in the Riximyo group and 4 (4.6%) patients in the MabThera group.

SAEs judged by the investigator to have a relationship to study drug were reported overall in 3 (3.5%) patients in the Riximyo group and 6 (6.9%) patients in the MabThera group. The most common of these were reported in the infections and infestations SOC: 3 (3.5%) patients in the Riximyo group (abscess, groin abscess, Klebsiella sepsis, and soft tissue infection) and 2 (2.3%) patients in the MabThera group (atypical pneumonia and pneumonia haemophilus).

The proportions of patients with other non-fatal SAEs or who discontinued study treatment due to AEs were generally comparable for the two treatment groups.

One patient in the R group died during the study due to a treatment-emergent adverse event of multi-organ failure after an accidental overdose of MTX (daily dose instead of weekly intake). As this event occurred 18 weeks after the first course of treatment, causality seems unlikely.

GP13-301

***Combination Phase***

During the Combination Phase, the incidence of SAEs was similar between the Riximyo (71 patients, 22.8%) and MabThera (63 patients, 20.0%) groups.

In the SOC of blood and lymphatic disorders, SAEs were reported for 23 (7.4%) Riximyo and 17 (5.4%) MabThera patients. The SAE of infusion-related reaction occurred in three Riximyo patients and one MabThera patients. For infections and infestations, the number of patients with an SAE was equal (21 patients each, 6.7%) for both treatment groups.

The incidence of individual SAEs was <5% in either treatment group; the majority of reported SAEs occurred in one or two patients. The most common SAEs were febrile neutropenia (Riximyo 4.8%; MabThera 2.9%), pyrexia (Riximyo 1.3%; MabThera 2.2%), abdominal pain (Riximyo 1.3%; MabThera 1.9%), neutropenia (Riximyo 1.3%; MabThera 1.6%), and sepsis (Riximyo 0.6%; MabThera 1.6%).

The incidence of study drug-related SAEs was similar between the Riximyo (32 patients, 10.3%) and MabThera (25 patients, 7.9%) groups. The incidence of specific SAEs was <4% for either treatment group. The most common related SAE was febrile neutropenia (Riximyo 11 patients, 3.5%; MabThera 9 patients, 2.9%). Differences between treatment groups for specific SAEs were <1%.

***Maintenance Phase***

During the Maintenance Phase, the incidence of SAEs was low and slightly higher for Riximyo (14 patients, 6.1%) than for MabThera (10 patients, 4.3%). This difference also decreased with the data update from 10-Jul-2016 (20 [7.9%] for Riximyo and 18 [7.1%] for MabThera). The incidence of individual SAEs was <1% for both treatment groups. The types of SAEs reported were similar between the two treatment groups. The SOC with the highest reported number of SAEs was infections and infestations (7 patients Riximyo; 6 patients MabThera). The causes of SAE were very diverse, and no clear pattern emerged

- Deaths

Mortality rates were similar between both treatments throughout Study GP13-301. During the entire study for all phases combined (Combination, Maintenance, and Posttreatment), 35 (5.6%) patients died (18 [5.8%] in the GP2013 group and 17 [5.4%] in the MabThera group). The most common cause of death during the study was Non- Hodgkin's lymphoma in both treatment arms, eight (2.6%) in the Riximyo group and six (1.9%) in the MabThera group.During the Maintenance Phase, 4 patients died (2 in the Riximyo group and 2 in the MabThera group). These cases were not considered related to rituximab treatment.

***Laboratory findings***

GP13-201

The incidence of clinically notable and newly occurred hematology values as well as values in clinical chemistry was low and similar between both treatment groups. The number of patients with increased serum creatinine was higher in the Riximyo group. No relevant differences in any vital signs were observed between Riximyo and MabThera groups in study GP13-201. ECG was only performed at screening, therefore, no analysis is available.

GP13-301

During the Combination the incidence of ECG abnormalities was higher in the Riximyo group (18 patients vs 10 patients in the MabThera group). Abnormalities in clinical chemistry were similar for both treatment groups, including abnormal values of CTCAE grade 3 or 4. No relevant differences in any vital signs were observed between Riximyo and MabThera groups.

In the monotherapy maintenance phase, the rate of haematological abnormalities, that worsened or newly emerged from the start of the maintenance phase (i.e. after finishing the combination with CVP phase), was similar for both treatments

***Safety in special populations***

**Table 47 - Safety according to age groups (NHL)**

| **MedDRA Terms** | **Age < 65 (number (percentage) N=5** | **Age 65 – 74 number (percentage) N=1** | **Age 75 – 84 number (percentage) N=0** | **Age 85+ number (percentage) N=0** |
|---|---|---|---|---|
| Total AEs | 4 (80%) | 1 (100%) | -- | -- |
| Serious AEs - Total | 0 (0%) | 0 (0%) | -- | -- |
| - Fatal | -- | -- | -- | -- |
| - Hospitalization/ prolong existing hospitalization | -- | -- | -- | -- |
| - Life-threatening | -- | -- | -- | -- |
| - Disability/incapacity | -- | -- | -- | -- |
| - Other (medically significant) | -- | -- | -- | -- |
| AE leading to drop-out | 0 (0%) | 0 (0%) | -- | -- |
| Psychiatric disorders | 0 (0%) | 0 (0%) | -- | -- |
| Nervous system disorders | 1 (20%) | 0 (0%) | -- | -- |
| Accidents and injuries | 1 (20%) | 0 (0%) | -- | -- |
| Cardiac disorders | 0 (0%) | 0 (0%) | -- | -- |
| Vascular disorders | 0 (0%) | 0 (0%) | -- | -- |
| Cerebrovascular disorders | 0 (0%) | 0 (0%) | -- | -- |
| Infections and infestations | 1 (20%) | 0 (0%) | -- | -- |
| Anticholinergic syndrome | 0 (0%) | 0 (0%) | -- | -- |

| MedDRA Terms | Age < 65 (number (percentage) N=5 | Age 65 – 74 number (percentage) N=1 | Age 75 – 84 number (percentage) N=0 | Age 85+ number (percentage) N=0 |
|---|---|---|---|---|
| Quality of life decreased | Not evaluated | Not evaluated | -- | -- |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 0 (0%) | 0 (0%) | -- | -- |
| < other AE appearing more frequently in older patients> | 0 (0%) | 0 (0%) | -- | -- |

