Saudi Public Assessment Report

Rixathon®

Active Pharmaceutical Ingredient(s): Rituximab

ATC code/CAS no.: L01XC02/174722-31-7.

Pharmaceutical/Dosage Form: Concentrate for solution for infusion.

Dosage Strength: 100mg/10mL and 500mg/50mL.

Route of adminstration: Intravenous use after dilution

Marketing Authorization Holder: Sandoz GmbH

Shelf life of an unopened vial: 3 years at 2°C – 8°C.

Storage conditions: Store in a refrigerator (2°C -8°C)

Keep the container in the outer carton, Protect from light.

Registration No.: 2908210991 - 2908210990

Decision and Decision Date: Approved on 29/08/2021

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1. Terms, Definitions, Abbreviations

Terms	Definitions
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AEs	Adverse events
ANOVA	Analyses of variance.
$AUC_{(0\text{-}inf)}$	Area under the serum concentration-time curve (time 0 to infinity)
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve (time 0 to time of last quantifiable concentration)
AUC_{all}	Area under the curve from the time of dosing to the time of the last observation, regardless of whether the last concentration is measurable or not.
AUEC	Area under the effect-time curve
BOR	Best overall response
C_{max}	Maximum serum concentration
CDC	Complement-dependent cytotoxicity
cGMP	current Good Manufacturing Practices
CHO	Chinese Hamster Ovary
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
C_{min}	Minimum serum concentration
CR	Complete response
CRP	C-reactive protein
C_{trough}	Pre-dose serum drug concentration determined at the end of a dosing interval
CV	Coefficient of variation
CVP	Cyclophosphamide, vincristine, prednisone chemotherapy.
DMARDs	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EMA	European Medicines Agency
FAS	Full analysis set
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GMR	Geometric means ratio
GP2013	The Sandoz internal code name for Rituximab
GPA	Granulomatosis with polyangiitis
HBV	Hepatitis B virus
HCl	Hydrochloric acid
HR	Hazard ratio
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG1	Immunoglobulin subclass G1

IPCs	In-process controls
IRT	Interactive response technology
IV	Intravenous
mAb	Monoclonal antibody
MAH	Marketing authorization holder
MPA	Microscopic polyangiitis
MTX	Methotrexate
Nab	Neutralizing antibodies
NaCl	Sodium chloride
NaOH	Sodium hydroxide
NHL	Non-Hodgkin's lymphoma
ORR	overall response rate
OS	Overall survival.
PAS	PK analysis set
PC	Process Characterization
PD	pharmacodynamics
PFS	progression free survival
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PP	Per-protocol population
PPS	per-protocol set
PR	partial response
PS 80	Polysorbate 80
QbD	Quality by Design
RA	Rheumatoid arthritis
RMM	Risk Minimization Measures
RMP	Risk Management Plan
SAEs	serious adverse events
SOC	System organ class
$T_{1/2}$	terminal elimination half-life
TEAEs	Treatment emergent adverse events
T_{max}	Time to attain maximum serum concentration
TNF	Tumor necrosis factor
US-FDA	U.U Food and Drug Administration
WCB	working cell bank
WFI	Water for injection

2. Background

2.1 Submission Details

Type of submission: New Biosimilar Drug

Pharmacological class: Antineoplastic agents, monoclonal antibodies.

Submitted Indication: Rixathon (also referred to as GP2013) is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)
Rixathon is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma (FL) in combination with chemotherapy.

Rixathon maintenance therapy is indicated for the treatment of FL patients responding to induction therapy.

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

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

Chronic lymphocytic leukaemia (CLL)

Rixathon in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

Rheumatoid arthritis (RA)

Rixathon 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 (GPA) and microscopic polyangiitis (MPA)

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

Submitted Dosage: 100 mg, 500 mg

2.2 Regulatory Background

This product is considered a New Biosimilar Drug for Saudi regulatory purposes.

This product is qualified for the following regulatory pathway:

☒ Normal submission

☐ Abridged

☐ Verification

☐ Priority

Regulatory status in other countries (approved countries):

Country	Brandname	Dosage form/Strength	MAH
Albania	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Algeria	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Argentina	Rixathon	Concentrate solution for infusion	NOVARTIS S.A.
Australia	Riximyo	Concentrate solution for infusion	SANDOZ PTY. LTD.
Belarus	Rixathon	Concentrate solution for infusion	SANDOZ PHARMACEUTICALS D.D.
Bosnia-Herz.	Rixathon	Concentrate solution for infusion	NOVARTIS BA D.O.O.,
Brazil	Riximyo	Concentrate solution for infusion	SANDOZ DO BRASIL INDUSTRIA FARMACEUTICA
Canada	Riximyo	Concentrate solution for infusion	SANDOZ CANADA INC
Chile	Rixathon	Concentrate solution for infusion	NOVARTIS CHILE S.A.
Colombia	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Costa Rica	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Dominican Rep.	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Ecuador	Rixathon	Concentrate solution for infusion	SANDOZ GMBH

Egypt	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
El Salvador	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
European Union	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
European Union	Riximyo	Concentrate solution for infusion	SANDOZ GMBH
Guatemala	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Honduras	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Hong Kong	Rixathon	Concentrate solution for infusion	NOVARTIS PHARMACEUTICALS (HK) LTD
Iceland	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Iceland	Riximyo	Concentrate solution for infusion	SANDOZ GMBH
Israel	Rixathon	Concentrate solution for infusion	NOVARTIS ISRAEL LTD
Japan	Rituximab BS	Intravenous Infusion	SANDOZ KK KAMINOYAMA SITE
Jordan	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Kosovo	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Lebanon	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Liechtenstein	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Liechtenstein	Riximyo	Concentrate solution for infusion	SANDOZ GMBH
Mexico	ARASAMILA	Concentrate solution for infusion	SANDOZ S.A. DE C.V.
Montenegro	Rixathon	Concentrate solution for infusion	GLOSARIJ D.O.O.
New Zealand	Riximyo	Concentrate solution for infusion	NOVARTIS NEW ZEALAND LTD.
North Macedonia	Rixathon	Concentrate solution for infusion	LEK SKOPJE DOOEL
Norway	Rixathon	Concentrate solution for infusion	SANDOZ GMBH

Norway	Riximyo	Concentrate solution for infusion	SANDOZ GMBH
Oman	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Palestine	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Panama	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Paraguay	Rixathon	Concentrate solution for infusion	CASA BOLLER S.A.
Peru	Rixathon	Concentrate solution for infusion	NOVARTIS BIOSCIENCES PERU S.A.
Qatar	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Serbia	Rixathon	Concentrate solution for infusion	SANDOZ PHARMACEUTICALS D.D. REP.OFFICE
Singapore	Rixathon	Concentrate solution for infusion	NOVARTIS (SINGAPORE) PTE LTD.
Switzerland	Rixathon	Concentrate solution for infusion	SANDOZ PHARMACEUTICALS AG
Taiwan	Rixathon	Concentrate solution for infusion	NOVARTIS CO., LTD
Thailand	Rixathon	Concentrate solution for infusion	NOVARTIS (THAILAND) LTD.
Trinidad,Tobago	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Ukraine	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
United Kingdom	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Uruguay	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Utd.Arab Emir.	Rixathon	Concentrate solution for infusion	SANDOZ GMBH
Vietnam	Rixathon	Concentrate solution for infusion	NOVARTIS (SINGAPORE) PTE LTD

2.3 Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

3. Scientific discussion about the product:

Rixathon is a genetically engineered murine/human chimeric Immunoglobulin G1(IgG1) kappa type monoclonal antibody (mAb) directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. The antibody has a molecular mass of 145 kilo-Dalton (kDa) and is composed of two light chains (213 amino acids) and two N-glycosylated heavy chains (451 amino acid), which are covalently associated with one another at defined cysteine residues via disulfide bridges. Rixathon has been produced by recombinant Deoxyribonucleic acid (DNA) technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system.

The qualitative and quantitative composition of the GP2013 formulation is identical to that of MabThera/Rituxan as a concentrate for solution for infusion in vials.

Drug substance (DS) and drug product (DP) are manufactured according to current Good Manufacturing Practices (cGMP). GP2013 DP is produced using standard manufacturing steps such as thawing of the DS, dissolving of excipients, compounding, sterile filtration and aseptic vial filling. Drug Substance (DS) is provided frozen as GP2013 bulk solution, which is formulated at pH 6.5 with citrate buffer. The production of GP2013 DP starts with thawing the DS. The GP2013 DP is formulated with the following excipients: citric acid monohydrate, sodium chloride (NaCl), polysorbate 80 (PS 80) and water for injection (WFI). Hydrochloric acid (HCl) and sodium hydroxide (NaOH) are used as processing agents for pH adjustment if required. The formulation is preservative-free.

3.1 Quality Aspects

3.1.1 Introduction

The manufacturing process of GP2013 DS was developed by Sandoz GmbH to target a product quality similar to the EU marketed reference product MabThera and US-licensed Rituxan. Cell line and process development for a biosimilar at Sandoz GmbH follow the same principles of quality by design (QbD) development as a new biopharmaceutical with the exception of much tighter targets for product quality. GP2013 DS manufactured according to current Good Manufacturing Practices (cGMP). Copies of the manufacturing authorizations and GMP certificates of the manufacturing site have been submitted. During the development process the manufacturing of the DS was subjected to process improvements. The impact of these changes was assessed in comparability studies to ensure that the introduced modifications do not adversely influence the quality, safety or efficacy of GP2013. The physicochemical parameters density, pH and osmolality of

GP2013 DS, DP and the corresponding matrices were determined and correlated with the originator product. The density of the DP corresponds well with the density of the originator product. Photo-stability study was conducted to test if this photo-stress will affect the quality of GP2013 DP. The slight and expected degradations after the applied photo-stress demand storage of GP2013 DP material protected from direct sunlight, but the light exposure in production will not harm the product.