**Table 48 - Safety according to age groups in study GP13-201 (Rheumatoid arthritis)**

| MedDRA Terms | Age < 65 (number (percentage) | | Age 65 – 74 number (percentage) | | Age 75 – 84 number (percentage) | | Age 85+ number (percentage) | |
|---|---|---|---|---|---|---|---|---|
| | Riximyo | Orig. | Riximyo | Orig. | Riximyo | Orig. | Riximyo | Orig. |
| | N=105 | N=141 | N=22 | N=35 | N=6 | N=3 | N=0 | N=0 |
| Total AEs | 67(63.8) | 80(56.7) | 13(59.1) | 25(71.4) | 5 (83.3) | 2(66.7) | -- | -- |
| Serious AEs - Total | 9 (8.6) | 14 (9.9) | 3 (13.6) | 5 (14.3) | 1 (16.7) | 0 (0.0) | -- | -- |
| - Fatal | 1 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | -- | -- |
| - Hospitalization/ prolong existing hospitalization | 7 (6.7) | 13 (9.2) | 3 (13.6) | 4 (11.4) | 1 (16.7) | 0 (0.0) | -- | -- |
| - Life-threatening | -- | -- | -- | -- | -- | -- | -- | -- |
| - Disability/ incapacity | -- | -- | -- | -- | -- | -- | -- | -- |
| - Other (medically significant) | -- | -- | -- | -- | -- | -- | -- | -- |
| AE leading to drop-out | 2 (1.9) | 6 (4.3) | 2 (9.1) | 2 (5.7) | 0 (0.0) | 0 (0.0) | -- | -- |
| Psychiatric disorders | 4 (3.8) | 5 (3.5) | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) | -- | -- |
| Nervous system disorders | 10 (9.5) | 16(11.3) | 3 (13.6) | 4 (11.4) | 0 (0.0) | 0 (0.0) | -- | -- |
| Accidents and injuries | 15(14.3) | 12 (8.5) | 3 (13.6) | 5 (14.3) | 1 (16.7) | 0 (0.0) | -- | -- |
| Cardiac disorders | 5 (4.8) | 4 (2.8) | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) | -- | -- |
| Vascular disorders | 9 (8.6) | 8 (5.7) | 1 (4.5) | 6 (17.1) | 2 (33.3) | 0 (0.0) | -- | -- |
| Cerebrovascular disorders | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | -- | -- |
| Infections and | 31(29.5 | 40(28.4 | 9 (40.9) | 11(31.4 | 1 (16.7) | 1(33.3 | -- | -- |

| MedDRA Terms | Age < 65 (number (percentage) | | Age 65 – 74 number (percentage) | | Age 75 – 84 number (percentage) | | Age 85+ number (percentage) | |
|---|---|---|---|---|---|---|---|---|
| infestations | ) | ) | | ) | | ) | | |
| Anticholinergic syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | -- | -- |
| Quality of life decreased | Not evaluated | | | | | | | |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 9 (8.6) | 4 (2.8) | 2 (9.1) | 3 (8.6) | 2 (33.3) | 0 (0.0) | -- | -- |
| < other AE appearing more frequently in older patients> | -- | -- | -- | -- | -- | -- | -- | -- |

GP13-201: data from GP13-201 Part 1 Week 52 and GP13-201 Part II Week 24 data combined.

The effect of intrinsic and extrinsic factors was not evaluated.

**Immunological events**

Immunogenicity was evaluated in terms of antibody formation and clinical symptoms (AEs).

GP13-201

In study GP13-201, blood samples for ADA assessments were collected before the first infusion and at Weeks 4, 16, 24, 38 and 52. If patients received a second treatment course, blood samples were again collected before the first infusion and at the follow-up visit 26 weeks after the first infusion of the second treatment course.

Across treatment arms, binding anti-rituximab antibodies were detected in 2 patients (1.2%) at randomization (pre-treatment). These 2 patients were excluded from further ADA analysis.

The overall incidence of binding anti-rituximab antibodies in the Riximyo group was numerically lower than that of the MabThera group. Overall, post-baseline ADA was detected in 9 patients (11%) in the Riximyo and 18 patients (21.4%) in the MabThera group. There were no relevant differences observed in terms of general safety between patients with- and without ADAs. Similarly, there was no meaningful difference in efficacy outcome of the patients with- and without binding anti-rituximab antibodies.

Samples with confirmed positive binding anti-rituximab antibodies were further assessed for the neutralizing capacity of the antibodies via a cell based assay (NAb assay). NAbs were detected in 3 patients in the Riximyo group (3.7%) compared to one patient in the MabThera group (1.2%). Among them, two patients (1 in each arm) showed elevated ADA titer (> 100 ug/mL).

No clinically relevant differences could be observed for potentially hyper-acute or acute infusion reactions or for potentially delayed reactions between both treatment groups.

There was no relevant difference in terms of efficacy between patients with- and without NAbs, as shown by the DAS28 (CRP) profiles.

GP13-301

In study GP13-301, blood samples for ADA assessments were collected at screening and at End of Treatment of Combination and Maintenance Phase, respectively. For patients who participated in a sparse pharmacokinetic sampling program, an additional sample was collected in Cycle 4 (pre-dose).

A total of 551 (87.6%) patients were included in the immunogenicity analysis, 268 (85.4%) patients in the Riximyo group and 283 (89.8%) patients in the MabThera group. Five patients with pre-existing anti-rituximab antibodies at screening visit were excluded from the immunogenicity assessment, 4 patients in the Riximyo group and 1 patient in the MabThera group. Of these 4 patients in the Riximyo group, 3 patients were tested negative post-treatment, one patient was tested positive.

Overall, the number of patients with detectable post-dose anti-rituximab antibodies was low in the study (8 out of 551 patients (1.5%)), with no clinically meaningful differences between the Riximyo group (5 out of 268 patients, 1.9%) and the MabThera group (3 out of 283 patients, 1.1%). Based on the limited PK data in ADA positive patients, there is no clear indication that ADA is having an impact on PK exposure.

At the EOT in the Combination Phase, there were one Riximyo patient (0.4%) and two MabThera patients (0.7%) who had confirmed positive results for binding-anti-rituximab antibodies.

At the EOT in the Maintenance Phase, there was only 1 patient (Riximyo) who was positive for binding ADA.

No clinically relevant differences could be observed for potentially hyper-acute or acute infusion reactions or for potentially delayed reactions between both treatment groups.

An assessment of safety parameters found that the four Riximyo patients who were tested ADA positive during the Combination Phase had no AEs of infusion-related reactions.

Delayed hypersensitivity reactions have not been analyzed as AE of special interest in study GP13-301. Therefore, only prominent potential AEs suspected to be related to study drug – like arthralgia, myalgia, urticaria, skin rash, and pruritus which may form part of delayed hypersensitivity reactions – can be compared without consideration of the time distance between the infusion and the occurrence of the AEs.

Neutralizing antidrug-antibodies were detected in two out of 268 (0.7%) patients in the Riximyo group and two out of 283 (0.7%) patients in the MabThera group.

NAb was detected in one of the patients in the Riximyo group at the end of Maintenance Phase.

All other NAb positive incidences were detected during the combination phase. These Nab incidences showed no obvious link with any immunogenicity-related SAEs or diminished efficacy.

***Safety related to drug-drug interactions and other interactions***

In the clinical development of Riximyo drug interactions have not been systematically investigated. Riximyo was developed as a biosimilar medicinal drug product; therefore, the identified and potential interactions of the reference product with other medicinal products MabThera as described in Section 4.5 of the MabThera SmPC also apply to Riximyo.

***Discontinuation due to adverse events***

GP13-201

The proportion of patients who prematurely discontinued study drug due to an AE was low for both treatment groups (Riximyo: 4.7%, MabThera: 8.0%).

GP13-301

***Combination Phase***

During the Combination Phase of study GP13-301, the incidence of AEs leading to discontinuation of study drug was similar for AEs of all grades between both treatment groups (Riximyo: 23 patients, 7.4%; MabThera: 22 patients, 7.0%). The incidence of Grade 3 or 4 AEs leading to discontinuation study drug was comparable between both treatment groups (Riximyo: 14 patients [4.5%], MabThera: 12 patients [3.8%]).

***Maintenance Phase***

During the Combination Phase of study GP13-301, the incidence of AEs leading to discontinuation of study drug was similar for AEs of all grades between both treatment groups (Riximyo: 23 patients, 7.4%; MabThera: 22 patients, 7.0%). The incidence of Grade 3 or 4 AEs leading to discontinuation study drug was comparable between both treatment groups (Riximyo: 14 patients [4.5%], MabThera: 12 patients [3.8%]).

***Post marketing experience***

N/A

## 2.6.1. Discussion on clinical safety

The safety of Riximyo was evaluated in three clinical studies conducted in adult patients with RA (study GP13-201), FL (study GP13-301) where MabThera was used as comparator, and other B-cell NHLs (study GP13-101). The safety sample size is considered sufficient for a biosimilar application.

Study GP13-201

Although the Phase II study GP13-201 in RA patients was not powered to confirm safety, the outcomes of this study are considered relevant especially as there is no other concurrent therapy.

The overall incidence of AEs was comparable between the treatment arms: (Riximyo: 56 patients, 65.1% vs. MabThera: 57 patients, 65.5%). The most commonly affected primary SOC were infections and infestations, musculoskeletal and connective tissue disorders and gastrointestinal disorders. The most common AEs included urinary tract infection, nasopharyngitis, (worsening of) rheumatoid arthritis, hypertension, upper respiratory tract infection and bronchitis. The overall incidence of AEs suspected to be related to study drug was similar for Riximyo (32.6%) and MabThera (33.3%) with urinary tract infection occurring more often in the Riximyo arm (5.8% [mostly mild, 1 moderate ] vs. 2.3%) and IRR, pruritus (each 1.2% vs. 4.6%) and rash (0 vs. 4.6%) occurring more often in the MabThera arm.

The rate of discontinuation and dose adjustments/interruptions due to AEs was lower in the Riximyo arm compared to the MabThera arm: 4.7% vs 8.0% and 7.0% vs. 12.6%, respectively.

No apparent differences in the frequency of SAEs were observed between the treatment groups: Riximyo (14 patients, 6.1%), MabThera (10 patients, 4.3%). 1 death occurred in the Riximyo arm which was attributed to an MTX overdose.

The incidence of AESI was similar between the treatment groups (Riximyo: 21 patients [24.4%]; MabThera: 22 patients [25.3%]). The most commonly reported AESI were rheumatoid arthritis (5.2% overall), hypertension (4.6% overall) and nausea (4.0% overall).

Infusion-related reactions (IRR) were more commonly observed in the MabThera treatment arm (Riximyo: 37.2%; MabThera: 42.5%). There were no notable differences in clinical laboratory parameters.

Study GP13-301

In study GP13-301 as expected, the incidence of AEs including SAE (about 20%) during the pivotal combination phase was higher than in the RA study, probably due to the more frequent rituximab dosing regimen and the background therapy of CVP (cyclophosphamide-vincristine-prednisolone). E.g. the higher incidence of nausea and neurological disorders is likely attributable to CVP. The overall incidence of infections was similar in Riximyo (42.3%) and MabThera (41.9%) treatment groups.

The incidence of AEs was similar in both treatment groups (Riximyo-CVP: 92.6%; MabThera-CVP 91.4%). The most commonly affected primary SOCs were gastrointestinal disorders (primarily constipation and nausea), nervous system disorders (primarily peripheral neuropathy, and paraesthesia), infections and infestations (primarily urinary tract infection and upper respiratory tract infection).