3.1.1 Drug Substance

Manufacture, characterization and process controls:

The description of the upstream process and purification process includes the process parameters, in-process controls (IPCs) and equipment are assessed and accepted from the manufacturing site. Single production batch being generated from a single working cell bank (WCB) vial upon culture expansion and protein production during the upstream process (cell culture) and the subsequent downstream process (purification). The manufacturing process reflects a standard process used for the manufacture of monoclonal antibodies.

Process characterization (PC) was conducted in accordance with current International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) requirements including quality by design (QbD) principles (process characterization data for current commercial scale, and laboratory studies). The Methodology used to assess the process- and product-related risks of the drug substance manufacturing process and to classify the process parameters (PPs) based on PC studies. The classification of PP is appropriate.

GP2013 is not defined as a single homogeneous molecule but rather as an array of molecular species containing variable physicochemical characteristics. These characteristics 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 as shown in Figure 1.

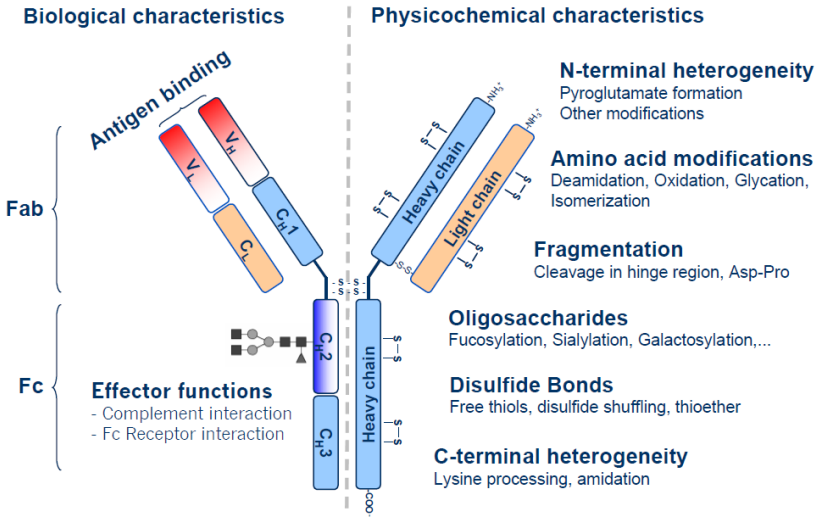


Figure 1: Scheme of a standard IgG1 antibody. Key parameters influencing heterogeneity

Control of the drug substance (DS):

The structural and functional characterization of the proposed biosimilar product GP2013 was achieved by the application of a number of different and orthogonal physicochemical methods.

By the evaluation of these methods, SFDA reviewers found that those methods can represent biochemical attributes such as identity showing the primary structure, higher-order structures (secondary and tertiary structures), carbohydrate structure, heterogeneity (e.g. by size, charge and hydrophobicity) and other attributes including biological activity, product related substances and impurities.

Specifications, test procedures and acceptance criteria submitted by the applicant follow the ICH Q6B guidelines, a detailed description of each method used for release and shelf life testing of GP2013 DS with the validation of each including detailed validation for the non-compendial analytical procedures. The presented specification parameters acceptance criteria were justified with data derived from a sufficient number of batches, which represent the current commercial scales confirmed by batch analysis data submitted under section (3.2.S.4.4) and stability data submitted under section (3.2.S.7.3).

Reference materials:

The early development working standards were produced out of samples of originator product and DS material during technical development. Subsequently, these working standards were replaced by reference materials which were produced out of representative DS batches manufactured under GMP conditions. Then the reference material was established from a batch produced during the validation campaign and was used for the release of commercial batches until it is replaced by the current primary in-house reference

material and the respective working standard. Based on this in-house primary reference material working standards are established and released by comparison to the primary reference material. These working standards primarily have the purpose to facilitate routine analytical testing.

Upon the SFDA analytical review team assessment for the methods used for release, re-testing and characterization of in-house reference materials and storage condition for both reference materials. They concluded that both current primary and working reference materials can be efficiently utilized in the routine release analysis of DS and DP batches specifications: identity, purity, content, and bioactivity parameters as well as comparability exercises used to evaluate process changes.

Stability:

The stability program shows the maintenance of GP2013 DS molecular identity, purity, content, and biological activity, during the intended shelf life. Stability studies were performed over the whole shelf life of the DS and included physicochemical and biological tests.

The results for all batches were within the shelf-life specifications during storage at long-term storage conditions for up to the end of the proposed shelf life in the proposed container closure system. No relevant changes were observed for any of the quality attributes except for one parameter that had a minor increase observed over time. This increase was taken into account in the justification of specification and does not influence the product quality, safety and efficacy.

3.1.2 Drug Product

GP2013 DP is manufactured and released by Lek Pharmaceuticals d.d. Ljubljana, Ljubljana, Slovenia. Alternatively, GP2013 DP can be released by Sandoz GmbH Schaftenau, Austria. GP2013 (INN: rituximab) 100 mg and 500 mg Concentrate for Solution for Infusion is a sterile concentrate for solution for infusion for intravenous (IV) use after dilution. The liquid formulation is based on rituximab as a DS at a concentration of 10 mg/mL provided in 10 mL vials (100 mg) and 50 mL vials (500 mg). The formulation of the DP was developed to maintain the similarity to the EU market authorized reference product MabThera, a registered trademark of Roche Registration Ltd., United Kingdom (UK). The only difference between the used excipients is the hydration form (GP2013 DP buffer solution is manufactured using citric acid monohydrate, the originator uses sodium citrate dehydrate). To guarantee the withdrawal of the recommended dosage suitable overfills are implemented, the DP is filled in clear, colorless vials made of tubular glass and closed with rubber stoppers. The rubber stoppers are made of chorobutyl rubber. The vial-stopper combination is crimped with an aluminum cap with a flip-off component.

Description of the product and Pharmaceutical Development:

The formulation of GP2013 DP is identical to the originator product and therefore no extensive formulation development was submitted. The container closure system of GP2013 DP was selected in order to resemble the primary packaging of the originator product as closely as possible. Three subsequent manufacturing process phases were submitted for GP2013 DP throughout the development history. By the assessment of the submitted data SFDA bio-manufacture evaluation team, concluded that the introduced modifications do not adversely affect the quality, safety and efficacy of the yielded DP the impact of these changes on relevant quality attributes was discussed in detail in the submitted comparability studies.

Manufacture of the product:

GP2013 DP manufactured using standard manufacturing steps such as the thawing of the DS, dissolving of excipients, compounding, sterile filtration and aseptic vial filling. Due to the thermal lability of the active pharmaceutical ingredient, rituximab sterile filtration by means of bacteria-retentive membrane filters followed by aseptic filling is applied. The submitted IPCs are considered appropriate tests since it is monitoring the whole manufacturing process and assure a consistent performance of the manufacture of the DP. Process validation of GP2013 DP 100 mg and 500 mg was performed involving the production of six validation batches, i.e. three consecutive batches of 100 mg and 500 mg vials each, with the same batch size of bulk DP solution, the manufacturing process, control of critical steps and process validation were evaluated by SFDA quality assessor, they report that validation and release testing results confirmed the described manufacturing procedures at both production sites are capable of consistently producing GP2013 DP 100 mg and 500 mg within the predefined specification limits and is therefore appropriate for regular production of the drug product. All the used excipients comply with the quality requirements of the applicable compendial monograph. Certificates of analysis provided.

Product control:

The specifications are identical for 10 mL and 50 mL vials, apart from the extractable volume. Description of each of the methods used for shelf life testing of GP2013 DP is presented in respective sections, non-compendial analytical procedures used for release and stability testing of GP2013 DP have been validated according to relevant guidelines. Batch analysis data submitted in this application showed that batches were released according to the specifications valid at the time of release for DP batches manufactured at Lek Pharmaceuticals d.d. Ljubljana, where two batch numbers are available, both of these batch numbers are listed in sections below. These two batch numbers correspond to the same bulk DP batch before and after visual inspection, respectively.

Container closure system:

GP2013 DP will be marketed as a concentrated liquid in vials for single use. GP2013 DP is filled in clear, colorless vials (10 mL and 50 mL) made of tubular glass and closed with rubber stoppers. The rubber stoppers are made of chorobutyl rubber and coated with an ethylentetrafluoroethylene layer at the product contact area. The coating provides a barrier to leachable and extractable, thus mitigating the risk of interaction over the DP shelf life. The vials stopper combination is crimped with an aluminum cap with a flip-off component. The cap does not come into contact with the DP and is therefore not considered a primary packaging component, by the assessment of the data under this section we concluded that the container closure system is suitable for its intended use for the entire proposed shelf life.

Stability of the product:

Unopened vial

The stability data of GP2013 DP in 10 mL vials (100 mg, 10 mg/mL) and 50 mL vials (500 mg, 10 mg/mL). Data is presented to justify the proposed shelf life for commercial supply. Consequently, a shelf life of 3 years is claimed for GP2013 DP 100 mg and 500 mg at long-term storage conditions (5 ± 3°C) in a refrigerator keeping the container in the outer carton to protect from light. This claim is based on available real time data over the complete shelf life and data evaluation according to ICH guideline Q1E.

GP2013 DP can also be stored in the original carton outside of refrigerated storage up to a maximum of 30°C for a single period of up to 7 days, but not beyond the original expiry date

Diluted solution

• After aseptic dilution in sodium chloride solution:
Chemical and physical stability of Rixathon diluted in 0.9% sodium chloride solution has been demonstrated for 30 days at 2°C - 8°C and subsequently 24 hours at room temperature (≤25°C).
• After aseptic dilution in glucose solution:
Chemical and physical stability of Rixathon diluted in 5% glucose solution has been demonstrated for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature (≤25°C).
From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

3.2 Clinical Aspects

3.2.1 Clinical Pharmacology

Suggested mechanism of action and drugs in the same pharmacological class:

Rituximab is a chimeric human-murine immunoglobulin G1 mAb that binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. This antigen is expressed on more than 95% of all B cell NHL.

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

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

3.2.1.1 Pharmacokinetic (PK) and pharmacodynamic (PD) studies

The pivotal clinical study in PK/PD assessment was conducted on (RA) patient population in the GP13-201 trial. Also in patients with FL in GP13-301 trial and in Japanese patients with indolent B-cell NHL in GP13-101 trial as supportive studies.

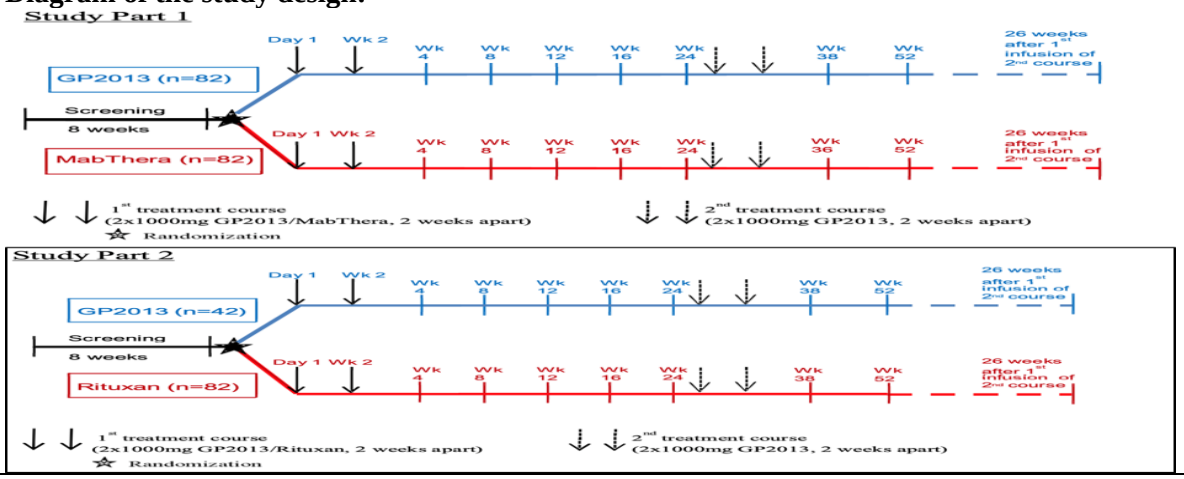
List of pharmacokinetic studies

Study ID/ Clinical trials identifier	Study design	Objective	Population	Findings
GP13-201 (Part I and II) **PK**/ PD, Safety and efficacy. "**pivotal**"	Randomized, multicenter, double-blind, parallel-group, Patients in Study Part I were randomized to either GP2013 or EU-Mabthera, While Patients in Study Part II are randomized to either GP2013 or US-Rituxan.	**Primary:** To assess bioequivalence between GP2013 and EU-Mabthera*/US-Rituxan and between Mabthera and Rituxan in combination with methotrexate with respect to primary PK parameter $AUC_{0\text{-}inf}$. **Secondary:** - To further compare GP2013 and Mabthera/Rituxan with respect to secondary PK parameters. - To assess equivalence in PD parameter "depletion of peripheral B cells" and safety. - To assess the non-inferiority of GP2013 to EU-Mabthera/US-Rituxan with respect to efficacy "change from baseline in DAS28 at Week 24".	In patients with active RA (N*=312)	Explained below
GP13-301 **Efficacy,** PK/ PD, Safety. "**Supportive**"	Randomized, multicenter, double-blind, active-controlled, parallel-group. The study consists of a combination treatment phase (GP2013 vs. Mabthera), followed by maintenance treatment	**Primary:** To demonstrate similarity of the overall response rate (ORR). **Secondary:** - To further demonstrate similarity with respect to secondary efficacy endpoints (CR, PR, progression free survival (PFS), and OS). - To evaluate the safety of Rixathon and the incidence of immunogenicity. - To evaluate the PK/PD of Rixathon and Mabthera (Cmax, Ctrough, AUC (0-t), all, AUEC (0-t)).	In patients with previously untreated, advanced stage FL (N=629)	**(Rixathon/Mabthera):** **PK:** - **C_{max}:** geometric means ratio (GMR) was 1.00 (90% CI: [0.925, 1.09]) - **C_{trough}**: the means were 66.42 mcg/mL (CV% 71.66 %) and 82.13 mcg/mL (CV% 74.9 %) for Rixathon vs. Mabthera, respectively. **$AUC_{(0\text{-}21d)}$:** the geometric means were 3210 mcg*day/mL [CV% 27.5], 3340 mcg*day/mL [CV% 34.9] in Rixathon

	phase (either GP2013 or Mabthera).			vs. Mabthera, respectively. **AUC_{all}:** the geometric means were 2510 $_{mcg*day/mL}$ [CV% 55.1] 2310 $_{mcg*day/mL}$ [CV% 109.1] in Rixathon vs. Mabthera, respectively. **PD:** **$AUEC_{(0-21d)}$:** GMR was 0.939 (90% CI: [0.845, 1.04]) The study was not powered to test bioequivalence of the two formulations based on PK endpoints. Therefore, the PK results were presented descriptively.
GP13-101 **PK**/safety. "**supportive**"	Phase I, multi-center, open label, single arm.	**Primary:** To evaluate PK and safety of GP2013 after the administration of weekly monotherapy. **Secondary:** - To evaluate efficacy of GP2013. - To evaluate the incidence of immunogenicity (ADA) formation against GP2013. - To evaluate PD biomarker "peripheral CD19 + B-cell count".	In Japanese patients with CD20 Positive Low Tumor Burden Indolent B-cell NHL. (N= 6).	**Descriptive analysis:** For (AUC_{0-7d}; C_{max}; AUC_{0-last}; C_{min}; T_{max}) assessed on Week 1/Day 1 and Week 8/Day 1. The PK results were reported to be consistent with the PK results in the package insert for Rituxan (Japanese-approved).

* The EU-Mabthera is the approved reference of Rituximab by SFDA, N= number of patients

Pivotal PK study (GP13-201):

Title: A randomized, double-blind, controlled study to evaluate PK, PD, safety and efficacy of GP2013 and rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies.	
Study identifier	Sponsor code: GP13-201 – EudraCT number : 2010-021184-32 – clinical trial.gov: NCT01274182
Design	This trial was 52-week, multicenter, randomized, double- blind, parallel group phase II trial. The study was designed to have two separate parts in order to meet the regulatory requirements of both the EMA and US-FDA. **Diagram of the study design:** 
Total study duration	Date of first screening to last follow-up(part I): 14 Dec 2010 – 10 Apr 2014 Date of first screening to last follow-up(part II): 28-Jun-2013 – 10 Nov 2016
Treatment arms	**Test treatment:** GP2013, 1000 mg, two IV infusions. Patients also received MTX (between 7.5 and 25 mg/week) and folic acid (≥ 5 mg per week) Throughout the study with each treatment arm.
	Reference treatment in part I: EU-Mabthera (Roche Registration Limited), 1000 mg, two IV infusions.
	Reference treatment in part II: US-Rituxan (Biogen Idec/Genentech, USA), 1000 mg, two IV infusions.
Randomization	**In study part I**, 173 patients were randomized in a ratio of 1:1 to either receive GP2013 (N=86) or Mabthera (N=87). At Visit 3 (Day 1), Patients received the first course of IV infusion of GP2013 or Mabthera on two separate occasions, two weeks apart (i.e. on Day 1 and on Day 15), patients were sampled for comparative PK (Week 24) and PD analysis (Week 52), the majority of randomized patients (n=142, 82.1%) completed the study up to 52 weeks. Efficacy and safety data were assessed on a regular basis until Week 52. There was an optional wash-out period between Visit 1(screening) and Visit 2 (baseline) for anti-TNF or DMARD (except MTX, sulfasalazine, chloroquine and hydrochloroquine) that might have taken up to 8 weeks. **In Study Part II**, A total of 139 patients were randomized in a ratio of 1:2 (GP2013: Rituxan). Patients in the GP2013 group were pooled from both Study Part I (n=86) and Study Part II (n=47), while patients in the Rituxan group were recruited in Study Part II (n=92) alone. **Analysis sets for Part I & II**