In the combination phase, neutropenia was far more commonly reported (Riximyo: 25.6%, MabThera: 29.5%), than in the RA study (1.2% for MabThera, no case for Riximyo). The rate of febrile neutropenias was also higher in the Riximyo group (4.8% vs 2.9%). This is likely due to concurrent cyclophosphamide treatment, but also the more intensive treatment of rituximab may further contribute to neutropenia. E.g. in the original registration trial for the FL indication, neutropenia occurred in 24% in the CVP+ rituximab arm, versus 13% in the CVP+ placebo arm. Notably, the incidence of neutropenia in this study is similar to the historical data.

At least 5% absolute differences in AEs were observed for peripheral neuropathy and paresthesia. However, differentiation of these terms may be difficult and when adding incidences for both terms these differences between the treatment groups disappear.

The incidence of treatment discontinuations due to AEs was comparable between the treatment arms (Riximyo: 23 patients, [7.4%]; MabThera: 22 patients, [7.0%]). The incidence of AEs requiring dose interruption and/or reduction was lower in the Riximyo arm.

Adverse events of special interest included CRS and PML. None of these were observed during the Combination Phase. The incidences of IRR considered to be related to study drug were comparable for Riximyo and MabThera during Combination Phase (13.1% and 11.7%, respectively).

Some adverse events which were observed more frequently in the Riximyo arm (urinary tract infections, increased serum creatinine in GP13-201; cardiac disorders, ECG abnormalities in the Combination Phase of study GP13-301) and especially during the Maintenance Phase of GP13-301 (higher incidences of AEs, Grade 4 AEs, SAEs, related AEs, discontinuation due to AEs, Neutropenia and infections and infestations SOC) were further analysed and the findings from the updates balanced out previous findings. The concern for neutropenia was resolved since it did not reflect in an increase

of infections and its evaluation of a carry-over effect of the earlier treatment combination phase with chemotherapy (CVP regimen).

Study GP13-301 - Maintenance Phase

The incidence of AEs was higher in Riximyo group (63.2%) compared to the MabThera group (57.1%) with injury, poisoning and procedural complications (Riximyo: 6.5%; MabThera: 3.0%) and vascular disorders (Riximyo: 5.6%; MabThera: 3.5%) being the SOCs with the largest absolute difference of 3.5% and 2.1%, respectively, and neutropenia and cough being the more frequently observed AEs by preferred term in the Riximyo group. More Grade 4 AEs were observed for the Riximyo treatment group compared to MabThera (12 patients [5.2%] vs. 4 patients [1.7%]) again with neutropenia being the most frequently observed AE. Treatment-related neutropenia occurred with a frequency > 5 % (Riximyo, all grades 6.9%, grade 3/4 4.3%; MabThera, all grades 5.2%, grade 3/4 3.5%).

Overall, the percentage difference for AEs during the maintenance phase for the Riximyo arm compared to the MabThera arm decreased from 6.1% to 1.6% with data cut-off from 10-Jul-2016.

The mechanism causing neutropenia following rituximab treatment is not well understood, as CD20 is not expressed on neutrophil granulocytes. The mechanism of rituximab induced neutropenia has still not been elucidated, while many hypotheses have been presented. Several authors suggest a disturbance of haematopoiesis after rituximab treatment (Expert Rev Hematol. 2011;4(6):619-625). As described in the SmPC of MabThera, neutropenia was not associated with a higher rate of infections in earlier studies.

When CVP was withdrawn in the maintenance phase, the rate of neutropenia dropped considerably, towards 10% (7.4 % grade 3/4) in the Riximyo arm, and 5.6% (3.9% Grade 3/4) in the MabThera arm. The modest discrepancy between treatment arms is difficult to interpret. Reassuringly, this was not associated with an enhanced rate of infections for Riximyo in the maintenance phase (cut –off 10-Jul-2016: SOC infections and infestations - Riximyo: 32.7%; MabThera: 36.5%)).

The incidences of AEs leading to dose adjustment or interruption and AEs requiring additional therapy were similar between the treatment groups. As for the slightly higher number of patients discontinuing treatment due to an AEin the Riximyo arm, this percentage difference decreased with the data update (10 [3.9%] in Riximyo and 7 [2.8%] in MabThera). There was a higher incidence of disease progression in the Riximyo arm (N=37 [16.0%]) compared to the MabThera arm (N=25 [10.8%]). However, the overall treatment discontinuation between the Riximyo arm and the MabThera arm is reducing with the maturation of data.

Adverse events of special interest included CRS and PML. None of these were observed during the Maintenance Phase. The incidences of IRR considered to be related to study drug were comparable for Riximyo and MabThera during Maintenance Phase (10.8% and 8.2%, respectively).

Combination and Maintenance Phase – Deaths, Laboratory, Immunogenicity

The number of deaths occurring in the Combination, Maintenance and Post-treatment was comparable between the treatment groups (Riximyo: 18 [5.8%]; MabThera: 17 [5.4%]).

There were no notable differences in laboratory findings.

The number of ADA-positive patients was low for both treatment arms (Riximyo: 5 (1.9%) patients; MabThera: 3 (1.1%) patients). NAbs were only detected in 4 patients (2 in each treatment arm). Clinical data did not reveal a negative impact of ADA-positivity on the efficacy and safety of Riximyo.

Immunogenicity studies GP13-201 and GP13-301

In the RA study, the rate of ADA formation was higher for MabThera than for Riximyo (21.4% versus 11.0%). In many cases, the ADAs were transient. The number of neutralising ADA was small without meaningful differences between groups (3.7% vs 1.2% for Riximyo and MabThera, respectively). There was no clear relationship between ADAs and safety/efficacy. Moreover, based on quality assays, no differences in immunogenicity are to be anticipated.