	Part I: **Analysis Set** / **GP2013 n (%)** / **MabThera® n (%)** / **Total n (%)** Full Analysis Set: 86 (100.0) / 87 (100.0) / 173 (100.0) Safety Analysis Set: 86 (100.0) / 87 (100.0) / 173 (100.0) PK Analysis Set: 86 (100.0) / 86 (98.9) / 172 (99.4) Per Protocol Set: 85 (98.8) / 82 (94.3) / 167 (96.5) 1. Percentages are based on the Full Analysis Set. Part II: **Analysis Set** / **GP2013 n (%)** / **Rituxan n (%)** / **Total n (%)** Full Analysis Set: 133 (100.0) / 92 (100.0) / 225 (100.0) Safety Analysis Set: 133 (100.0) / 92 (100.0) / 225 (100.0) Per Protocol Set: 128 (96.2) / 85 (92.4) / 213 (94.7) PK Analysis Set: PAS+A: 131 (98.5) / 89 (96.7) / 220 (97.8) PK Analysis Set: PAS PAS1: 131 (98.5) / 86 (93.5) / 217 (96.4) PAS2: 119 (89.5) / 79 (85.9) / 198 (88.0)
Primary PK Endpoint	- $AUC_{0\text{-}inf}$
Secondary PK endpoints	- $AUC_{(0\text{-}14d)}$, - $AUC_{(0\text{-}12w)}$, - $AUC_{(0\text{-}24w)}$, - C_{max}[1] - T_{max}[2]
Secondary PD endpoints	-$AUEC_{(0\text{-}14d)}$ for depletion of CD20+ peripheral B-cells.
Statistical analysis	**For the primary PK parameters:** - Bioequivalence was to be concluded if the 90% CI for the ratio of geometric means of two treatments falls completely within the pre-specified limits of 0.8-1.25 for the primary PK parameters. - **Statistical methods:** - The PK analyses were performed on the **PK Analysis Set (PAS).** - **(ANOVA):** on the log-transformed $AUC_{0\text{-}inf}$, $AUC_{(0\text{-}14d)}$, $AUC_{(0\text{-}12w)}$, $AUC_{(0\text{-}24w)}$, C_{max}, with treatment as the factor and gender as a covariate, to test the bioequivalence. - For T_{max} a non-parametric Hodges-Lehmann method was performed on the medians. - **Descriptive statistics**: were provided for all primary and secondary PK parameters. - As **a sensitivity analysis** of the $AUC_{(0\text{-}inf)}$, body surface area (as a continuous variable) was added as a covariate to the ANOVA model. **For the secondary PD endpoints:** - Bioequivalence was to be concluded if the 95% CI for the ratio of geometric means of two treatments falls completely within the limits of 0.80 to 1.25 for $AUCE_{0\text{-}14d}$. **Statistical methods:** - The PD analyses were performed on the PAS. - **(ANOVA):** on $AUEC_{(0\text{-}14d)}$, The ratio of the geometric means and 95% CI of the $AUEC_{(0\text{-}14d)}$ were estimated by ANOVA on log transformed PD parameters with treatment as the factor. - **Descriptive statistics**: were provided for all PD and safety parameters.

***** 1- after the second infusion (Cmax2), **2-** (for both infusions, i.e. Tmax1 and Tmax2)

Determination of Sample Size

PK bioequivalence is defined as AUC $_{(0\text{-inf})}$ of the study drugs being comparable, i.e. the **90% CI** for the ratio of the geometric means (GP2013/Mabthera) and for (GP2013/Rituxan) must be within the pre-specified bioequivalence limits of **0.8 to 1.25**.

For the sample size calculation, the published coefficient of variation **(CV) of 0.33** for AUC following the administration of rituximab in combination with Methotrexate (MTX) in RA patients was used *(Breedveld et al 2007*). Therefore, the study should have sufficient **power of 90%** for each of the three comparisons even if the **ratio of the geometric means** of the AUCs between GP2013 and Mabthera is **1.06**. That ratio was observed in preclinical studies conducted in cynomolgus monkeys comparing GP2013 and Mabthera. For each comparison, a total of **132** evaluable patients (66 patients in each group) were needed. In order to account for a 20% loss of patients in the PK analysis set, a total of 82 patients need to be randomized in each treatment group.

In Part II: The inclusion of additional 42 patients in (GP2013) arm to be randomized in parallel with Rituxan patients is not based on statistical considerations but is required in order to maintain blinded randomized treatment allocation. This number was chosen to ensure a ratio of 1:2 (GP2013: Rituxan) for the inclusion of patients in the second part of patient recruitment.

In Part II analysis patients of GP2013 treatment group from Part I were pooled with Part II GP2013 treatment group assuming Part I and Part II baseline characteristics are similar. The sample size of GP2013 in Part II is 124 (42+82) which is expected to achieve at least 90% power.

Results:

Pharmacokinetics Results of Study (GP13-201/part I):
Summary of Bioequivalence Analysis on Primary PK endpoint (AUC_{0-inf}) of GP2013 in Serum:

PK Parameter (unit)	Treatment	n	Adjusted Geometric mean	Treatment Comparison		
				Comparison	Geometric mean ratio	90% CI of mean ratio
AUC(0-inf) (day*ug/mL)	GP2013	75	6738.51	GP2013/ MabThera®	1.064	(0.968, 1.169)
	MabThera®	70	6334.41			

A sensitivity analysis provided similar results. The ratio of the geometric means (GP2013/Mabthera) was 1.054. The corresponding 90% CI (0.965, 1.151) was within the pre-specified bioequivalence limits.

Results of Primary PK endpoint (AUC_{0-inf}) in part II of Study (GP13-201):

PK Parameter (unit)	Treatment	n	Adjusted Geometric mean	Treatment Comparison		
				Comparison	Geometric mean ratio	90% CI of mean ratio
AUC_{0-inf} (day*mcg/mL)	GP2013	124	7627.44	GP2013/ Rituxan	1.012	(0.925, 1.108)
	Rituxan	80	7536.89	Rituxan/ MabThera	1.093	(0.989, 1.208)
	MabThera	79	6896.97			

PAS+A: All qualifying patients including ADA positive.

Results of secondary PK endpoints in part I of Study (GP13-201):

PK parameter (unit)	Treatment	n	Adjusted Geometric mean	Comparison	Treatment Comparison: Geometric mean ratio	Treatment Comparison: 90% CI of mean ratio
$AUC_{(0-14d)}$ (day*ug/mL)	GP2013	78	1955.45	GP2013/ MabThera®	1.106	(1.010, 1.210)
	MabThera®	74	1768.78			
$AUC_{(0-12w)}$ (day*ug/mL)	GP2013	76	6575.23	GP2013/ MabThera®	1.091	(0.988, 1.205)
	MabThera®	72	6024.81			
$AUC_{(0-24w)}$ (day*ug/mL)	GP2013	73	6696.36	GP2013/ MabThera®	1.087	(0.980, 1.206)
	MabThera®	72	6159.42			
$C_{max}2$ (2^{nd} inf) (ug/mL)	GP2013	76	386.22	GP2013/ MabThera®	1.036	(0.944, 1.138)
	MabThera®	75	372.63			
T_{max} (1^{st} inf) (hours) [5]	GP2013	79	4.42	GP2013/ MabThera®	-0.083	(-0.167, -0.017)
	MabThera®	77	4.33			
T_{max} (2^{nd} inf) (hours) [5]	GP2013	76	3.43	GP2013/ MabThera®	0.000	(-0.083, 0.150)
	MabThera®	75	3.45			

1. n = number of patients with non-missing values.
2. Ratio of geometric means and 90% CI were estimated by **analysis of variance (ANOVA)** ~~analysis of covariance (ANCOVA)~~ on log-transformed PK parameters with treatment as the factor and gender (male/female) as a covariate. Results were then back-transformed to the original scale.
3. PK concentrations below the limit of quantification (0.8 µg/mL) were treated as zero for the calculation of pharmacokinetic parameters.
4. No imputation of missing values was performed.
5. For T_{max}, median is presented under 'Adjusted Geometric mean', Hodges-Lehmann estimate of the differences between GP2013 and MabThera® under 'Geometric mean ratio' and distribution free CI under '90% CI of mean ratio'. No statistical equivalence testing was performed for T_{max}.

Results of secondary PK endpoints in part II of Study (GP13-201):

PK Parameter (unit)	Treatment	n	Adjusted Geometric mean	Comparison	Treatment Comparison: Geometric mean ratio	Treatment Comparison: 90% CI of mean ratio
AUC_{0-14d} (day*mcg/mL)	GP2013	127	2109.11	GP2013/ Rituxan	1.047	(0.967, 1.134)
	Rituxan	84	2013.87	Rituxan/ MabThera	1.058	(0.970, 1.156)
	MabThera	82	1902.64			
AUC_{0-12w} (day*mcg/mL)	GP2013	125	7318.98	GP2013/ Rituxan	1.013	(0.926, 1.109)
	Rituxan	81	7223.71	Rituxan/ MabThera	1.121	(1.015, 1.239)
	MabThera	81	6442.28			
AUC_{0-24w} (day*mcg/mL)	GP2013	125	7563.81	GP2013/ Rituxan	1.008	(0.917, 1.107)
	Rituxan	80	7506.53	Rituxan/ MabThera	1.120	(1.009, 1.242)
	MabThera	80	6702.97			
T_{max} (1st inf) (hours)	GP2013	120	4.35	GP2013/ Rituxan	0.017	(0.000, 0.083)
	Rituxan	82	4.42	Rituxan/ MabThera	-0.083	(-.167, -.017)
	MabThera	78	4.33			
C_{max} (2nd inf) (mcg/mL)	GP2013	116	423.12	GP2013/ Rituxan	1.076	(0.988, 1.172)
	Rituxan	82	393.07	Rituxan/ MabThera	1.006	(0.915, 1.106)
	MabThera	75	390.73			
T_{max} (2nd inf) (hours)	GP2013	116	3.48	GP2013/ Rituxan	0.000	(-.083, 0.083)
	Rituxan	82	3.49	Rituxan/ MabThera	0.000	(-.083, 0.100)
	MabThera	75	3.45			

Pharmacodynamics Results of Study (GP13-201 part I):

Summary of Bioequivalence Analysis for the key secondary PD endpoint: B-cell depletion – AUEC (0-14d) in GP2013 vs. Rituxan and Rituxan vs. Mabthera:

					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			

The key secondary PD endpoint was the (AUEC(0-14d)) of the percent change of blood CD20+ B-cell count relative to baseline, met the equivalence criteria, with the 95% CI being within the pre-specified equivalence limit of 0.8 to 1.25.

(Part II):

					Treatment Comparison	
PD Parameter (unit)	Treatment	N	Adjusted Geometric mean	Comparison	Geometric mean ratio	95% CI of mean ratio
$AUEC_{0-14d}$ (%*day)	GP2013	110	1226.53	GP2013/ Rituxan	0.989	(0.974, 1.004)
	Rituxan	80	1240.57	Rituxan/ MabThera	1.033	(1.016, 1.050)
	MabThera	76	1201.15			
PAS+A: All qualifying patients including ADA positive						

3.2.1.2 Pharmacodynamic studies

The pharmacodynamic study was part of the previously explained pivotal PK study, the results are presented in the previous section.

Assessors' comments on clinical pharmacology

The pivotal PK/PD Study (**GP13-201**) concluded that the PK and PD results demonstrated the bioequivalence of GP2013 to both Mabthera and Rituxan, as well as between EU-Mabthera and US-Rituxan, and thus the "PK scientific Bridge" between both EU/US reference licensed products has been established.

The pivotal PK bioequivalence results from Study **(GP13-201)** in patients with RA are supported by the descriptive PK results in terms of the extent of exposure from the supportive Study **(GP13-301)** in patients with FL, the totality of evidence from both trials concluded that the PK/PD results support PK/PD similarity of Rixathon to EU-Mabthera and the US-Rituxan. There were limited descriptive PK data relating to Rixathon from the

supportive Phase I Study (**GP13-101)** in Japanese patients with CD20+ low tumor burden indolent B-cell NHL, due to the small size of the study (i.e.=6 patients), this study was not powered to detect uncommon treatment-associated events.

3.2.2 Clinical Efficacy

3.2.2.1 List of submitted clinical efficacy studies

Study ID*	No. of study centres / locations	Design	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
GP13-301 **"pivotal"**	159 centres in 26 countries. [Argentina 3 centres, Australia 4 centres, Austria 2 centres, Brazil 16 centres, Bulgaria 6 centres, Colombia 1 centre, France 3 centres, Germany 2 centres, Greece 5 centres, Hungary 2 centres, India 23 centres, Ireland 1 centre, Israel 2 centres, Italy 7 centres, Japan 12 centres, Malaysia 10 centres, Netherlands 7 centres, Peru 4 centres, Poland 6 centres, Portugal 5 centres, Romania 6 centres, Russia 9 centres, South Africa 6 centres, Spain 9 centres, Ukraine 7 centres, and the United Kingdom 1 centre).	Randomized, double-blind, parallel-group, Multicentre study.	**Primary objective:** To demonstrate similarity of the ORR in patients with previously untreated, advanced stage FL who receive GP2013-CVP to patients who receive Mabthera - CVP combination treatment. **Secondary:** - To evaluate CR, PR, PFS, OS. - To describe safety of GP2013 in comparison to Mabthera. - To evaluate the incidence of immunogenicity (ADA formation) against GP2013 and Mabthera	(N=629) GP2013 (n = 314), Mabthera (n = 315).	**Duration of treatment:** 8 cycles (approximately 6 months). **Maintenance phase:** 2 years, **Follow up:** 3 years from the date of randomization.	Patients with previously untreated, advanced FL.	ORR (objective response rate) during the combination treatment period.

			To evaluate the PK/PD of GP2013 and Mabthera.				
GP13-201 **"supportive"**	A total of 67 centers in 15 countries: [Argentina (4), Austria (2), Belgium (1), Brazil (7), Estonia (1), France (3), Germany (13), Hungary (2), India (6), Italy (2), Romania (4), Russia (4), Spain (6), Turkey (3) and US (9)]	Randomized, double-blind, parallel-group, multi- center study.	Trial's objectives were listed previously in the pharmacokinetics studies section.	Study part **I**: N= 173 Study Part **II**: N= 139	**Date of first screening to last follow-up(part I):** 14 Dec 2010 – 10 Apr 2014 **Date of first screening to last follow-up(part II):** 28-Jun-2013 – 10 Nov 2016	Patients with active RA.	$AUC_{0\text{-}inf}$

<table>
<tr><th>Study ID*</th><th>Study design</th><th>Study Objective</th><th>Findings</th></tr>
<tr>
<td>GP13-302

NCT02514772

“supportive”</td>
<td>Randomized, double-blind, parallel-group, multi- center, to assess the safety/ immunogenicity of transitioning to GP2013 or re-treatment with Rituxan or Mabthera in patients with active RA, previously treated with Rituxan or Mabthera . 107 patients were randomized to either GP2013 (n=53) or Rituxan/Mabthera (n=54).</td>
<td>- Primary objective: to identify the potential safety risk of the transition in terms of general safety and immunogenicity.

safety parameters:
- Incidence of AEs, SAEs, hypersensitivity, anaphylactic and infusion-related reactions
- Immunogenicity (development of (ADA))
- Other safety parameters vital signs, lab values, body weight.</td>
<td>- All safety parameters will be analyzed descriptively only.
<table>
<tr><th></th><th>GP2013 N=53, n [%]</th><th>Rituxan/Mabthera N=54, n [%]</th></tr>
<tr><td>Hypersensitivity</td><td>5 [9.4%]</td><td>6 [11.1%]</td></tr>
<tr><td>Anaphylactic</td><td>0 [0%]</td><td>1 [1.9%]</td></tr>
<tr><td>Infusion-related</td><td>6[11.3%]</td><td>10 [18.5%]</td></tr>
<tr><td>Immunogenicity</td><td>0 [0%]</td><td>1 [1.9%]</td></tr>
</table>
AEs and SAEs: more patients in the GP2013 group reported at least one AE compared to the Rituxan/ Mabthera group (GP2013: 37 patients [69.8%]; Rituxan/Mabthera: 28 patients [51.9%]).</td>
</tr>
</table>

Overall, the results of the key safety parameters did not show clinically meaningful differences between both treatment groups. An additional safety risk if patients transition from the originator products to GP2013 could not be detected.

3.2.2.2 Data integrity and GCP

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

3.2.2.3 Inter-changeability studies

The safety and immunogenicity of GP2013 after switching from either EU-MabThera or US-Rituxan in RA was evaluated in GP13-302 phase III study.

Assessors’ comments on the submitted clinical studies

Rixathon was received as an electronic submission in eCTD format. The clinical documents were of acceptable quality and integrity. The clinical development program was designed to establish bio-similarity of the product to the reference product Mabthera. The program consisted of four studies: two pivotal studies (Phase II PK/PD and phase III Efficacy and safety), and two supportive studies (phase I PK and phase III interchangeability); the pivotal PK/PD study involved 312 Rheumatoid arthritis patients that received either Rixathon with EU-Mabthera or Rixathon with US-Rituxan. The primary PK parameter was (AUC0-inf).

The pivotal phase III clinical study (GP13-301), assessed the clinical efficacy and safety in 629 patients with previously untreated, advanced stage FL who received Rixathon or Mabthera with cyclophosphamide, vincristine and prednisone chemotherapy combination treatment. The primary endpoint was the ORR.

The safety of the drug was evaluated in all studies based on incidence and frequency of the side effects in addition to comparing immunogenicity.

Immunogenicity was assessed in all studies, in which no clinical differences were found between the two arms in regards to the presence of anti-drug antibodies.

Generally, the conducted clinical development program and studies designs and the selected endpoints were acceptable and scientifically justified for biosimilar product requirements.

Pivotal efficacy Study (GP13-301):

Title: A randomized, controlled, double-blind Phase III trial to compare the efficacy, safety and pharmacokinetics of GP2013 plus CVP vs. Mabthera plus CVP, followed by GP2013 or Mabthera maintenance therapy in patients with previously untreated, advanced stage FL.		
Study identifier	Sponsor code: GP13-301 - EudraCT number : 2010-019522-13 - Clinical trial.gov: NCT01419665	
Design	This is a randomized, double-blind, parallel-group, Multicentre (159 centres in 26 countries) study with two treatment arms GP2013 + CVP vs Mabthera + CVP, followed by GP2013 or Mabthera maintenance therapy. During the Combination phase patients randomized in a 1:1 ratio to receive 8 cycles of GP2013+CVP (N=312) or Mabthera+CVP (N=315), IV, on Day 1 of each cycle administered every 21 days (±3 days). In the Maintenance phase, patients with PR or CR after 8 cycles of combination treatment will receive 8 treatment cycles of GP2013 or Mabthera, IV, administered every 3 months for a further 2 years. The primary efficacy analysis was performed following the completion of the Combination phase.	
	Duration of main phase (combination phase):	8 cycles (approximately 6 months), **Maintenance phase:** 2 years, **Follow up:** 3 years from the date of randomization.
	Duration of Run-in phase	Not applicable
	Duration of Extension phase	Not applicable.
Hypothesis	Equivalence	
Treatments arms	**Test Treatment**: Rixathon 375 mg/m^2 + CVP, IV, every 21 days for 8 cycles.	
	Reference Treatment: Mabthera 375 mg/m^2 + CVP, IV, every 21 days for 8 cycles.	
Randomization	Randomization will be stratified by both FLIPI score risk group and region. Within each strata level, a list of randomization numbers will be generated by interactive response technology (IRT) with a 1:1 randomization ratio to GP2013-CVP or Mabthera -CVP.	
Blinding	This is a double-blind study. Patients, investigator site staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock.	