CVP including high dosages of prednisolone may suppress ADA formation more than methotrexate, which was the background therapy in the RA study. Moreover, the dosages of rituximab were considerable higher in the FL study in comparison to the RA study, which may further suppress antibody formation. This may explain the low incidence of ADA of 1.5% in the combination phase. Also in the maintenance phase the incidence of ADA remained low. However, as the data are yet incomplete of this ongoing study, an update of ADA data is requested, also considering that the number of subjects from the RA study was limited, and carry-over effect of CVP is expected to decrease in due time (see RMP).

There were no relevant differences observed in terms of general safety between patients with and without NAbs. No SAEs were reported for the NAb positive patients in the Riximyo arm, whereas two suspected drug-related SAEs of moderate intensities (gastroenteritis and infusion reaction) were reported for the patient in the MabThera arm. The study drug was permanently discontinued due to the event. No relevant differences were observed in the DAS28 (CRP) profiles of ADA positive patients as compared to the ADA negative patients. The DAS profiles of ADA positive and ADA negative patients were equally distributed; no trending was observed which would suggest that ADA positivity leads to either better or worse DAS28 response.

Immunogenicity results from study GP13-201 may indicate slight differences with respect to the ADA incidence being 2-fold lower in RA patients treated with Riximyo compared to MabThera (11.0 % vs. 21.4 %), however, the data in the RA study were limited and at any rate, it is likely that the difference of -10% could be a chance finding and ultimately it is not of concern since immunogenicity –if anything—is lower than that of RMP which is in accordance with the overarching guidelines (CHMP/437/04 Rev 1;  EMEA/CHMP/BMWP/42832/2005 Rev1). In study GP13-301 there was no signal of differences in immunogenicity and ADA formation between Riximyo (2.1%) and MabThera (0.9%). The ADA formation may be suppressed by concurrent use of CVP in the main treatment phase of the pivotal trial.

From the safety database of rituximab all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics which follows the one of Mabthera.

## 2.6.2. Conclusions on the clinical safety

Overall, the safety profile of Riximyo appears to be comparable to the reference product MabThera with most common reported events being infections, infusion related reactions, and in the NHL study, neutropenia. In general, the frequencies and nature of the adverse events were similar between Riximyo and MabThera, and in line with earlier reports for the Reference product MabThera in the RA and FL study populations. Final reports from the ongoing studies will provide further information on clinical safety (see RMP).

## *2.7. Risk Management Plan*

***Safety concerns***

**Table 49 - Summary of the safety concerns**

| | |
|---|---|
| **Important identified risks** | **NHL**<br>Infusion-related reactions<br>Infections (including serious infections)<br>Serious viral infections<br>Impaired immunization response<br>PML<br>Neutropenia (including prolonged)<br>HBV reactivation<br>Tumour lysis syndrome<br>GI perforation<br>Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis<br><br>**RA**<br>Infusion-related reactions<br>Infections (including serious infections)<br>Impaired immunization response<br>PML<br>Neutropenia (including prolonged)<br>HBV reactivation<br>Hypogammaglobulinemia<br>Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis<br><br>**GPA/MPA**<br>Infusion-related reactions<br>Infections (including serious infections)<br>Impaired immunization response<br>PML<br>Neutropenia (including prolonged)<br>HBV reactivation<br>Hypogammaglobulinemia<br>Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis |
| **Important potential risks** | **NHL**<br>PRES<br>Opportunistic infections<br>Prolonged B-cell depletion<br>Increased risk of grade 3/4 serious blood and lymphatic system<br>AML/MDS<br>Second malignancies<br>Off-label use in pediatric patients<br>Administration route error<br><br>**RA**<br>PRES<br>Opportunistic infections<br>Malignant events<br>Impact on cardiovascular disease<br>GI perforation<br>Prolonged B-cell depletion<br>Off-label use in autoimmune disease<br>Off-label use in pediatric patientsGPA/MPA<br>PRES<br>Opportunistic infections<br>Malignant events<br>Impact on cardiovascular disease |

| | |
|---|---|
| | GI perforation<br>Prolonged B-cell depletion<br>Off-label use in autoimmune disease<br>Off-label use in pediatric patients<br>Relapses |
| **Missing information** | **NHL**<br>Use in Pregnancy and Lactation<br><br>**RA**<br>Use in Pregnancy and Lactation<br>Immunogenicity and autoimmune disease<br><br>**GPA/MPA**<br>Use in Pregnancy and Lactation<br>Immunogenicity and autoimmune disease<br>Long term use in GPA/MPA patients |

***Pharmacovigilance plan***

**Table 50 - On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan**

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| GP13-201 (Study Part 2): A randomized, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of Riximyo and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies<br>Category 3 | Primary objective: To assess bioequivalence between Riximyo and rituximab<br>Safety objectives:<br>- Overall safety and tolerability<br>- Incidence of anti-drug antibodies | Immunogenicity, infusion related reactions, infections (including serious infections) | Ongoing | Part I:<br>Will be part of the submission for marketing authorization in Apr 2016<br>Part II<br>24 week interim report: Dec 2016 (finalized)<br>52 week final report: Nov 2017 |
| GP13-301: A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety | Primary objective<br>To demonstrate comparability of the overall response rate (ORR) | Infusion related reactions, infections (including serious infections), serious viral infections, | Ongoing | Combination phase (cut-off date 10 Jul 2015):<br>Will be part of the submission for marketing authorization in Apr 2016<br>Interims Analysis (cut-off |

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| and pharmacokinetics of Riximyo plus cyclophosphamide, vincristine, prednisone vs. MabThera® plus cyclophosphamide, vincristine, prednisone, followed by Riximyo or MabThera® maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma<br>Category 3 | Safety objective<br>- Safety of Riximyo in comparison to MabThera® either as single agent or in combination with CVP<br>- Incidence of immunogenicity (anti-drug antibody formation) | neutropenia (including prolonged neutropenia), opportunistic infections | | date 10 Jul 2016): Dec 2016 (finalized)<br>Final report: Aug 2018 |
| GP13-302: A randomized, double- blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to Rixiymo or re-treatment with Rituxan® or MabThera® in patients with active rheumatoid arthritis, previously treated with Rituxan or MabThera®<br>Category 3 | Identify potential safety risk of the transition from reference product to Riximyo as compared to continuing with respective treatment weight | Immunogenicity, acute infusion related reactions, infections (including serious viral infections) | Ongoing | 12 week interim report: Feb 2017<br>24 week report: Jul 2017 |
| British Society of | Provide additional supporting safety | *For all 3 registries:* | Planned, (Start at time of | Interim report planned yearly in Q4 for 4 years |

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|---|---|---|---|
| Rheumatology Biologics Register (BSRBR),<br>Swedish registry (ARTIS)<br>German registry (RABBIT)<br>Category 3 | data in RA to further characterize the nature of events, demographics of patients at risk, and the presence of risk factors and confounding factors. | Infusion-related reactions, Infections (including serious infections), Impaired immunization response, PML, Neutropenia (including prolonged), HBV reactivation, Posterior reversible encephalopathy syndrome (PRES), Opportunistic infections, Malignant events, Impact on cardiovascular disease, GI perforation, Prolonged B-cell depletion, Immunogenicity and autoimmune disease | drug availability in country following EMA approval) | starting in 2018, final report within 6-12 months after study completion |

***Risk minimisation measures***

**Table 51 - Summary table of Risk Minimization Measures**

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| Infusion-related reactions | For NHL: 4.2, 4.4, 4.8 of the SmPC | |
| | For RA: 4.2, 4.4, 4.8, 5.1 of the SmPC | HCP educational leaflet |
| | For GPA/MPA: 4.2, 4.4, 4.8 of the SmPC | HCP educational leaflet |
| Infections (including serious infections) | For NHL, GPA/MPA: 4.3, 4.4, 4.8 of the SmPC | GPA/MPA: HCP educational leaflet, Patient educational leaflet, Patient alert card |
| | For RA: 4.3, 4.4, 4.5, 4.8 of the SmPC | HCP educational leaflet, Patient educational leaflet, Patient alert card |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| Serious viral infections | For NHL: 4.3, 4.4, 4.8 of the SmPC | None |
| Impaired immunization response | For NHL, RA, GPA/MPA: 4.4 of the SmPC | None |
| PML | For NHL: 4.3, 4.4, 4.8 of the SmPC | None |
| | For RA: 4.3, 4.4, 4.8, 5.1 of the SmPC | HCP educational leaflet, Patient educational leaflet, Patient alert card |
| | For GPA/MPA: 4.3, 4.4 of the SmPC | HCP educational leaflet, Patient educational leaflet, Patient alert card |
| Neutropenia (including prolonged) | For NHL, RA, MPA/GPA: 4.4, 4.8 of the SmPC | None |
| HBV reactivation | For NHL, RA, MPA/GPA: 4.4, 4.8 of the SmPC | None |
| Tumour lysis syndrome | For NHL: 4.2, 4.4, 4.8 of the SmPC | None |
| GI perforation | For NHL, RA, MPA/GPA: 4.8 of the SmPC | None |
| Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis | For NHL, RA, MPA/GPA: 4.4, 4.8 of the SmPC | None |
| Hypogammaglobulinemia | For RA, MPA/GPA: 4.4, 4.8 of the SmPC | None |
| PRES | For NHL, RA, GPA/MPA: 4.8 of the SmPC | None |
| Opportunistic infections | For NHL, GPA/MPA: 4.3, 4.4, 4.8 of the SmPC | None |
| | For RA: 4.3, 4.4, 4.5, 4.8 of the SmPC | None |
| Prolonged B-cell depletion | For NHL, RA: 4.8, 5.1 of the SmPC | None |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|---|---|---|
| | For GPA/MPA: 5.1 of the SmPC | None |
| AML/MDS | For NHL/CLL: 4.4 of the SmPC | None |
| Second malignancies | For NHL: 4.4 of the SmPC | None |
| Off-label use in pediatric patients | For NHL, RA: 4.2 of the SmPC | None |
| | For GPA/MPA: 4.1, 4.2 of the SmPC | None |
| Administration route error | For NHL: 4.2 of the SmPC | HCP educational leaflet |
| | The outer carton as well as the vial label of the product states: For intravenous use after dilution. | |
| Malignant events | For RA: 4.4 5.1 of the SmPC | None |
| | For GPA/MPA: 4.8 of the SmPC | None |
| Impact on cardiovascular disease | For RA, GPA/MPA: 4.2, 4.3, 4.4, 4.8 of the SmPC | None |
| Off-label use in autoimmune disease | For RA, GPA/MPA: 4.8 of the SmPC | None |
| Relapses | For GPA/MPA: Currently available data do not support the need for risk minimization. | None |
| Use in Pregnancy and Lactation | For NHL, RA, GPA/MPA: 4.6, 5.3 of the SmPC | None |
| Immunogenicity and autoimmune disease | For RA, GPA/MPA: 4.5, 5.1 of the SmPC | None |
| Long term use in GPA/MPA patients | For GPA/MPA: Currently available data do not support the need for risk minimization. | None |

***Conclusion***

The CHMP and PRAC considered that the risk management plan version 1.4 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.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* 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. 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, Riximyo (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. Benefit-Risk Balance

## *3.1. Therapeutic Context*

The therapeutic context of rituximab is very well described over the years since it first received the MA in the EU (2nd June 1998), as Mabthera.

Riximyo (rituximab) has been developed as a biosimilar of MabThera, the reference product.

### 3.1.1. Disease or condition

The approval is sought for all approved indications of the reference product MabThera in the EU, according to the MabThera Summary of Product Characteristics (SmPC); Non-Hodgkin's lymphoma (NHL: diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL)); Rheumatoid arthritis (RA) and Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

### 3.1.2. Available therapies and unmet medical need

The originator MabThera is available in the EU since 1998; therefore there is no unmet medical need.

### 3.1.3. Main clinical studies

A pivotal PK/PD study was performed in 173 patients with RA who were irresponsive or intolerant to one or more TNF-alpha inhibitors, comparing a standard treatment course of either Riximyo to MabThera of 1,000 mg per iv infusion, two weeks apart. After 24 weeks, patients could be re-treated based on the presence of residual disease activity (DAS28>2.6), in line with the approved posology of MabThera. The study was powered to assess equivalence of PK in terms of the area under the serum concentration-time curve from time zero to infinity (AUC(0-inf)) and PD in terms of B-cell depletion between Riximyo and MabThera (GP13- 201 Study Part I). The study also provides data on key efficacy and safety including immunogenicity variables.

A pivotal efficacy and safety study in 627 patients with previously untreated advanced FL (study GP13-301). In total 627 subjects received at least one study treatment. Patients were randomised to either Riximyo or MabThera 375 mg/m$^2$ IV for 8 cycles (every 3 weeks), in combination with CVP (cyclophosphamide, vincristine, prednisone). The study was powered to demonstrate equivalence of clinical response (ORR at week 24) as the primary endpoint between Riximyo and MabThera (equivalence margin -/+ 12%) and to provide data on PK/PD and safety including immunogenicity assessments. Primary analyses were performed in the Per-Protocol Set (n=624). PK-PD data were obtained from a small subset of 48 subjects. The study consisted of a Combination Treatment Phase followed by a Maintenance Treatment Phase in which responding patients continued earlier assigned treatment with Riximyo or MabThera as monotherapy (375 mg/m$^2$ every 2-3 months) for another 24 months (n=462). This part of the study is still ongoing at the time of data cut-off of for this MAA.

## *3.2. Favourable effects*

Since the favourable effects of rituximab (as Mabthera) are well established, this application aims to prove similarity between Riximyo (GP2013) and the originator MabThera. This is confirmed on non-clinical grounds with regard to: antibody Dependent Cellular Cytotoxicity (ADCC) in different assay set-ups; B-cell depletion in cynomolgus monkeys after repeated dosing of 20 or 100 mg/kg 4qw; survival in xenografted mouse models; tumour growth in xenografted mouse models.
The required bioequivalence criterion of 90% CI of 80 - 125% between Riximyo and MabThera for the primary parameter AUC0-inf was fulfilled and this was confirmed by a sensitivity analysis including body surface area as an additional covariate in the pivotal study GP13-201 performed in RA patients. In Study GP13-201, the ratio of the geometric means of $AUEC_{(0\text{-}14d)}$ between Riximyo and MabThera was 1.019 (95% CI 0.997, 1.042), which is well within the pre-set bioequivalence margin of 0.80-1.25. This is further supported by exploratory analyses in the two NHL studies, showing a rapid induction and persistent low level of B-cells during treatment of GP-2012, similar to MabThera.

In study GP13-201 the key secondary efficacy endpoint was change from baseline in DAS28 (CRP) at Week 24. The criterion for non-inferiority was met. Results from the ACR20 response analysis at week 24 and averaged ACR20 responders between week 4 and week 24 showed that Riximyo and MabThera are similar regarding ACR20 rates with when applying equivalence margins of ±15%.

In the pivotal efficacy and safety study GP13-301 equivalence with regards to ORR (primary efficacy endpoint) was demonstrated as the entire 95% CI for the difference in ORR between the two treatments was within the pre-specified equivalence margin of ±12%. BOR was assessed as secondary efficacy endpoint. The proportions of patients in Combination Treatment Phase with the best overall response (BOR) based on central blinded review of tumour assessments (CR, PR, stable disease and progressive disease) and their associated 90% CIs were similar for the four tumour assessment categories.

## 3.3. Uncertainties and limitations about favourable effects

There are no uncertainties regarding the biosimilarity of Riximyo to MabTthera in terms of the pharmacokinetic and pharmacodynamic profile.

In study GP13-301 at (data cut-off: 31-Dec-2016) more patients in the MabThera arm are on ongoing treatment whereas a higher number of patients treated with Riximyo than MabThera ended treatment in the maintenance phase with the primary reason for discontinuation being disease progression (20.9% versus 14.3%). The HR for PFS (Riximyo/MabThera) was 1.31 (90% CI [1.02, 1.69]), at the December cut-off, in the same range as observed with the first PFS analysis (data cut off: 10-Jul-2016) where the PFS HR was calculated to be 1.25 (90% CI: [0.96, 1.61]). However, as study GP13-301 was not powered for time-to-event outcomes, hence, for PFS and OS the currently observed data are still immature. Moreover, the follow-up time up to now is too short to allow for an estimation of median PFS and the number of PFS events low and the rate of censoring high. The availability of the study report will provide further information on PFS (see RMP).

## 3.4. Unfavourable effects

The safety profile of Riximyo in study GP13-201_was comparable to MabThera with regards to the incidence of overall adverse events, SAEs and AESI. The following incidences were even lower in the Riximyo arm: premature discontinuation and dose adjustments/interruptions due to AEs, Infusion-related reactions and overall ADA.

Infections and infusion-related reactions were the most commonly reported events (RA Study GP13-201: Riximyo: 31.4 and 37.2%, respectively; MabThera: 35.6% and 42.5%, respectively).

In study GP13-301 during the Combination Phase the safety profile of Riximyo was comparable to MabThera with regards to the incidence of overall adverse events, Grade 3-4 adverse events, suspected treatment related adverse events, treatment discontinuation due to AEs, dose adjustment or interruption and AEs requiring additional therapy as well as deaths.

The incidences of IRR considered to be related to study drug were comparable for Riximyo and MabThera during Combination Phase.

Overall, in the Maintenance Phase, the following incidences were higher in the Riximyo group: Overall Adverse events, Grade 4 AEs, suspected treatment-related AEs, treatment discontinuation due to AEs, serious adverse events, Neutropenia all Grades, Infections and infestation most frequent SOC in serious adverse events and reason for treatment discontinuation. With the data update from the cut-off from 10 July 2016 the percentage difference for AEs during the maintenance phase for the Riximyo arm compared to the MabThera arm decreased from 6.1% to 1.6%. The percentage number of SAEs and discontinuation due to AEs was comparable between the treatment arms. Although, the number of AEs suspected to be related to study drug is slightly higher for the Riximyo arm, the number of Grade 3-4 AEs as well as the number of SAEs are comparable between the treatment arms.

There were no meaningful differences in ADA formation between Riximyo and MabThera. In the RA study, ADAs were detected in 11.0% versus 21.4% in the Riximyo and MabThera arm, respectively. Neutralising ADAs were detected in 3.7% of the Riximyo arm and 1.2% of the MabThera arm. There was no clear relationship between the presence of ADA's and efficacy/safety. Overall, the number of patients with ADA was low in Study GP13-301 in Follicular Lymphoma (8 /551 subjects, 1.5%), without meaningful differences between treatment assignments. The rate of ADA formation may be reduced by concurrent chemotherapy or prednisolone.

In order to further investigate the risks of Immunogenicity, infusion related reactions, infections (including serious infections), neutropenia, the applicant will conduct and submit the results of:

- GP13-201 (Study Part 2), a randomised, double-blind, controlled study to evaluate pharmacokinetics, pharmacodynamics, safety and efficacy of Riximyo and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies.

- GP13-301, a randomised, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of Riximyo plus cyclophosphamide, vincristine, prednisone vs. MabThera plus cyclophosphamide, vincristine, prednisone, followed by Riximyo or MabThera maintenance therapy in patients with previously untreated, advanced stage follicular lymphomain patients with previously untreated, advanced stage follicular lymphoma.

- GP13-302: A randomized, double- blind, controlled, parallel-group, multicenter study to assess the safety and immunogenicity of transitioning to Riximyo or re-treatment with Rituxan / Riximyo or MabThera in patients with active rheumatoid arthritis, previously treated with Rituxan / Riximyo or MabThera.

- Data deriving from the following registries: British Society of Rheumatology Biologics Register (BSRBR), Swedish registry (ARTIS) and German registry (RABBIT).

Please see RMP section 2.7.

## *3.5. Uncertainties and limitations about unfavourable effects*

There are no uncertainties concerning the comparability of the clinical safety of Riximyo with Mabthera. Further long term safety information will be provided with the final study report (see RMP).

## *3.6. Effects Table*

Not applicable for biosimilars.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

A comprehensive biosimilarity exercise, which covered all relevant structural and functional characteristics of the rituximab molecule, was submitted. The presented results support the biosimilarity claim; similarity between Riximyo and the EU reference product MabThera is considered demonstrated at the quality level. Any minor differences observed have been adequately justified with respect to the efficacy/safety profile of Riximyo.

Comparability data on three relevant mechanisms of action (CDC, ADCC, ADCP and apoptosis), which are considered important for lysis of the B-cell subsequent to binding of rituximab to the CD20 antigen were provided. Bioequivalence was demonstrated for the primary PK endpoint AUC(0-inf) as well as mostly all other secondary PK endpoints. The descriptive data for the PK parameters determined in study GP13-201 indicate comparability between Riximyo and MabThera.

The key secondary efficacy endpoint in study GP13-201 was met and results of the analyses for the ACR20 rates of response at week 24 and averaged ACR20 responders between week 4 and week 24 were within the applied equivalence margins of ±15% thereby suggesting similarity.

The primary efficacy endpoint (ORR) in GP13-301 was met. Updated OS and PFS data will be submitted with the final study report (see RMP).

The adverse events with Riximyo were in overall in line with the well-established safety profile of Mabthera. Overall, the rates of ADA formation were low in both the RA trial and the study in FL. Updates on safety will be submitted with the final CSRs of the ongoing studies (see RMP).

### 3.7.2. Balance of benefits and risks

Biosimilarity of Riximyo to the originator Mabthera has been demonstrated with regards to PK/PD, efficacy and safety parameters in two clinical trials and two different indications Rheumatoid Arthritis and Follicular Lymphoma.

### 3.7.3. Additional considerations on the benefit-risk balance

With regards to the efficacy, it is well established that the mechanism of action and PD aspects are common across autoimmune and across oncology indications of Mabthera. Therefore, and in line with the EMA guidelines on the similar biological medicinal products, the efficacy results obtained with Riximyo, demonstrating equivalence with Mabthera in RA and FL patients can be reasonably extrapolated to the other approved therapeutic indications of Mabthera.

The applicant claims the same therapeutic indications for adult patients for the biosimilar Riximyo as granted for Mabthera for iv administration in the EU. However, as Mabthera is also marketed in the subcutaneous indication, a risk of medication error has been identified. Adequate risk minimisation measures to avoid the potential route of administration error have been included in the RMP.

## *3.8. Conclusions*

Riximyo is considered biosimilar to Mabthera and therefore the overall Benefit Risk balance of Riximyo is considered positive in the following indications:

Non-Hodgkin's lymphoma (NHL)
Riximyo is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
Riximyo maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.
Riximyo monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.
Riximyo 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.

Rheumatoid arthritis
Riximyo 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.
Riximyo 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
Riximyo, 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).

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Riximyo is not similar to Imbruvica (Ibrutinib), Arzerra (Ofatuzumab), Gazyvaro (Obinutuzumab) and Venclyxto (Venetoclax) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Riximyo is favourable in the following indications:

Riximyo is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

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

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

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

Riximyo 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.

Rheumatoid arthritis

Riximyo 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.

Riximyo 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

Riximyo, 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 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 Riximyo are provided with the following:

- Product information
- Physician information
- Patient information
- Patient Alert card

The Physician information about Riximyo 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 Riximyo 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 Riximyo 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 Riximyo 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 Riximyo 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 Riximyo are provided with the following:

- Product information
- Physician information

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

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

The Physician information and Patient information must be agreed with the National Competent Authorities prior to distribution and Patient Alert Card should be included as part of inner packaging.