Endpoints and definitions	**Primary efficacy endpoint**	ORR	Defined as the proportion of patients whose best overall disease response is either CR or PR during the combination treatment period based on independent central radiology review.
	Secondary efficacy endpoint	PFS	Defined as from date of randomization to date of first documented progression of disease, or death due to any cause, with up to 3 years of follow-up post randomization.
	Secondary efficacy endpoint	OS	Defined as from date of randomization to date of death due to any cause, with up to 3 years of follow-up post randomization.
	Secondary Safety endpoint	-Incidence and severity of AEs. -Percentage of patients with immunogenicity.	− **<u>ADA formation (immunogenicity):</u>** − Analysis was performed by using a validated affinity capture elution ECL assay. − Samples confirmed as positive for ADA were further analyzed in the confirmatory assay.
Statistical Analysis	Equivalence was concluded as the entire 95% CIs for the difference in primary endpoint ORR between the two treatments was within the pre-specified equivalence margin of ± 12%. - **Primary Efficacy Analysis:** (Normal approximation to the binomial distribution) was used to generate the 95% CI. In addition a (logistic regression model) with treatment group as explanatory variable and FLIPI score categories as stratification variable was used to generate the 90% CI of the Odd Ratios (OR) of treatment difference. - **Kaplan-Meier:** Was used in the time-to-event analysis to estimate the median time to PFS and OS for each treatment group. The associated 90% and 95% CIs were also derived. Furthermore, the Cox regression analysis with treatment as covariate and FLIPI score as stratification factor was used to estimate the hazard ratio (HR) between the two treatment groups. - **Interim analysis:** Three interim analyses were performed by a request of various regulatory authorities (i.e. the EMA, PMDA and US-FDA). - **Sensitivity Analysis:** will be performed on ORR at the end of the Combination Phase using the updated per-protocol set (PPS) and the tumor assessment data updates. - **Supportive analyses:** the analysis of ORR will be repeated using full analysis set (FAS), also sub-group analyses of ORR on both PPS and FAS by age and FLIPI score risk group were performed.		

	- The primary efficacy analysis of ORR will be based on the PPS population. The primary analysis of PFS and OS was based on the FAS population.

Analysis set[1]	GP2013 N=314 n (%)	MabThera N=315 n (%)	Switched MabThera[2] N=44 n (%)	All patients N=629 n (%)
Full analysis set	312 (99.4)	315 (100)	NA[2]	627 (99.7)
Safety analysis set	312 (99.4)	315 (100)	NA[2]	627 (99.7)
Per-protocol set	310 (98.7)	312 (99.0)	NA[2]	622 (98.9)
Modified per-protocol set	310 (98.7)	310 (98.4)	NA[2]	620 (98.6)
Maintenance analysis set[3]	210 (77.8)	252 (80.0)	44 (100)	506 (80.4)
Pharmacokinetic analysis set 1	119 (37.9)	120 (38.1)	NA[2]	239 (38.0)
Pharmacokinetic analysis set 2	27 (8.6)	22 (7.0)	NA[2]	49 (7.8)
Pharmacodynamic analysis set	24 (7.6)	24 (7.6)	NA[2]	48 (7.6)
Immunogenicity analysis set	233 (86.3)	287 (91.1)	42 (95.5)	562 (89.3)
Open-label analysis set[3]	NA[3]	39 (12.4)	44 (100)	83 (13.2)
Follow-up analysis set	257 (95.2)	306 (97.1)	43 (97.7)	606 (96.3)

Database lock	**27 April 2018**

CVP: cyclophosphamide, vincristine, and prednisone.

Determination of Sample Size

Assuming an expected ORR of 81% for each treatment group and the pre-specified equivalence margin of 12% based on the historical data of a phase III study *(Marcus et al 2005, Marcus et al 2008).* A total of 556 patients were required for the study with 90% power to show equivalence of GP2013 to the reference drug at a two one-sided significance level of 2.5%. In order to allow for 10% of drop-outs and major protocol deviations, a total of 618 patients were required; 629 patients were actually randomized into the study.

Results

The analysis of ORR in the PP Set was 87.1% in the GP2013 group and 87.5% in the Mabthera group. The 95% CI as well as the 90% CI or the difference of the ORR were contained within the pre-specified equivalence margin of ±12% (difference -0.40; 95% CI (-5.94, 5.14); 90% CI (-5.10, 4.30)). A sensitivity analysis using the PPS confirmed the result of the primary analysis: The ORR was 87.7% in the GP2013 group and 87.5% in the Mabthera group. The 95% CI as well as the 90% CI of the difference of the ORR were contained within the pre-specified equivalence margin of ±12% (difference -0.24; 95% CI (-5.26, 5.74); 90% CI (-4.42, 4.91)).

The proportions of patients were similar for the two treatment groups within each Best overall response (BOR) category (CR, PR, stable disease, progressive disease) for the PPS

as defined for the primary analysis and the FAS. More patients in the GP2013 group (31.1%) than in the Mabthera group (24.8%) had a PFS event (based on investigator assessment) during the study. The Hazard ratio (HR) of PFS was 1.30 (90% CI: (1.02, 1.68); 95% CI: (0.97, 1.76)). Similar proportions of patients in both treatment groups died during the study (GP2013: 9.3%; Mabthera: 9.8%). The HR of OS was 0.92 (90% CI: (0.60, 1.40); 95% CI: (0.55, 1.52)).

It is to be noted that the study was not powered for comparing PFS or OS between the two treatment groups. Therefore, the generation of estimate and its associated CIs was for descriptive purposes only and was not associated with any hypothesis testing.

Primary efficacy analysis of ORR based on central blinded review of tumor assessment by treatment (Per-protocol set1):

	GP2013 N=311		MabThera N=313		Difference GP2013 – MabThera		
	n (%)	90% CI[2]	n (%)	90% CI[2]	Diff	95% CI[3]	90% CI[3]
ORR (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)

CI=confidence interval; CR=complete response; Diff=difference; ORR=overall response rate; PR=partial response.

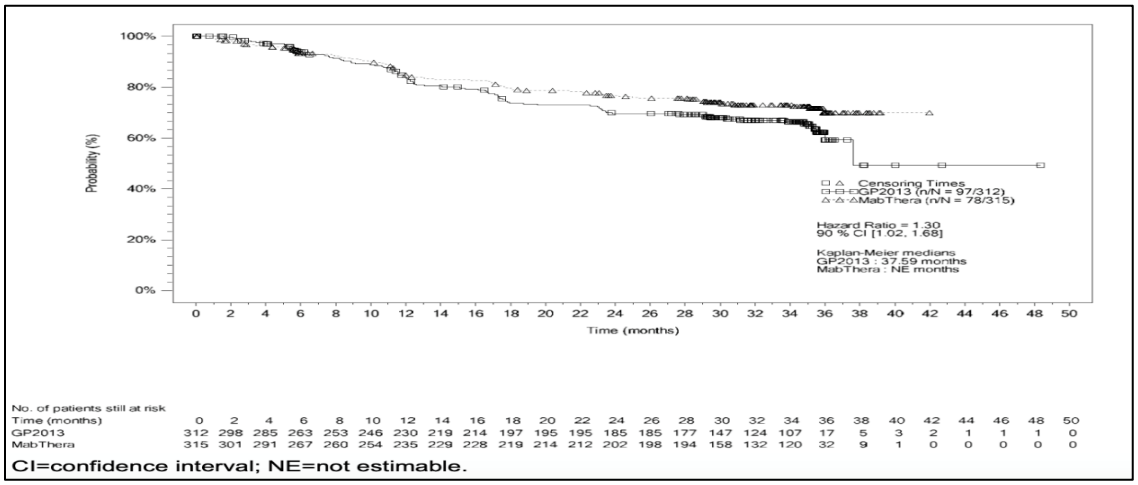
[1] Per-protocol set as defined for the primary analysis (CSR dated 04-Feb-2016).

[2] The 90% CIs of ORR are exact intervals derived using the Clopper-Pearson formula.

[3] The 95% and 90% CIs for differences in proportions are based on normal approximation to the binomial distribution.

Secondary Endpoints:

Kaplan-Meier plot of PFS by treatment (FAS) (GP13-301):

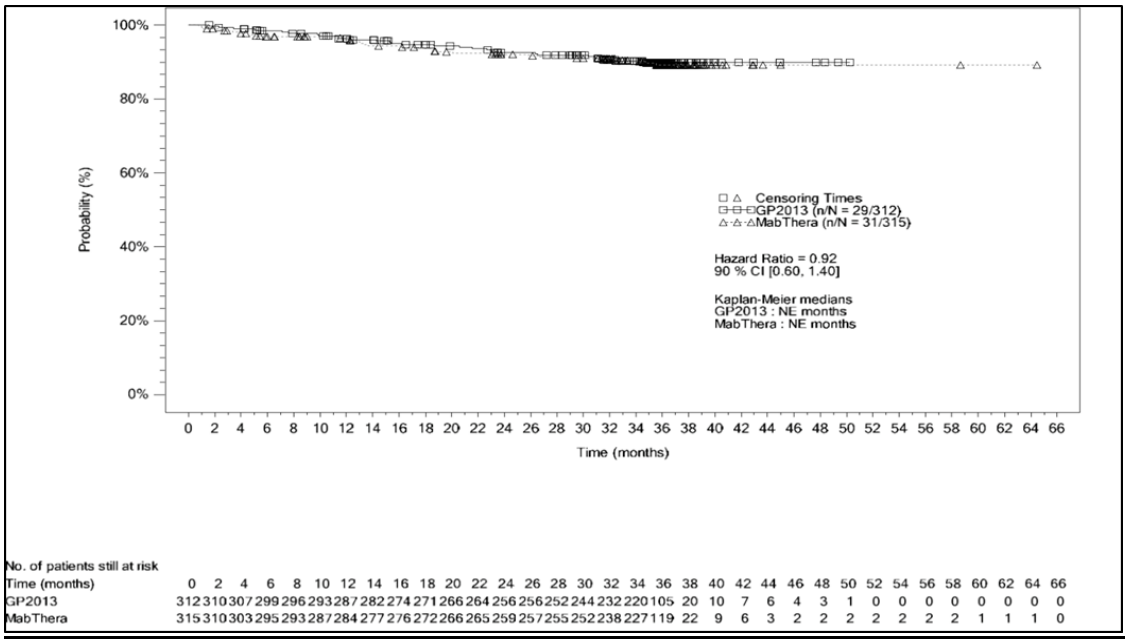


No. of patients still at risk

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	298	285	263	253	246	230	219	214	197	195	195	185	185	177	147	124	107	17	5	3	2	1	1	1	0
MabThera	315	301	291	267	260	254	235	229	228	219	214	212	202	198	194	158	132	120	32	9	1	0	0	0	0	0

CI=confidence interval; NE=not estimable.

Kaplan-Meier plot of OS by treatment (FAS) (GP13-301):



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	52	54	56	58	60	62	64	66
GP2013	312	310	307	299	296	293	287	282	274	271	266	264	256	256	252	244	232	220	105	20	10	7	6	4	3	1	0	0	0	0	0	0	0	0
MabThera	315	310	303	295	293	287	284	277	276	272	266	265	259	257	255	252	238	227	119	22	9	6	3	2	2	2	2	2	2	1	1	1	1	0

Analysis of PFS using the Kaplan- Meier and Cox-regression method (on FAS, Study GP13-301):

		Median (time to event)			Cox Model[1]		
All Patients	Event/N (%)	Median time in months	90% CI	95% CI	Hazard Ratio	90% CI	95% CI
GP2013	97/312 (31.1)	37.6	(37.59, NE)	(37.59, NE)	1.30	(1.02, 1.68)	(0.97, 1.76)
MabThera	78/315 (24.8)	NE	NE	NE			

Analysis of overall survival using the Kaplan-Meier and Cox- regression method (on FAS, Study GP13-301):

		Median (time to event)			Cox Model[1]		
All Patients	Event/N (%)	Median time in months	90% CI	95% CI	Hazard Ratio	90% CI	95% CI
GP2013	29/312 (9.3)	NE	NE	NE	0.92	[0.60, 1.40]	[0.55, 1.52]
MabThera	31/315 (9.8)	NE	NE	NE			

3.2.3 Overall conclusion of clinical efficacy

The clinical data from pivotal (**GP13-301)** trial has shown a comparable efficacy between Rixathon and Mabthera. The primary efficacy endpoint of ORR was met and Rixathon was declared clinically equivalent to EU-Mabthera as both the 95% and the 90% CI was within the pre-specified equivalence range of [-12% ,+12%]. Results from sensitivity analyses also corroborated the primary analysis result.

However, in the supportive subgroup analyses the ORR based on FLIPI prognostic scores failed to demonstrate equivalence of the two treatments, favoring Mabthera (91.2% vs. 82.8% in Rixathon) in the subset with a FLIPI score 0-2 (low-intermediate risk), and favoring Rixathon (90.4% vs. 84.7%) in the subset with a FLIPI score 3-5 (high risk), while the subgroup analyses of the ORR based on age demonstrated equivalence of the two treatments, such findings did not preclude the conclusion of biosimilarity. Because the ORR was high in both treatment arms suggesting that both products are effective in both subgroups.

In the supportive study **(GP13-201)**, Rixathon was demonstrated to be non-inferior to Mabthera and Rituxan in active RA patients, with regard to the key secondary efficacy endpoint Change from Baseline in DAS28 (CRP), with the upper limit of the 95% CI for the mean difference between the two treatment arms being less than the pre-defined non-inferiority margin (0.6). Of note, an equivalence margin of [-0.6, +0.6] is defined for the

difference between the two treatment arms for efficacy endpoint, as the 95% CI of the mean difference is within the equivalence margin was achieved. The similarity of Rixathon, Mabthera and Rituxan was also supported by a range of descriptive efficacy analyses.

3.2.3 Clinical Safety

The applicant evaluated the similarity of safety between GP2013 and EU-US rituximab across the 4 clinical studies: 2 studies in active RA patients (**GP13-201** and **GP13-302**), one comparative safety and efficacy study in patients with FL (**GP13-301**) and one in Japanese patients with B-cell NHL (**GP13-101**).

GP13-201:

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

GP13-301:

The overall incidence of AEs during the combination phase was similar in both treatment groups (Rixathon-CVP: 92.6%; Mabthera-CVP 91.4%). The incidence of AEs was higher than in the RA study, probably due to the more frequent rituximab dosing regimen and the background chemotherapy of CVP.

GP13-302:

The overall incidence of AEs was similar in both treatment groups (GP2013: 69.8% vs. Rituxan/Mabthera: 51.9%).

Generally, no deaths or discontinuations related to study treatment and most treatment emergent adverse events (TEAEs) reported during the studies were consistent with the clinical data of the reference product. Low serious AEs (SAEs) or unexpected TEAEs were reported, the majority of AEs occurred with similar incidences in both treatment groups. The most affected SOC were “musculoskeletal”, “gastrointestinal disorders” and “nervous system disorders (primarily peripheral neuropathy, and paresthesia) in FL”. The majority of all AEs were of mild or moderate severity in both treatment groups.

AEs, regardless of study drug relationship, by SOC (SAF) study (201):

System organ class	GP2013 N = 86 n (%)	MabThera® N = 87 n (%)	Total N = 173 n (%)
-Any adverse event -Total	56 (65.1)	57 (65.5)	113 (65.3)
Infections and infestations	27 (31.4)	31 (35.6)	58 (33.5)
Musculoskeletal and connective tissue disorders	16 (18.6)	14 (16.1)	30 (17.3)
Gastrointestinal disorders	13 (15.1)	15 (17.2)	28 (16.2)
General disorders and administration site conditions	12 (14.0)	9 (10.3)	21 (12.1)
Injury, poisoning and procedural complications	9 (10.5)	11 (12.6)	20 (11.6)
Skin and subcutaneous tissue disorders	9 (10.5)	11 (12.6)	20 (11.6)
Metabolism and nutrition disorders	7 (8.1)	4 (4.6)	11 (6.4)
Nervous system disorders	7 (8.1)	10 (11.5)	17 (9.8)
Respiratory, thoracic and mediastinal disorders	7 (8.1)	12 (13.8)	19 (11.0)
Vascular disorders	7 (8.1)	10 (11.5)	17 (9.8)
Investigations	6 (7.0)	7 (8.0)	13 (7.5)
Blood and lymphatic system disorders	5 (5.8)	6 (6.9)	11 (6.4)
Cardiac disorders	4 (4.7)	4 (4.6)	8 (4.6)
Ear and labyrinth disorders	3 (3.5)	4 (4.6)	7 (4.0)
Reproductive system and breast disorders	3 (3.5)	1 (1.1)	4 (2.3)
Immune system disorders	2 (2.3)	1 (1.1)	3 (1.7)
Renal and urinary disorders	2 (2.3)	1 (1.1)	3 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.2)	2 (2.3)	3 (1.7)
Psychiatric disorders	1 (1.2)	1 (1.1)	2 (1.2)
Endocrine disorders	0	1 (1.1)	1 (0.6)
Eye disorders	0	3 (3.4)	3 (1.7)
Hepatobiliary disorders	0	1 (1.1)	1 (0.6)

Summary of adverse event categories by treatment – Combination Phase (SAF) study (301):

	GP2013 N=312 n (%)	MabThera N=315 n (%)	All patients N=627 n (%)
Number of patients with at least one AE	289 (92.6)	289 (91.7)	578 (92.2)
Suspected to be drug related	232 (74.4)	224 (71.1)	456 (72.7)
Number of patients with at least one grade 3-4 AE	136 (43.6)	145 (46.0)	281 (44.8)
Suspected to be drug related	90 (28.8)	99 (31.4)	189 (30.1)
Number of patients with at least one SAE	71 (22.8)	63 (20.0)	134 (21.4)
Suspected to be drug related	32 (10.3)	26 (8.3)	58 (9.3)
Number of patients with at least one grade 3-4 AE	63 (20.2)	57 (18.1)	120 (19.1)
Suspected to be drug related	29 (9.3)	26 (8.3)	55 (8.8)
Number of patients with at least one AE leading to discontinuation	22 (7.1)	21 (6.7)	43 (6.9)
Suspected to be drug related	13 (4.2)	15 (4.8)	28 (4.5)
Number of patients with at least one potential infusion-related reaction	228 (73.1)	224 (71.1)	452 (72.1)
Suspected to be drug related	155 (49.7)	153 (48.6)	308 (49.1)
Number of patients with at least one AE requiring dose interruption and/or reduction[1]	127 (40.7)	140 (44.4)	267 (42.6)
Suspected to be drug related	94 (30.1)	102 (32.4)	196 (31.3)

Summary of adverse event categories by treatment –study GP13-302):

Number of patients with	GP2013 N=53 n (%)	Rituxan/ MabThera N=54 n (%)	Total N=107 n (%)
Adverse events (AEs)	37 (69.8)	28 (51.9)	65 (60.7)
Suspected to be related to study drug	6 (11.3)	11 (20.4)	17 (15.9)
Adverse events with maximum severity			
Mild	16 (30.2)	17 (31.5)	33 (30.8)
Suspected to be related to study drug	5 (9.4)	7 (13.0)	12 (11.2)
Moderate	20 (37.7)	8 (14.8)	28 (26.2)
Suspected to be related to study drug	0	2 (3.7)	2 (1.9)
Severe	1 (1.9)	3 (5.6)	4 (3.7)
Suspected to be related to study drug	1 (1.9)	0	1 (0.9)
Deaths	0	1 (1.9)	1 (0.9)
Suspected to be related to study drug	0	0	0
Serious adverse events (SAEs)	0	3 (5.6)	3 (2.8)
Suspected to be related to study drug	0	0	0
Adverse events leading to discontinuation of study drug	1 (1.9)	0	1 (0.9)
Suspected to be related to study drug	1 (1.9)	0	1 (0.9)
Adverse events requiring dose adjustment(s) or interruption(s) of study drug	2 (3.8)	5 (9.3)	7 (6.5)
Suspected to be related to study drug	1 (1.9)	5 (9.3)	6 (5.6)

3.2.3.2 Immunogenicity studies

The Incidences of Anti-drug antibodies (ADAs) were very low during the studies, No SAEs were reported for the Neutralizing antibodies (Nab) positive patients. The results of the clinical assessment indicate consistencies in the incidence of ADA between GP2013 and the reference product.

3.2.3.3 Adverse events

Serious adverse events and deaths

- As described above

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 Rixathon group. No relevant differences in any vital signs were observed between Rixathon and Mabthera groups in study GP13-201.

GP13-301

- During the combination phase, the incidence of ECG abnormalities was higher in the Rixathon group (18 patients vs 10 patients in the Mabthera group). Abnormalities in clinical chemistry were similar for both treatment groups. No relevant differences in any vital signs were observed between Rixathon and Mabthera groups.

Safety in special populations

According to age groups in (NHL) patients:

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%)	--	--
	N=5	**N=1**	**N=0**	**N=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%)	--	--
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%)	--	--

According to age groups in (RA) patients from study (GP13-201):

MedDRA Terms	Age < 65 (number (percentage)		Age 65 – 74 number (percentage)		Age 75 – 84 number (percentage)		Age 85+ number (percentage)	
	Rixathon N=105	Orig. N=141	Rixathon N=22	Orig. N=35	Rixathon N=6	Orig. N=3	Rixathon N=0	Orig. 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 infestations	31(29.5)	40(28.4)	9 (40.9)	11(31.4)	1 (16.7)	1(33.3)	--	--
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.

Safety related to drug-drug interactions and other interactions

- Drug interactions have not been studied. Rixathon is a biosimilar product; therefore, it has the same identified and potential interactions of the reference product (Mabthera) with other medicinal products.

Discontinuation due to AES

GP13-201

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

GP13-301(Combination Phase)

- The incidence of AEs leading to discontinuation of study drug was similar for AEs of all grades between both treatment groups (Rixathon: 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 (Rixathon: 14 patients [4.5%], Mabthera: 12 patients [3.8%]).

Post-marketing experience

N/A

3.2.3.3 Overall conclusion on clinical safety

In conclusion, the safety and immunogenicity profiles of Rixathon and EU-US licensed Mabthera and Rituxan appeared generally similar in all 4 studies. Moreover, adverse events were similar between Rixathon and the reference products, the majority of all AEs were of mild or moderate severity in both treatment groups, and no safety signals were different from what is currently known for Mabthera. The applicant presented within this application an integrated immunogenicity analysis, which provided supportive evidence on the similarity of the immunogenicity profile.

3.2.4 Discussion on clinical efficacy and safety aspects

Based on the submitted clinical development program, which provides totality of the evidence on clinical data, biosimilarity of Rixathon with the reference products EU-US rituximab can be concluded. The Clinical studies section recommends approval for Rixathon (GP2013) for the same list of indications that the reference Mabthera has been approved by SFDA.

4. Risk Management Plan

Risk Management Plan provides information about measures to be undertaken to prevent or minimize risks associated with the use of medicines and information on plans for studies and other activities to have more knowledge about the safety and efficacy of the medicinal product. The SFDA has reviewed the Rixathon RMP Version 6.0 and concluded the following Safety Concerns:

Table of Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Infections (including serious infections) (all indications) • Progressive multifocal leukoencephalopathy (PML) (all indications) • Hepatitis B (HBV) reactivation (all indications) • Hypogammaglobulinemia (non-oncology indications)
Important potential risks	• Administration route error (NHL/CLL) • Relapses (for GPA/MPA)
Missing information	• Long-term use in GPA/MPA patients (GPA/MPA)

4.1 Pharmacovigilance Activities

4.1.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond Adverse Drug Reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for PML, HBV reactivation.
- Other forms of routine pharmacovigilance activities for all included risks and missing information:
  Follow up of case reports: The minimum desired case information for rituximab includes the brand name and batch number of the suspect product.

4.1.2 Additional Pharmacovigilance Activities

None

4.2 Risk Minimization Measures

4.2.1 Routine Risk Minimization Measures:

Measures to minimize the risks identified for medicines can be:

- Specific information, such as warnings, precautions.
- Important information on the medicine packaging.
- The authorized package size.
- The medicines legal status.

In addition to these measures, information about adverse events is collected continuously and regularly analyses, including PSUR assessment so that immediate action can be taken as necessary.

4.2.2 Additional Risk Minimization Measure:

1. Health Care Professional (HCP) alert card.

   Objectives:

   To avoid administration route errors.

2. HCP educational leaflet.

   Objectives:

   To minimize the occurrence and severity of

   - Infections (including serious infections)

   - Progressive multifocal leukoencephalopathy (PML)

3. Patient educational leaflet.

   Objectives:

   To minimize the occurrence and severity of

   - Infections (including serious infections)

   - Progressive multifocal leukoencephalopathy (PML).

4. Patient alert card.

   Objectives:

   To minimize the occurrence and severity of

- Infections (including serious infections)
- Progressive multifocal leukoencephalopathy (PML).

4.3 Artwork and Trade Name assessment Artwork available in appendix

Proposed trade Name	Dosage Form
Rixathon	Vial

Look –alike/Sound-alike (LA/SA) Error Risk Potential:

Rixathon name LA/SA confusion risk potential has been assessed based on the evaluation of LA/SA similarities from our data sources (SFDA registered Drug List, Martindale, ISMP Confused Drug Name List, INN and USAN STEM) and the pharmaceutical characteristic of the product:

LA/SA for Product name	SFDA	Shared File/ Excel Sheet	Martindale	Stem Book 2018
Rixathon	NO	NO	NO	NO

Trade Name Recommendation:

Based on the submitted data, the proposed name Rixathon is accepted.

Outer package:

Based on the submitted data, the proposed name Rixathon is accepted.

Inner package:

Based on the submitted data, the proposed name Rixathon is accepted.

5. Overall Conclusion

Based on a review of data on quality, safety and efficacy, SFDA considered that the benefit/risk profile of Rixathon was favorable and decided to grant the marketing authorization of Rixathon for the treatment of adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

Rixathon is indicated for the treatment of previously untreated patients with stage III-IV FL in combination with chemotherapy.

Rixathon maintenance therapy is indicated for the treatment of FL patients responding to induction therapy.

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

Rixathon is indicated for the treatment of patients with CD20 positive diffuse large B cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

Rixathon in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

Rheumatoid arthritis (RA)

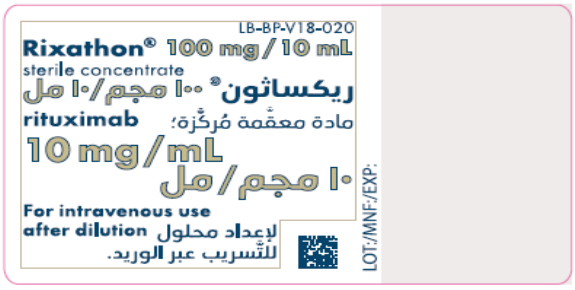
Rixathon in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more TNF inhibitor therapies.

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 (GPA) and microscopic polyangiitis (MPA)

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

6. Appendix



The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not incorporated into the Saudi PAR. New finding that could impair the quality, efficacy or safety of the medicinal product are recorded and published only at SDI.

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa