Amsterdam, 12 December 2019
EMA/CHMP/141953/2020
Committee for Medicinal Products for Human Use (CHMP)

# Withdrawal assessment report

## Rituximab Mabion

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/004807 & EMEA/H/C/005387

## Note

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

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## List of abbreviations

| | |
|---|---|
| ACPA | Anti-cyclic citrullinated protein antibodies |
| ACR | American College of Rheumatology |
| ACR20 | American College of Rheumatology 20% Response Criteria |
| ACR50 | American College of Rheumatology 50% Response Criteria |
| ACR70 | American College of Rheumatology 70% Response Criteria |
| ADA | Anti-drug antibodies |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AUC | Area under the concentration-time curve |
| AUC(0-inf) | Area under the serum concentration-time curve from time zero to infinity |
| AUClast | Area under the serum concentration-time curve from time zero to the last measured time point |
| AUC(0-t) | Area under the serum concentration-time curve from time zero to final time point |
| BSA | Body surface area |
| CDC | Complement-dependent cytotoxicity |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOP | Cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine] and prednisone |
| CI | Confidence interval(s) |
| CL | Clearance |
| 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 |
| CSR | Clinical study report |
| CT | Computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough | The minimum observed serum drug concentration which is measured right before the next infusion dose administration |
| CV | Coefficient of variation |
| 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 |
| DP | Drug product |
| DS | Drug substance |
| DTL | Drug Tolerance Level |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ELISA | Enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| EOT | End of treatment |
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| EULAR | European League Against Rheumatism |
| FACS | Fluorescence-activated cell sorting |

| | |
|---|---|
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FL | Follicular lymphoma |
| FMEA | Failure mode and effect analysis |
| GCP | Good clinical practice |
| GPA | Granulomatosis with polyangiitis |
| HAQ-DI | Health Assessment Questionnaire – Disability Index |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HQC | High quality control |
| HR | Hazard ratio |
| IMP | Investigational medicinal product |
| INN | International Nonproprietary Name |
| IPC | In-process control |
| IPI | International prognostic index |
| IRR | Infusion-related reaction |
| ISR | Incurred sample reanalysis |
| ITT | Intention-to-Treat |
| i.v. | Intravenous |
| $k_{el}$ | Elimination rate constant |
| KPP | Key process parameter |
| LLN | Lower level of normal |
| LLOQ | Lower limit of quantification |
| LOQ | Limit of quantification |
| LQC | Low quality control |
| LS | Least Square |
| MAA | Marketing Authorization Application |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFI | Mean fluorescence intensity |
| MoA | Mode of action |
| MPA | Microscopic polyangiitis |
| MQC | Mid quality control |
| MRI | Magnetic Resonance Imaging |
| MTX | Methotrexate |
| NAb | Neutralizing antibody |
| NCA | National Competent Authority |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin’s Lymphoma |
| NK | Natural Killer |
| NKPP | Non-key process parameter |
| ORR | Overall response rate |
| PAS | PK analysis set |
| PC | Process characterization |
| PD | Pharmacodynamics |
| PD | Progressive disease |
| PI | Package Insert |
| PK | Pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |

| | |
|---|---|
| PML | Progressive multifocal leukoencephalopathy |
| PP | Process parameter |
| PPS | Per Protocol Set |
| PR | Partial response |
| PT | Preferred term |
| QbD | Quality by design |
| QC | Quality control |
| QTPP | Quality target product profile |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| SA | Scientific Advice |
| SAE | Serious adverse event |
| SAF | Safety Set |
| sCD20 | Soluble cluster of differentiation 20 |
| SD | Standard deviation |
| SD | Stable disease |
| SDV | Source data verification |
| SmPC | Summary of Product Characteristics |
| SOC | System organ class |
| SS | Steady State |
| $T_{1/2}$ | Elimination half-life |
| TEAE | Treatment emergent adverse event |
| Tmax | The time to reach maximum (peak) serum rituximab concentration |
| TNF | Tumor necrosis factor |
| ULOQ | Upper limit of quantification |
| VAS | Visual analog scale |
| $V_D$ | Volume of distribution |

# 1. Recommendation

Based on the review of the data on quality, safety and efficacy, on 12th of December the CHMP considers that the application for Rituximab Mabion (also referred MabionCD20), in the treatment of Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Rheumatoid arthritis (RA), Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Biosimilarity of MabionCD20 to the originator Mabthera-EU has not been demonstrated on several levels as follows:

- The current development status of the commercial process, the fact that the material to be commercialized was not used in clinical trials and the finding that comparability studies for manufacturing changes during clinical development were not in compliance with ICH Q5E are of concern.
- It is acknowledged that recently GMP compliance has been confirmed for Mabion S.A. manufacturing site (Konstantynów Łódzki, Poland). Nevertheless, the information provided in the reports identified multiple major deficiencies during the aforementioned product related GMP inspections. Although recent improvements in the quality system are acknowledged, these cannot resolve for the previous concerns raised during clinical development and transfer to the commercial site.
- Inconsistent findings in non-clinical models underscore the uncertainties as regards the anti-tumor activity related to the known MoA and the quality differences to the originator.
- Thorough statistical analyses of differences of treatment effects raise the concern that they might be due to differences between the originator and biosimilar product.
- It is noted that the ACR20 response rates with rituximab + MTX as derived from the meta-analysis are shown to be much lower than in the biosimilarity study. Hence, the assay sensitivity with such high response rates could be questioned.
- Critical findings from the GCP inspection were handled in a pragmatic but imperfect way.

## *Proposal for questions to be posed to additional experts*

None

## *Proposal for inspection*

**GMP inspection(s)**

A request for GMP inspection has been raised for the Mabion S.A. site (Konstantynów Łódzki, Poland) in order to verify the GMP compliance status. The inspection was conducted 14-17 May 2019. Responses to the deficiencies were found acceptable and it was concluded that the site meets GMP requirements.

**GCP inspection**

In connection with the examination of this application, the Committee for Medicinal Products for Human Use has asked for an inspection to be carried out of the conduct of the clinical studies.

**New active substance status**

Based on the review of the data the CHMP consider that the active substance rituximab contained in the medicinal product Rituximab Mabion is not to be qualified as a new active substance. Rituximab Mabion has been developed as a similar biological medicinal product to the European Union (EU)-authorized reference product MabThera (rituximab).

**Similarity with orphan medicinal products**

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

# 2. Executive summary

## 2.1.1. Disease or condition

The medicinal product is a biosimilar and the applicant has proposed the same indication (see originator MabThera):

Non-Hodgkin's lymphoma (NHL)

MabionCD20 is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

MabionCD20 maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabionCD20 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.

MabionCD20 is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

MabionCD20 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)

MabionCD20 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

MabionCD20, 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).

### 2.1.2. Epidemiology

N/A

### 2.1.3. Biologic features

Rituximab binds specifically to CD20 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. Upon binding to CD20, rituximab mediates B cell lysis (leading to B cell depletion) by three distinct modes of action (MOA): ADCC, CDC and apoptosis.

### 2.1.4. Clinical presentation

500 mg Concentrate for solution for infusion

Each mL contains 10 mg of rituximab.

50 mL vial: Each vial contains 500 mg of rituximab.

### 2.1.5. Management

N/A

## *2.2. About the product*

Rituximab Mabion (also referred as MabionCD20) has been developed as a similar biological medicinal product to the European Union (EU)-authorized reference product MabThera® (rituximab).

## *2.3. The development programme/compliance with CHMP guidance/scientific advice*

Two Scientific Advice meetings were held with EMA, and follow-up advice provided 2 times. Based on the current review of the dossier it is understood that CHMP advice on quality and clinical aspects was received but not followed completely. National advice was received from the Dutch and German (PEI) agencies.

Changes during development and transfer to the commercial site were not addressed as per relevant ICH guidance i.e. ICH Q7 and ICH Q5E.

A quality target product profile (QTPP) based on "extensive characterization of the reference medicinal product" (EMA/CHMP/BWP/247713/2012 rev.1) was not established until very late clinical development. General comments on compliance with GMP, GLP, GCP.

GMP

The site MABION SPÓŁKA AKCYJNA, ul. Langiewicza 60, 95-050 Konstantynów Łódzki, Poland is responsible for manufacture of the biological active substance and finished product including QC.

Based on the issues identified during initial assessment of the quality dossier concerning the manufacturing process and quality control for MabionCD20 a GMP inspection was requested in the context of the current MAA. The respective inspection reports (inspection held in August 2018 and the requested inspection held in May 2019) including respective CAPA plans and responses by the applicant are provided.

It is acknowledged that GMP compliance has been confirmed.

GCP

The Applicant has stated that the trials have been conducted in compliance with GCP and GLP requirements. QA statement of audits assuring compliance to GCP, GLP was issued by Head-QA. A statement is also provided to confirm that the study carried out outside the EU meets the ethical requirements of Directive 2001/20/EC.

GCP inspection findings were reported in two sites and at the sponsor site inspection at Mabion.

The GCP inspectors concluded with regard to the quality of data, ethical conduct and GCP compliance that the study data is considered acceptable for Mabion Rituximab evaluation and the report observations seen at the inspected sites on the full study was left to the CHMP for their consideration (see section 1. Recommendation).

The Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) reviewed all appropriate study documentation before studies were started and before any amendment was implemented. The studies were conducted only at sites approved by the IRBs/IECs.

## *2.4. Type of application and other comments on the submitted dossier*

The marketing authorisation application of Rituximab Mabion is an abridged application for a biosimilar under Article 10 (4) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

# 3. Scientific overview and discussion

## *3.1. Quality aspects*

### 3.1.1. Introduction

Rituximab Mabion 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. 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.

MabionCD20 is a sterile concentrate for solution for infusion for intravenous (IV) use after dilution. The liquid formulation is based on rituximab as drug substance at a concentration of 10 mg/mL provided in 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.

### 3.1.2. Active Substance

### General Information

Rituximab Mabion is a murine/human chimeric IgG1 kappa type monoclonal antibody directed against the CD20 antigen.

### Manufacture, process controls and characterisation

**Manufacturing process**

MabionCD20 drug substance (MabionCD20DS) is manufactured according to current Good Manufacturing Practices (cGMPs). The site is responsible for manufacture of the biological active substance and finished product including QC.

The manufacturing process reflects a standard process used for the manufacture of monoclonal antibodies. MabionCD20DS is produced using a fed-batch culture at single-use bioreactor.

The cell culture fluid is harvested, purified and formulated as a single batch of drug substance. The formulated MabionCD20DS is filtered and stored at 2-8°C.

Reprocessing is not allowed for MabionCD20DS process.

**Control of materials**

MabionCD20 is produced in a CHO based expression system which is in accordance with the cell line used for the production of the reference medicinal product. Gene sequences were obtained from publicly available sources.

No raw materials of human or animal origin were used in manufacture of MCB/WCB.

In accordance with ICH Q5A and ICH Q5D MCB, WCB and ECB were tested for identity, purity and contamination by adventitious agents such as bacteria, fungi, mycoplasmas, and viruses. Additional analysis that confirmed the genetic stability and gene integrity in the MCB and EoPCB has been performed.

The stability of the MCB and WCB during storage is monitored.

Overall, the information provided in this section is considered sufficient.

**Control of critical steps and intermediates**

Critical and non-critical output parameters are defined in section 3.2.S.2.4. Critical In-Process controls for the individual manufacturing steps are listed in a tabulated manner and brief justifications for the respective acceptance criteria are provided.

With the response to the d120 LoQ the applicant provided the missing data on process characterization. Process characterization (PC) studies were performed based on a risk assessment using Failures Mode and Effects Analysis (FMEA). PC studies were performed in qualified SDMs of the USP and DSP. The classification of the bioreactor process parameters and the defined PARs and NORs are justified based on PC studies. For the DSP the classification of process parameters and the defined PARs/NORs are also justified. For the studies prediction profiler plot with acceptance criteria are provided allowing to draw own conclusions. As requested, "high importance" quality attributes are classified as CQAs. An appropriate strategy for control of output parameters is provided. The definition if IPCs, IPTs and IPM is considered justified. Consequences when pre-defined acceptance criteria are not met are indicated.

**Process validation**

Process Validation of MabionCD20 at the proposed commercial scale was performed at the commercial site. At time of the validation, the process characterization studies were not completed. The pre-classified Critical (CPP) or Key Process Parameters (KPP) were chosen for validation. Based on the actual data obtained for the three PV batches using the proposed commercial process, MabionCD20 of consistent quality was manufactured.

The manufacturing process of MabionCD20 mainly involves disposable materials. A risk assessment of potential extractables and leachables from plastic materials in the bioreactor consumables and equipment used for the manufacturing of MabionCD20 is provided. The conclusion is considered acceptable.

As requested, hold time studies were performed, the maximum hold time has now been revised to 14 days which is supported by physicochemical and microbiological data. As requested, a summary of the column lifetime investigations and re-use of columns used during the purification process is provided and deemed acceptable.

**Manufacturing process development**

Numerical inconsistencies have been identified in the documents during review of the MAA. Although several inconsistencies have been clarified (new ones have been identified too) and most of the respective sections were updated, some uncertainty remains with regard to reliability of the data presented in the dossier. The response provided during the procedure was not considered sufficient to demonstrate full comparability of the clinical and the proposed commercial material. In order to address the concern with regard to the lower than min-max levels in species in the proposed commercial batches the Applicant should set up a proper specification.

In addition, for manufacturing of the most recent batch the applicant modified certain steps to address Agency's concern of difference in afucosylated forms. The data provided show that the change has a significant impact on a product quality attribute and is therefore considered a major change in the manufacturing process. It is also noted that batch data manufactured today under the newly proposed conditions is limited. Therefore, the applicant's proposal to revisit the specification when data from commercial MabionCD20 batches with the modified process is available is not considered sufficient to evaluate the change. A minimum requirement would be MabionCD20 batches manufactured under the

newly proposed conditions prior approval, also demonstrating that there is no additional impact on other quality attributes in accordance to ICH Q5E.

Furthermore, in order to justify the developmental approach, the applicant clarified that during early development Mabthera batches were tested. The applicant is asked for further clarification.

To further support the continued evaluation of all biological functions the applicant provided an additional report. It is noted that testing for ADCC activity (Promega kit) was performed after completion of the clinical trials. This information provided might not answer the query. The closeness might not be sufficient to develop/establish the QTPP profile. The issue is not considered solved and adds to the concerns/uncertainties identified during review of the MAA.

Sufficient information on process characterization is provided. Process Hazard Assessment and classification were based on FMEA analysis. PC studies were performed in qualified SDMs of the USP and DSP. The classification of the bioreactor process parameters and the defined PARs and NORs are considered justified based on PC studies. For the DSP the classification of process parameters and the defined PARs/NORs are also justified based on multivariate/bivariate and univariate studies. The applicant has provided prediction profiler plots enabling an objective assessment. As requested, "high importance" quality attributes are classified as CQAs. An appropriate strategy for control of output parameters is provided. The definition if IPCs, IPTs and IPM is considered justified. Consequences when pre-defined acceptance criteria are not met are indicated.

**Current conclusion of the manufacturing development**

The applicant introduced changes/improvements during the development of MabionCD20 manufacturing process which were not appropriately introduced and evaluated, and not compliant with GMP principles and ICH guidance (i.e. ICH Q5E, ICH Q7).

Based on all available data from the retrospective approach using the current methods the conclusion of the applicant that the clinical and the commercial material is comparable might be acceptable for most QA, except for the sum of afucosylated species.

It can be concluded that the proposed manufacturing process is still under development and not considered finalized for commercial manufacturing.

**Characterization**

For the characterisation of MabionCD20 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 MabionCD20. The batches used for characterization were manufactured with the proposed small scale commercial process (not used in the clinical trials). MabionCD20 on its own seems sufficiently characterized. The characterization of MabionCD20 will also be discussed in the context of biosimilarity to the reference product.

Product-related impurities have been adequately defined. As requested, results for the isolated fractions of MabionCD20 (and Mabthera) for various functional assays are provided. However, the levels of isoforms required are much higher than the observed levels in MabionCD20 and Mabthera batches. Thus, the applicant concluded that the differences observed between MabionCD20 and Mabthera are not relevant. No significant impact on induction of apoptosis is seen.

The batch results indicate that levels of process-related impurities are consistently low among the DS batches.

## Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications set for the release and stability of MabionCD20 drug substance have been set taking ICH Q6B guideline into account as well as the QTPP for the RMP. The specifications set for release and shelf-life are identical except for certain parameters. Different acceptance criteria for a parameter at release and for shelf life are generally considered acceptable. As recommended, the acceptance criterion for HCP content was tightened and upper and lower limits for basic, acidic and main forms are proposed for control of DS charge profile.

Further revision on the proposed specification for certain quality attributes that impact biological function is requested.

As requested, the applicant implemented an orthogonal method for purity testing of MabionCD20 DS and DP. Based on retrospective analyses of frozen MabionCD20 and Mabthera batches the applicant proposes a preliminary (wide) acceptance range for certain parameters for DS release, DP release and stability as indicated in section 3.2.S.4.1. The limits in the relevant sections are now aligned, but will be further evaluated when additional data on non-frozen samples is available.

**Analytical methods**

General tests (Colour, and pH) and Safety tests (Endotoxin) and microbial enumeration (membrane filtration) are performed according to the Ph. Eur. Monographs. Non-compendial methods are briefly described including preparation, procedure, system suitability criteria. Summaries of the validation results of the analytical procedure are provided and considered appropriate. It can be concluded that the assays are sensitive to depict changes and are well qualified.

In order to establish the acceptance criteria for the commercial specifications, batch data from clinical and process validation batches were evaluated. The applicant justified that the selection of the batches for the justification of acceptance criteria was primarily based on the fact that there were method changes during development and these batches were analyzed using the current method.

**Batch analysis**

Only limited data is currently available for batches manufactured with the proposed commercial process. Results that were initially not included in the batch analysis data were provided with the responses to d120 LoQ. It is agreed that sterility is no longer tested for DS release and stability testing.

Batch analysis data of clinical MabionCD20 DS batches are provided. According to the information provided in Table 1 Description of the batches additional MabionCD20 batches were used in the phase III clinical trials.

All acceptance criteria in place at the time of testing were met.

**Reference materials**

Two interim reference standards (IRS) have been used during clinical development. The current Primary Reference Standard (PRS) was prepared from drug product manufactured with the proposed commercial manufacturing process and was compared to the previous interim reference standard IRS 2.

A stability protocol including information on re-testing time-points and specifications for the current PRS is provided. The acceptance criteria for certain parameters should be aligned with DS release specification.

Further clarification is requested in relation to batch release procedure of the clinical material and implementation of the interim reference standard. The proposed MabionCD20-specific reference material is sufficiently characterized with regard to structural, physicochemical and biological functions.

**Container closure system**

MabionCD20 DS is stored in single-use bags.

## Stability

Real-time and real-temperature stability data has been provided for clinical batches and process validation batches. With regard to the proposed commercial batches 6 months real-time, real temperature stability data are available. All acceptance criteria were met. The real-time and real-temperature studies are completed. No extrapolation is proposed beyond the period covered by long-term stability study. As recommended, the applicant performed accelerated stability studies on MabionCD20DS.

## 3.1.3. Finished Medicinal Product

## Description of the product and Pharmaceutical Development

MabionCD20 is a sterile concentrate for solution for infusion for intravenous (IV) use after dilution. The liquid formulation is based on rituximab as drug substance at a concentration of 10 mg/mL provided in 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 concluded that the additional data presented adequately demonstrated comparability of the proposed MabionCD20 to the lots used in the clinical phase III trials. Similar to the DS comparability there were some remaining issues, with regard to the analysis used which do not allow an objective conclusion on comparability of MabionCD20 lots used in the clinical trials and the proposed commercial MabionCD20 DP lots. This was considered a major concern. In addition, differences in quality attributes that impact biological activity of the product were identified in some of the proposed commercial batches compared to the clinical batches tested.

## Manufacture of the product and process controls

**Manufacturing process**

MabionCD20 DP is manufactured and released at Mabion S.A., Poland. The manufacturing process encompasses sterile filtration, filling, visual inspection labelling and packaging. Updated flow charts and descriptions of each step of the DP manufacturing process are provided. Reprocessing is not indicated for manufacturing of MabionCD20 DP.

Process and performance parameters were classified based on risk assessment (Process Hazard Assessment) and process experience during development. Critical Process Parameters (CPP) or Key Process Parameters (KPP) were chosen for validation.

MabionCD20 manufacturing process is continually monitored by evaluating the process for CPP, and CQAs according to batch release test. Based on the trends, the assessment for the process variability, capability and consistency will be made.

**Process validation**

Process validation studies were performed using MabionCD20 batches manufactured with the proposed commercial process. The studies included manufacturing process steps, aseptic process (media fills) and sterilization validation. MabionCD20 DP vials are prepared and transported at controlled conditions according to shipping validation. The final transport validation report is provided.

During initial review there were several issues of concern for drug product process validation. With the responses provided, the applicant explained and clarified the issues and inconsistencies have been corrected.

**Product specification, analytical procedures, batch analysis**

The specifications for the release of MabionCD20 have been set taking the principles of the guideline ICH Q6B and the QTPP into account. The acceptance criteria used for stability testing are wider concerning testing of charged variants which is considered acceptable. As requested purity testing was implemented as an orthogonal method for DP release and stability testing. The limits in the relevant sections are now aligned. The justification of specification for purity testing is based on the retrospective analysis of MabionCD20 and MabThera. As purity testing is a stability indicating method an impact on this quality attribute over long-term storage cannot be completely excluded. Therefore, the current limits for purity testing will be further evaluated, when more data is available.

**Analytical methods**

Analytical methods specific for the DP are described. For compendial methods the applicant refers to the corresponding Ph. Eur. monographs. For methods identical for the DS testing the applicant refers to the corresponding DS sections.

**Batch analysis**

Batch analyses data from drug product lots manufactured at the clinical trial facility and the proposed commercial site are provided, including the most recent post-PV batch.

Several inconsistencies in the results reported were identified during initial assessment and a possible trend for certain parameter in the clinical MabionCD20 batches was identified during initial review of the batch data analysis. Results were corrected, nonetheless, based on the numerous inconsistencies identified during review of the MAA dossier, a reasonable level of uncertainty remains with regard to the reliability of the data presented. Although recent improvements in the quality system are acknowledged, these cannot resolve for the previous concerns raised during clinical development and transfer to the commercial site. Therefore, the applicant is asked to clarify if and how data integrity has been verified for all dossier sections of the present MAA i.e. results from clinical and commercial site.

The impurities of MabionCD20 DP are identical to the impurities applicable to the MabionCD20 DS. The potential sources of elemental impurities were identified. Heavy metal concentration analysis in the drug product for representative lots showed that elemental impurities present in MabionCD20 DP are below PDE level.

**Reference materials**

For MabionCD20 drug product the same reference materials are used as for MabionCD20 drug substance.

**Container closure system**

The primary packaging for MabionCD20 500 mg concentrate for solution for infusion consists of a type I glass vial (complying with a USP/Ph. Eur.).

## Stability of the product

The stability program for MabionCD20 DP provided with the MAA includes long-term, accelerated, stressed (forced degradation) conditions as well as freeze / thaw, and photo-stress studies. All samples were stored individually in their immediate pack comprised of capped glass vial.

Long-term stability data for the proposed commercial MabionCD20 DP batches is ongoing. The applicant provides supportive stability data on clinical MabionCD20 batches.

The shelf life for MabionCD20 will be assessed based on the data submitted during the course of the MA procedure.

As recommended, the applicant performed an additional study at thermal stress conditions. In addition, as required per protocol for the comparative forced degradation study, the results for biological and purity testing are now provided.

The results of the freeze / thaw studies did not reveal a significant impact on the quality attributes of MabionCD20 DP. Photo-stress impacted the potency of the product.

Further clarification is requested on the approach used for certain stability testing. In-use stability in a bags is completed. Infusion Stability was performed for MabionCD20. Stability in glucose solution was performed for MabionCD20. All acceptance criteria were met.

## Biosimilarity

The applicant performed a head-to-head similarity study including commercial process validation and clinical trial MabionCD20 batches and MabThera batches. As requested, the head-to-head report and the quality target product profile (QTPP) report were provided.

In the QTPP the applicant provided details of the batch numbers, the manufacturing date, the date of freezing and the analysis performed on each of the batches. It is understood that the "age during testing" is the age prior to freezing. The rationale for not analysing all batches with all methods is provided and can be accepted.

The QTPP forms the basis for the development of the biosimilar product and its manufacturing process. In this respect it should be noted that the QTPP was discussed in the context of an EMA scientific advice procedure. The approach taken by the company was not considered appropriate.

In order to further support the developmental approach, the applicant provided information on the early development of the target profile. It is concluded that a reasonable QTPP based on "extensive characterisation of the reference medicinal product" (EMA/CHMP/BWP/247713/2012 rev.1) was not established until late clinical development.

With regard to the MabThera batches used in the head-to-head study it can be assumed that the batches used are representative for most of the parameters analysed; however with regard to certain parameters it seems that the actual activity of the MabThera batches is underestimated using these batches. In conclusion, the results for the MabThera batches might not represent the whole range of a functional assay activity for all MabThera batches analysed, thus, the head-to-head study might be of limited value. The statistical approach used to evaluate the similarity is based on the range based on mean ± 2SD vs. ± 3SD obtained for the Mabthera batches. The rationale provided for the statistical QTPP ranges can be followed for most QA. Some ranges are fairly wide. As stated by the applicant for a functional assay where the observed range of MabThera batches was very broad the QTPP range was calculated on the mean ± 2SD range. A summary of the qualification/validation data for the bioassays is provided and the applicant concluded that the assays are suitable for the intended use. Few

questions remain with regard to the assigned potency to PRS, the recalculated analytical similarity ranges and specification for certain parameter, which was proposed by the applicant during the procedure.

With regard to the characterization of biosimilarity, comprehensive structural, physicochemical, and biological attributes were analysed and qualified analytical methods were used to evaluate the primary, secondary, and higher-order structures, as well as posttranslational modifications, product-related variants, and functional attributes, which is deemed acceptable.

During the initial assessment clear differences were identified on QA that might impact potency/efficacy and safety of the product. The applicant provided additional information and results to demonstrate that the differences identified in certain parameters have no impact on biological function at the observed levels. The conclusion of the applicant is agreed. Nevertheless, it should be noted that the approach to develop a biosimilar candidate should follow the principle to produce the most similar candidate to the reference medicinal product instead of justifying several differences.

With regard to the differences detected in the levels of afucosylation, an impact on potency/efficacy of the product is expected. As requested, the applicant conducted studies to correlate functional activity and glycans.

In summary, with the additional studies provided by the applicant using sensitive methods, it is considered demonstrated that the different levels of afucosylation obtained in the MabionCD20 batches do translate to lower biological activity for MabionCD20 compared to the reference medicinal product Mabthera. Similarity is not considered demonstrated (ref. 3.1.4).

## Post approval change management protocol(s)

The initially proposed post-approval change management protocols have been removed from the dossier as recommended by CHMP during initial assessment.

## Adventitious agents

**TSE compliance**

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) is demonstrated. MabionCD20 is produced in a serum-free medium and no materials of animal or human origin are used during manufacturing.

**Virus safety**

MabionCD20 is expressed in CHO cells. Other than the cells themselves, no material of animal origin is added during fermentation. The cell banking system has been extensively screened for adventitious viruses using a variety of in vitro and in vivo assays.

In summary, the virus safety of MabionCD20 has been sufficiently demonstrated.

## GMO

The manufacturing process for MabionCD20 drug substance uses a recombinant Chinese hamster ovary (CHO) cell line that contains the DNA encoding the sequence for rituximab.

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

MabionCD20 (Rituximab Mabion) has been developed by Mabion S.A. as a proposed similar biological medicinal product to EU-approved MabThera (rituximab, Roche Registration GmbH).

After the assessment of the responses to the d180 LoQ, a major concern with regard to quality/biosimilarity remains to be solved.

The manufacturing process reflects a standard process used for the manufacture of monoclonal antibodies. The individual steps are described in detail.

After completion of the clinical trials the manufacturing process had been transferred to the commercial facility. Hence, a pre-requisite for biosimilarity is the comparability of MabionCD20 used in the phase III clinical trials vs. the proposed commercial MabionCD20.

The applicant performed a retrospective approach to demonstrate comparability based on available data from the batches, supported by comparability and stability data. The approach taken by the company to demonstrate comparability is neither considered appropriate nor compliant with GMP principles and ICH Q5E. Moreover, based on the inconsistencies identified during review of the MAA, a reasonable uncertainty in respect to reliability of the data presented in the dossier remains.

Although the Applicant claims that all clinical and the proposed commercial batches are comparable, it is difficult to evaluate comparability and consistency throughout the clinical material. In addition, a few proposed commercial PV batches exhibit lower levels of afucosylation, which impacts functional activity, than all clinical MabionCD20 batches analysed.

It can be concluded that the proposed manufacturing process is not considered finalised for commercial manufacturing. For the characterization, a comprehensive series of analytical methods have been used. Differences are identified in the levels of afucosylation between the clinical MabionCD20 batches and the proposed commercial batches.

DS and DP specifications are considered sufficient for most of the parameters tested. Few questions remain with regard to acceptance criteria of glycosylation and purity. Analytical methods have been validated.

A reasonable QTPP based on "extensive characterisation of the reference medicinal product" (EMA/CHMP/BWP/247713/2012 rev.1) was not established, which impacts the clinical development and the biosimilarity exercise.

A major objection is related to biosimilarity of MabionCD20 and the reference medicinal product MabThera based on the lower levels in sum of afucosylated species observed in MabionCD20 which translates to a lower functional activity of the MabionCD20 compared to MabThera.

Other identified differences were demonstrated to have no impact on biological activity of the product. Nevertheless, the approach to develop a biosimilar candidate should follow the principle to produce the most similar candidate to the reference medicinal product instead of justifying several differences.

It should be noted that almost all MabThera batches were frozen prior to all analysis and were stored for several months or even years. The approach to freeze the samples and analyse them months or years later is not considered appropriate and as some uncertainty remains with regard to the obtained results.

Rituximab Mabion is currently not considered suitable for approval as Biosimilar to MabThera.

### 3.1.5. Conclusion on quality aspects

The current MAA is not approvable from a quality point of view since major concerns are raised regarding biosimilarity to the reference product MabThera.

## *3.2. Non clinical aspects*

### 3.2.1. Pharmacology

Mabion has developed Rituximab Mabion as a similar biological medicinal product (or biosimilar) to MabThera (rituximab) under Article 10.4. of Directive 2001/83/EU, as amended. Rituximab Mabion is intended for adult patients for treatment in all indications currently approved for MabThera.

Rituximab binds specifically to CD20 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. Upon binding to CD20, rituximab mediates B cell lysis (leading to B cell depletion) by three distinct modes of action (MOA): ADCC, CDC and apoptosis.

The nonclinical development program is also in-line with the initial scientific advice received from the CHMP (2011, 2012, 2015, and 2016) and National competent authorities DE (PEI 2011 and 2017) and NL (MEB 2017).

MabionCD20 is being developed as a similar biological medicinal product (or biosimilar) to MabThera (rituximab). Therefore an abridged non-clinical program was performed consisting of comprehensive quality and analytical similarity studies with regard to physio-chemical characteristics. Biological activity was evaluated by a range of in vitro assays to determine effects of rituximab. Quality attributes are ranked for their criticality using a risk assessment approach based on two parameters: severity and likelihood. The risk scoring system represents a simplified approach but is considered acceptable. To determine the approach used for statistical analysis of the data obtained (for the similarity and comparability experiments) a criticality assessment of physiochemical and biological attributes was conducted which is deemed acceptable. Mabion has re-established the QTPP ranges based on mean ± 3SD approach.

For the majority of QA it is agreed that MabionCD20 and Mabthera can be considered highly similar. Nevertheless, for some QA potentially impacting efficacy or safety the values obtained for Rituximab Mabion were outside of the Min/Max range or even the similarity range, which was defined based on the chosen statistical approach. The applicant provided justifications for these deviations based on literature or based on biological assays under physiological conditions. In some attributes differences in highly enriched charge variants can be seen but it is agreed that the differences in charge variant content are unlikely to impact clinical efficacy or safety. Newly provided data show that oxidative agents have an impact the MabionCD20 attributes. The performed correlation analysis demonstrated a strong structure function correlation for a specific parameter for both MabionCD20 and Mabthera. Other correlations seen for Mabthera were not confirmed for MabionCD20 presumably due to the limited number of batches.

The objectives of the in vivo Study in rhesus monkey was to identify possible differences in PD, PK, or safety profiles of MabionCD20 and MabThera after a single administration. The data indicate B-cell depletion caused by both MabionCD20 and MabThera. Whether the effect is similar cannot be judged due to the low amount of animals and the variability in B-cell count at baseline. The Applicant justifies the variations of pre-dose white blood cells and B-cell lymphocytes in both groups were found to have typical variation and were within historical ranges.

### 3.2.2. Pharmacokinetics

Two studies comparing the PK of MabionCD20 to that of the reference MabThera were performed. PK was analysed in a single-dose comparative PK, pharmacodynamics (PD) and safety and as part of the repeat dose toxicity study.

The results of the method validation demonstrate that the method is appropriate for the measurement of MabionCD20 and Mabthera antibody concentrations in monkey sera.

Overall the results of PK analysis revealed no major differences in the PK profiles for MabionCD20 and MabThera both after a single intravenous infusion of 10 mg/kg and after 4 repeated once weekly intravenous infusions of 30 mg/kg to rhesus macaque monkeys.

### 3.2.3. Toxicology

Results from the comparative repeat-dose toxicology study in rhesus macaque monkeys revealed no clinically relevant differences in organs weights, clinical observation, body weight values, clinical pathology values, immunoglobulin values, ECG, body temperature, blood pressure, breathing frequency, and gross pathology, as well as histopathology examination were found between the animals administered MabionCD20 and the animals administered MabThera after intravenous infusion of 50 mg/hour in the doses of 30 mg/kg. The decrease in mean white blood cell counts observed in both treatment groups was statistically different on Day 15 prior to administration.

It is emphasized that the gain of knowledge of these kinds of studies is questioned due to the limited number of animals used in the study. Conclusive results from the comparability exercise and well-designed PD studies are preferred over toxicity studies with limited data sets.

### 3.2.4. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, {active substance} is not expected to pose a risk to the environment.

### 3.2.5. Discussion on non-clinical aspects

MabionCD20 has been developed as a similar biological medicinal product to the innovator product Mabthera (rituximab). The submission for MabionCD20 is an abridged application for a biosimilar under the scope of the Article 10(4) of Directive 2001/83/EC. 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 that MabionCD20 is comparable to Mabthera with respect to PD/PK and toxicity. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity and on local tolerance are not required for non-clinical testing of biosimilars.

### 3.2.6. Conclusion on non-clinical aspects

The overall data on PD/PK and toxicology do currently indicate that MabionCD20 could be considered approvable. Regarding the quality and analytical similarity studies of physio-chemical characteristics and biological activity please refer to the conclusion on quality aspects above.

## *3.3. Clinical aspects*

Two clinical trials were conducted; a pivotal clinical equivalence, PK bioequivalence and safety trial in RA, and a supportive bioequivalence and safety trial in NHL. Aim of these trials was to support the claim that MabionCD20 is biosimilar to MabThera by demonstrating equivalence of pharmacokinetic, pharmacodynamics, efficacy, and safety data between the two monoclonal antibodies.

The clinical data were not generated with the commercial product.

- ***Tabular overview of clinical studies***

| Trial ID | Objective/Aim | Trial design | Treatments | N |
|---|---|---|---|---|
| MabionCD20-001RA[1] | Primary: to compare the efficacy of MabionCD20DP and MabThera in patients with RA<br>Secondary: to assess PK, PD, efficacy, immunogenicity and safety of both treatments | Randomised (1:1), double-blind (24 weeks), clinical efficacy trial.<br>Open label: week 24 to 48[3] | Single course of MabionCD20DP or MabThera (1000 mg, given twice at a 2-week interval, IV) and re-treatment if the criteria were satisfied - at Week 24 (1000 mg, given twice at a 2-week interval, IV);<br>Concomitant methotrexate treatment | Safety set: MabionCD20DP 358; MabThera 349<br>ITT set: MabionCD20DP 355, MabThera 348<br>PP set: MabionCD20DP 334, MabThera 330<br>PK sub-study (PP set) MabionCD20DP 66, MabThera 58<br>PK sub-study (ITT set) MabionCD20DP 99, MabThera 102 |
| MabionCD20-002NHL[2] | Primary: to compare the PK profile of MabionCD20DP and MabThera in patients with DLBCL.<br>Secondary: to assess efficacy, PK, PD, immunogenicity and safety of both treatments | Randomised (5:2)[4], double-blind (26 weeks), bioequivalence trial<br>Patients were randomly assigned (5:2) to either MabionCD20DP or MabThera. Follow-up from Week 26 to Week 46[3] | Eight cycles of MabionCD20DP or MabThera (375mg/m² IV)<br>Concomitant CHOP chemotherapy | Safety set<br>MabionCD20DP 100; MabThera 40<br>ITT set:<br>MabionCD20DP 98, MabThera 38<br>PP set (week1-4):<br>MabionCD20DP 94, MabThera 35<br>PP set (week13-26):<br>MabionCD20DP 74, MabThera 29 |

## 3.3.1. Pharmacokinetics

The clinical development program for MabionCD20 did not include specific clinical pharmacology studies. However, PK and PD analysis were included in the two clinical trials MabionCD20-001RA and MabionCD20-002NHL.

Analytical method for the quantitative determination of rituximab in human serum

Two separate PK assay methods have been developed for the quantitative determination of rituximab in study MabionCD20-001RA and study MabionCD20-002NHL. Rituximab concentrations in study MabionCD20-001RA were assessed by one assay, while rituximab concentrations in MabionCD20-002NHL were analysed using another method. In both cases, a single assay approach with MabionCD20 as single calibrator was used.

Both methods have been validated with adequate accuracy and precision. MabionCD20 and MabThera batches used for validation were also used in the pivotal clinical trials. The validation was performed with samples diluted in the respective matrices: RA serum for study MabionCD20-001RA and NHL serum for study MabionCD20-002NHL. Specificity of the one method was demonstrated by analysis of cross-reactivity to Herceptin® (trastuzumab), while specificity of the another assay was analysed by addition of human recombinant full-length CD20 receptor to the validation samples. During validation of both PK assays, dilutional linearity with no Hook effect and adequate selectivity was demonstrated. Long-term frozen matrix stability was shown.

Analytical method for the determination of anti-MabionCD20 and anti-MabThera antibodies

For the detection of anti-rituximab antibodies a bridging immunoassay format combined with the detection platform was utilized. The method was structured into 4 tiers: screening, confirmation, titration, and neutralizing antibody. An acid dissociation step was included.

As demonstrated in the validation experiment, the ADA assay performed with adequate precision. ADA sensitivity for both RA and NHL serum was below 100 ng/mL. Validation was performed using both NHL and RA serum separately. The specificity exercise revealed that no irrelevant ADA (ADA to Herceptin) are detected by the assay. No matrix effects, no Hook effect and no interference with RF and soluble CD20 (up to 1600 pg/mL) were observed. The drug tolerance level was identified to 100 µg/mL. The ADA assay was not tolerant to haemolysed samples and long-term stability and robustness was not assessed during validation.

A cell-based assay was used for the detection of NAb. The validation revealed that except for the LPC in the RA method the NAb assay performed with accurate intra- and inter-assay precision. Inter-assay precision at the LPC was 26% for the RA method and thus failed to meet acceptance criteria. The drug tolerance level was determined to 50 µg/mL for the RA method and 30 µg/mL for the NHL method. Interference experiments demonstrated that the NAb assay was tolerant to 20 IU/mL RF and 800 pg/mL soluble CD20.

Pharmacokinetics

In the first step of the clinical program, the applicant conducted **study MabionCD20-001RA** which was a multicentre, randomised, double-blind, parallel-group, active-control, comparative bioequivalence trial primarily aiming at the demonstration of comparable efficacy between MabionCD20 and MabThera in patients with active RA. In this trial, patients received 2 IV infusions of 1000 mg rituximab (MabionCD20 or MabThera) on Day 1 and Day 15 during the 24-Week treatment period. PK samples were collected up to Day 168 (24 weeks). PK and PD parameters were determined in a sub-population of patients enrolled at selected medical centers in Poland and Ukraine, only. Analyses were performed on the PK-PP and PK-ITT population.

$AUC_{(0\text{-}t)}$ and $C_{max\text{-}second}$ were investigated as primary PK endpoints. The ANOVA analysis of the PK-PP population demonstrated that the estimated least square (LS)-means of $AUC_{(0\text{-}t)}$ were 211893 µg*h/mL for MabionCD20 and 207906 µg*h/mL for MabThera. The estimated ratio was calculated to be 101.92% with the 90% confidence intervals (CI) between 93.47 – 111.13%. In case of $C_{max\text{-}second}$, the estimated LS-means were 414.44 µg/mL for MabionCD20 and 417.76 µg/mL for MabThera. The estimated ratio was thus 99.2% and the 90% CI ranged between 93.49 – 105.27% (Table PK17). For both primary endpoints, the criteria for bioequivalence were fulfilled. Results of the PK-ITT population confirmed those of the PK-PP population (Table PK18).

**Table PK17: Results of ANOVA analysis - primary PK endpoints (PK-PP population) - Study MabionCD20-001RA**

| | MabionCD20DP | | MabThera | | Results from ANOVA model | |
|---|---|---|---|---|---|---|
| | N | Estimated LS-mean | N | Estimated LS-mean | Estimated ratio | Two-sided 90%CI |
| $AUC_{0\text{-}t}$, µg*h)/mL | 66 | 211893.08 | 58 | 207906.22 | 101.92% | 93.47–111.13 |
| $C_{max\text{-}second}$, µg/mL | 66 | 414.44 | 58 | 417.76 | 99.20% | 93.49–105.27 |

**Table PK18: Results of ANOVA analysis – primary PK endpoints (PK-ITT population) - Study MabionCD20-001RA**

| | MabionCD20 | | MabThera | | MabionCD20/MabThera | |
|---|---|---|---|---|---|---|
| Parameter [unit] | N | LS-Mean | N | LS-Mean | Ratio of LS-Means | Two-sided 90% CI |
| $AUC_{0-t}$ [(µg*h)/mL] | 99 | 206680.68 | 102 | 199374.54 | 103.66% | [94.86; 113.29%] |
| $C_{max}$-second [µg/mL] | 99 | 405.02 | 101 | 411.57 | 98.41% | [93.56; 103.51%] |

Descriptive statistics and ANOVA analysis of the secondary PK endpoints ($AUC_{(0-inf)}$, $C_{max-first}$, $C_{trough}$, $T_{1/2}$, $V_D$ and CL) in the PK-PP population verified that MabionCD20 and MabThera are biosimilar, since the ratio of the LS means was again close to 100% and respective 90% CIs were contained within the predefined bioequivalence margin of 80 – 125% (Table PK19).

**Table PK19: Results of ANOVA analysis – secondary PK endpoints (PK-PP population) - Study MabionCD20-001RA**

| | MabionCD20 | | MabThera | | MabionCD20/MabThera | |
|---|---|---|---|---|---|---|
| Parameter [unit] | N | LS-Mean | N | LS-Mean | Ratio of LS-Means | Two-sided 90% CI |
| $AUC_{0-inf}$ [(µg*h)/mL] | 66 | 214025.18 | 58 | 210006.91 | 101.91% | [93.48; 111.11%] |
| $C_{max}$-first [µg/mL] | 66 | 323.61 | 58 | 319.70 | 101.22% | [94.57; 108.34%] |
| $C_{trough}$ [µg/mL] | 66 | 77.06 | 58 | 75.98 | 101.43% | [92.13; 111.66%] |
| $t_{½}$ [h] | 66 | 470.20 | 58 | 456.34 | 103.04% | [95.42; 111.26%] |
| CL [mL/h] | 66 | 4.67 | 58 | 4.76 | 98.12% | [90.00; 106.98%] |
| VD [mL] | 66 | 7457.02 | 58 | 7269.54 | 102.58% | [95.50; 110.18%] |

The comparative PK **study MabionCD20-002NHL** was conducted in the second step of the clinical development program. This study was a randomized, parallel-group, double-blind, comparative bioequivalence trial and was primarily designed to demonstrate PK similarity of MabionCD20 and the reference product MabThera in patients with CD20-positive Diffuse Large B-cell Lymphoma (DLBCL). Patients were randomized in a 5:2 ratio to receive 375 mg/m² MabionCD20 or MabThera every 3 weeks for 8 cycles in parallel to CHOP chemotherapy. The study consisted of a 26-Week double-blind treatment period and a follow-up period up to Week 46.

Results from descriptive statistics and ANOVA analysis of the primary PK endpoints $AUC_{(1-4)}$ and $AUC_{(13-26)}$ showed that MabionCD20 and MabThera can be considered biosimilar. In the PP population, the estimated mean of $AUC_{(1-4)}$ was 1521.6 µg*day/mL for MabionCD20 and 1462.2 µg*day/mL for MabThera and the estimated LS mean ratio was 104.06% with 90% CI between 95.65 – 113.21%. The estimated mean of $AUC_{(13-26)}$ was 16148.3 µg*day/mL for MabionCD20 and 15218 µg*day/mL for MabThera and the estimated LS mean ratio was 106.11% with 90% CI between 98.22 – 114.64%. The results of the ITT population confirmed those of the PP population. In all cases, the 90% CI was contained within the pre-defined equivalence margin of 70 – 143% (Table PK25).

**Table PK25: ANOVA analysis - primary PK endpoints (PP + ITT population) - Study MabionCD20-002NHL**

| | MabionCD20 | | MabThera | | Results from ANOVA model | |
|---|---|---|---|---|---|---|
| | N | Estimated mean | N | Estimated mean | Estimated Geo LS mean ratio (%) | 90% CI |
| Per protocol | | | | | | |
| $AUC_{(1-4)}$, (µg*day/ml) | 94 | 1521.57 | 35 | 1462.22 | 104.06 | 95.65–113.21 |
| $AUC_{(13-26)}$, (µg*day/ml) | 74 | 16148.33 | 29 | 15218.02 | 106.11 | 98.22–114.64 |
| Intent to treat | | | | | | |
| $AUC_{(1-4)}$, (µg*day/ml) | 98 | 1538.72 | 38 | 1507.77 | 102.05 | 93.76–111.08 |
| $AUC_{(13-26)}$, (µg*day/ml) | 90 | 15432.75 | 35 | 14648.4 | 105.35 | 96.86–118.26 |

The analysis of secondary PK endpoints ($AUC_{(1-26)}$, $C_{trough}$, $C_{max}$, $K_{el}$, $T_{1/2}$, CL) mainly supported the results of the primary analysis. The ANOVA analysis for $C_{trough}$ revealed an estimated geometric LS mean ratio of 116% with 90% CI between 98.98 – 136.90%, indicating higher $C_{trough}$ concentrations in the MabionCD20 treatment arm. However, the 90% CIs were completely contained within the pre-defined 70 – 143% margin (Table PK26).

**Table PK26: ANOVA analysis - secondary PK endpoints (PP populations) - Study MabionCD20-002NHL**

| | Results from ANOVA model | |
|---|---|---|
| | Estimated Geo LS mean ratio (%) | 90% CI* |
| $AUC_{(1-26)}$ | 105.83 | 98.46–113.75 |
| $C_{trough}$ | 116.41 | 98.98–136.90 |
| $C_{max}$_5th | 102.67 | 93.04–113.30 |
| $C_{max}$_8th | 100.48 | 92.94–108.64 |
| Kel_Lambda_z_5th | 105.29 | 92.03–120.47 |
| HL_Lambda_z_5th | 94.97 | 83.01–108.67 |
| Kel_Lambda_z_(8th) | 96.1 | 85.60–107.90 |
| HL_Lambda_z_(8th) | 104.06 | 92.68–116.82 |
| CLss_(5th) | 98.24 | 86.20–109.41 |
| CLss_(8th) | 97.02 | 86.06-109.38 |

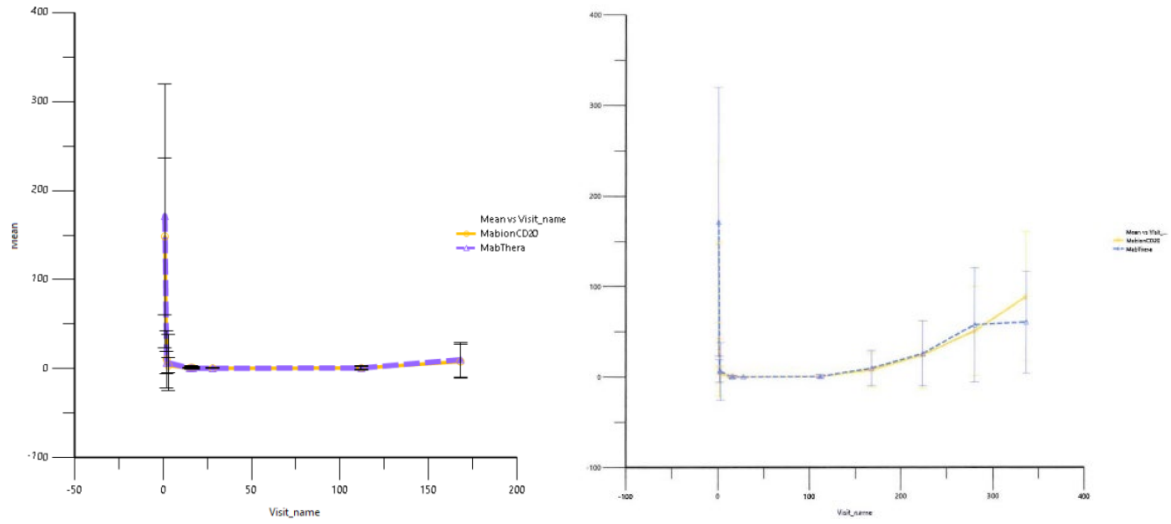
## 3.3.2. Pharmacodynamics

Effect on Circulating CD19+ B-Cells

Independent of indication, the ultimate effect of rituximab on the cell level is B-cell elimination, which is why the magnitude of B-cell depletion was selected as a pharmacodynamics marker. The expression profile of CD19 on peripheral B-cells is highly similar to the expression of CD20. Since the presence of rituximab in serum interferes with detection of CD20, peripheral B-cells expressing CD19 were measured as a surrogate for peripheral CD20+ B-cells. The levels of circulating CD19+ B-cells were measured using fluorescence-activated cell sorting (FACS).

The pharmacodynamic endpoints chosen for **study MabionCD20-001RA** were $C_{min\ B\text{-}cell}$, $AUC_{0\text{-}t\ B\text{-}cell}$, $T_{min\ B\text{-}cell}$ and $T_{B\text{-}cell}$. Descriptive statistics of the PD-PP and PD-ITT population reveal that PD parameters were roughly comparable. The minimum level of circulating CD19+ B-cells ($C_{min\ B\ cell}$) was zero in the majority of patients (Figure PD3): only 4 patients in the MabionCD20 group and 7 patients in the MabThera group had a $C_{min\ B\text{-}cell}$ that was slightly above zero. The median for $C_{min\ B\ cell}$ was 0 in both treatment groups. Geometric mean of $AUC_{0\text{-}t\ B\text{-}cell}$ was 208.7 cells*days/µL for MabionCD20 and 257.8 cells*days/µL for MabThera in the PD-PP population. PD results in the PD-ITT population were largely similar.

**Figure PD3: Time course of circulating CD19+ B-cell level for MabionCD20 and MabThera; 24 weeks (left) and 48 weeks (right) – PD-PP population – MabionCD20-001RA trial**




Curves represent mean circulating CD19+ B Cells (± SD, µL/mL) in blood versus nominal time in days (PD-PP population).

The ANOVA analysis demonstrated that the LS mean ratio for $C_{min\ B\text{-}cell}$ was 231.49% [95% CI: 136.9; 391.5] and the LS mean ratio for $AUC_{0\text{-}t\ B\text{-}cell}$ was 78.91% [95% CI: 51.81; 120.19] in the PD-PP population. In the PD-ITT population, the LS mean ratio for $C_{min\ B\text{-}cell}$ was 140.80% [95% CI: 91.85; 215.83] and the LS mean ratio for $AUC_{0\text{-}t\ B\text{-}cell}$ was 75.75% [95% CI: 55.79; 102.85]. Conclusively, ranges of the 95% CI were outside of the 80 – 125% equivalence margin and biosimilarity in PD endpoints could not be confirmed (Table PD4 and Table PD5).

**Table PD4: ANOVA for primary PD parameters – PD-PP population – MabionCD20-001RA trial**

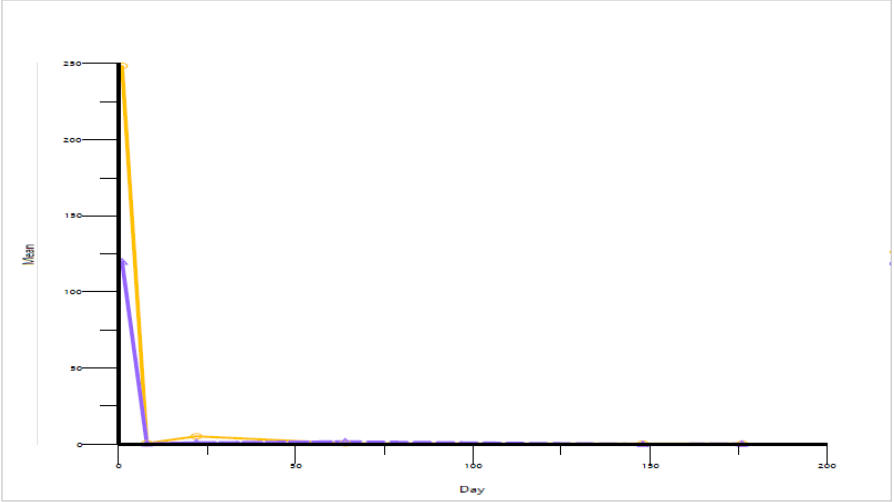
| | MabionCD20 | | Mabthera | | Results from ANOVA model | |
|---|---|---|---|---|---|---|
| | N | Estimated mean | N | Estimated mean | Estimated ratio | 95%CI |
| AUC0-t B-cell | 54 | 192.40 | 59 | 243.81 | 78.91 | 51.81-120.19 |
| $C_{min\ B\text{-}cell}$ | 54 | 0.78 | 59 | 0.34 | 231.49 | 136.88-391.49 |

**Table PD5: ANOVA for primary PD parameters – PD-ITT population – MabionCD20-001RA trial**

| | MabionCD20 | | Mabthera | | Results from ANOVA model | |
|---|---|---|---|---|---|---|
| | N | Estimated mean | N | Estimated mean | Estimated ratio | 95%CI |
| AUC0-t B-cell | 99 | 197.53 | 59 | 260.77 | 75.75 | 55.79-102.85 |
| $C_{min\ B\text{-}cell}$ | 99 | 0.58 | 59 | 0.41 | 140.80 | 91.85-215.83 |

The pharmacodynamic endpoint investigated in **study MabionCD20-002NHL** was $AUC_{(1-26)\ B\text{-}cell}$. Complete and sustained reduction in MFI was shown for both MabionCD20 and MabThera after exclusion of 11 patients identified as outliers using post-hoc Rosner's Extreme Studentized Deviate test (Figure PD5). A priori, no procedure for dealing with outliers was foreseen in the protocol.

**Figure PD5: Time course of MFI of CD19+ of MabionCD20 and MabThera after removal of outliers – MabionCD20-002NHL trial**




Similar to the PD analysis in study MabionCD20-001RA, PD parameters in study MabionCD20-002NHL failed to meet the equivalence criteria and PD similarity between MabionCD20 and MabThera could not be confirmed statistically. The estimated mean ratio of $AUC_{(1-26)\ B\text{-}cell}$ (without outliers) was 48.46% and the respective 95% CI ranged from 22.65 – 103.69% (Table PD7).

**Table PD7: ANOVA for PD parameters (ITT) – with/without outliers – MabionCD20-002NHL trial**

| | MabionCD20 (N=98) | | MabThera (N=38) | | Results from ANOVA model | |
|---|---|---|---|---|---|---|
| | N | Estimated mean | N | Estimated mean | Estimated Geo LS mean ratio (%) | 95% CI |
| $AUC_{(1-26)}$ B-cell (all data) | 98 | 150.84 | 37 | 437.61 | 34.47 | 15.01 – 79.14 |
| $AUC_{(1-26)}$ B-cell (without outliers)[1] | 93 | 120.76 | 31 | 249.20 | 48.46 | 22.65 - 103.69 |
| $AUC_{(1-26)}$ B-cell (outliers only) | 5 | 23959.45 | 6 | 8879.48 | 269.83 | 8.54 - 8522.77 |

Immunogenicity

In **study MabionCD20-001RA**, ADA sampling was conducted at Visit 1 (Baseline), Visit 2 (Day 7), Visit 3 (Day 15), Visit 5 (Day 28) and Visit 10 (Week 24). The incidence of patients with treatment emergent ADA up to Visit 10 (Week 24) was comparable between MabionCD20 and MabThera (12.1% in MabionCD20 vs. 11.1% in MabThera, Table PD8). Neutralizing antibodies were only detected in 2 patients in each treatment group (0.6% in MabionCD20 vs. 0.6% in MabThera, Table PD9). In the MabThera group, NAb were solely detected at baseline, whereas in the MabionCD20 group patients were found to be positive for NAb also at V3, V5 and V10. However, the presence of NAb in the two patients in the MabionCD20 group did not seem to have an impact on the efficacy outcome.

**Table PD8: ADA positive incidence per visit – MabionCD20-001RA trial**

| ADA positive | MabionCD20 | | | MabThera | | |
|---|---|---|---|---|---|---|
| | n | n1 | % | n | n1 | % |
| V1 (baseline) | 18 | 354 | (5.1%) | 14 | 339 | (4.1%) |
| V2 | 5 | 356 | (1.4%) | 4 | 338 | (1.2%) |
| V3 | 14 | 349 | (4.0%) | 12 | 342 | (3.5%) |
| V5 | 9 | 342 | (2.6%) | 7 | 335 | (2.1%) |
| V10 | 38 | 333 | (11.4%) | 37 | 327 | (11.3%) |
| Total (samples) | 84 | 1734 | (4.8%) | 74 | 1681 | (4.4%) |
| Total patients | 61 | 356 | (17.1%) | 51 | 342 | (14.9%) |
| Total Treatment Emergent ADA positive | 43 | 356 | (12.1%) | 38 | 342 | (11.1%) |

**Table PD9: NAb positive incidence per visit – MabionCD20-001RA trial**

| Nab positive | MabionCD20 | | | MabThera | | |
|---|---|---|---|---|---|---|
| | n | n1 | % | n | n1 | % |
| V1 (baseline) | 1 | 354 | (0.3%) | 2 | 339 | (0.6%) |
| V2 | 0 | 356 | (0.0%) | 0 | 338 | (0.0%) |
| V3 | 2 | 349 | (0.6%) | 0 | 342 | (0.0%) |
| V5 | 1 | 342 | (0.3%) | 0 | 335 | (0.0%) |
| V10 | 1 | 333 | (0.3%) | 0 | 327 | (0.0%) |
| Total (samples) | 5 | 1734 | (0.3%) | 2 | 1681 | (0.1%) |
| Total patients | 2 | 356 | (0.6%) | 2 | 342 | (0.6%) |

In **study MabionCD20-002NHL**, ADA samples were taken at Baseline (Visit 1), Week 2 (Visit 2), Week 10 (Visit 6), Week 22 (Visit 11), and Week 26 (Visit 13). Only 3% of patients in the MabionCD20 arm vs. 0% of patients in the MabThera arm were identified to be ADA positive. None of the ADA-positive patients had infusion related reactions or allergic or immune mediated AEs and all adverse events experienced were non-serious. All samples confirmed positive for ADA were tested negative for NAb (Table PD10).

**Table PD10: Frequency of patients with detectable ADA and NAb by visit – MabionCD20-002NHL trial**

| | | | MabionCD20 N=99 | Mabthera N=39 |
|---|---|---|---|---|
| **ADA positive** | | | | |
| | **Visit** | **Cycle** | n/n1 (%) | n/n1 (%) |
| | **0** | - | 7/99 (7.1) | 2/37 (5.4) |
| | **2** | 1 | 2/98 (2.0)[1] | 2/39 (5.1)[4] |
| | **6** | 4 | 2/92 (2.2)[2] | 2/39 (5.1)[4] |
| | **11** | 8 | 2/84 (2.4)[3] | 2/34 (5.9)[4] |
| | **13** | 8 | 2/83 (2.4)[3] | 2/34 (5.9)[4] |
| Total | | | 15/459 (3.3) | 10/187 (5.3) |
| Total patients | | | 10/99 (10.1)* | 2/39 (5.1)* |
| Total patients with Treatment Emergent ADA | | | 3/99 (3.0) | 0/39 (0.0) |
| **NAb positive** | | | | |
| | **Visit** | **Cycle** | n/n1 (%) | n/n1 (%) |
| | 0 | - | 0/99 (0) | 0/37 (0) |
| | 2 | 1 | 0/98 (0) | 0/39 (0) |
| | 6 | 4 | 0/92 (0) | 0/39(0) |
| | 11 | 8 | 0/84 (0) | 0/34 (0) |
| | 13 | 8 | 0/83 (0) | 0/34 (0) |
| Total | | | 0/459 (0) | 0/187 (0) |
| Total patients | | | 0/99 (0) | 0/39 (0) |

ANOVA analysis of primary PK parameters grouped by ADA status revealed that PK exposure in ADA-negative patients was comparable between MabionCD20 and MabThera. On the contrary, in ADA-

positive patients of the ITT population, the estimated LS mean of $AUC_{(1-4)}$ was 1729 µg*day/mL for MabionCD20 and 1160 µg*day/mL for MabThera and $AUC_{(13-26)}$ was 17366 µg*day/mL for MabionCD20 and 13093 µg*day/mL for MabThera (Table PD11).

**Table PD11: ANOVA for primary PK parameters (PP and ITT population) by ADA status – MabionCD20-002NHL trial**

| | | MabionCD20 | | MabThera | | Results from ANOVA model | |
|---|---|---|---|---|---|---|---|
| | | N | Estimated LS mean | N | Estimated mean | Estimated Geo LS mean ratio (%) | 90% CI |
| **Per protocol** | ADA status | | | | | | |
| **$AUC_{(1-4)}$** | Negative | 88 | 1512.10 | 32 | 1473.00 | 102.65 | 94.10–111.99 |
| | Positive | 2 | 1729.34 | 2 | 1159.65 | 149.13 | 42.99–517.33 |
| | Unknown | 4 | 1519.54 | 1 | 1548.23 | 98.15 | 51.94–185.47 |
| **$AUC_{(13-26)}$** | Negative | 65 | 15914.61 | 25 | 15352.30 | 103.66 | 95.18–112.90 |
| | Positive | 3 | 17953.82 | 2 | 13093.22 | 137.12 | 82.28–228.52 |
| | Unknown | 6 | 18090.68 | 2 | 15757.7 | 114.81 | 84.60–155.79 |
| **Intent to treat** | ADA status | | | | | | |
| **$AUC_{(1-4)}$** | Negative | 92 | 1531.36 | 35 | 1521.63 | 100.64 | 92.18–109.88 |
| | Positive | 2 | 1729.34 | 2 | 1159.65 | 149.13 | 42.99–517.33 |
| | Unknown | 4 | 1519.54 | 1 | 1548.23 | 98.15 | 51.94–85.47 |
| **$AUC_{(13-26)}$** | Negative | 74 | 16164.32 | 27 | 15541.07 | 104.01 | 96.04–112.64 |
| | Positive | 4 | 17366.26 | 2 | 13093.22 | 132.64 | 82.37–196.85 |
| | Unknown | 12 | 10908.08 | 6 | 11054.65 | 98.67 | 53.57-181.76 |

## 3.3.3. Discussion on clinical pharmacology

**Pharmacokinetics**

The two pivotal clinical trials MabionCD20-001RA and MabionCD20-002NHL provided data on pharmacokinetics of the proposed biosimilar MabionCD20 and the reference product MabThera. In contrast to the conventional approach taken in the clinical development of biosimilars (EMA/CHMP/BMWP/403543/2010), the applicant conducted a comparative efficacy study (MabionCD20-001RA) prior to a comparative PK study (MabionCD20-002NHL), which usually forms the first step in clinical development.

In the efficacy trial MabionCD20-001RA, pharmacokinetics, pharmacodynamics and immunogenicity were assessed as secondary objectives. The subsequent, supportive study MabionCD20-002NHL primarily aimed at demonstration of bioequivalence in pharmacokinetics and further analysed pharmacodynamics and immunogenicity as well as efficacy in an oncology setting as secondary endpoints.

For the quantitative determination of rituximab in human serum, two separate PK assay methods have been developed and validated. Rituximab concentrations were assessed by ELISA or by another assay in study MabionCD20-001RA and MabionCD20-002NHL, respectively. In both cases, a single assay approach with MabionCD20 as single calibrator was used, which necessitates the establishment of bioanalytical similarity of MabionCD20 and MabThera calibration curves and quality controls during assay development. Overall, both methods have been accurately validated.

For the detection of anti-MabionCD20 and anti-MabThera antibodies a bridging immunoassay format combined with the MSD platform was utilized. The method included an acid dissociation step and was structured into 4 tiers: screening, confirmation, titration, and neutralizing antibody. In general, validation for the ADA method was accurate and the assay is considered sufficiently sensitive.

However, questions on the number and impact of inconclusive samples considering the drug tolerance level of the assay remain.

A commercially available cell-based assay was used for the detection of NAb. The validation revealed that except for the LPC in the RA method the NAb assay performed with accurate precision. With reference to the low drug tolerance level of the NAb assay, rituximab concentrations in the majority of clinical samples were above the DTL and therefore would have led to false negative results. The applicant sufficiently explained the observation and it is agreed that NAb assessment in the MabionCD20-002NHL study was not significantly impacted by the drug tolerance of the assay.

In addition, regarding to the "Naïve Human Sera Pool", it was noticed that only one race (black) is represented in the female samples pool. It is known that RF is often found in the serum of patients with autoimmune diseases like rheumatoid arthritis, but rheumatoid factor can sometimes also be found in serum of patients with other diseases or even healthy individuals.

In **Study MabionCD-001RA** patients with RA received 2 IV infusions of 1000 mg rituximab (MabionCD20 or MabThera) on Day 1 and Day 15 during the 24-Week treatment period. PK samples were collected up to Day 168. This period is considered sufficiently long to cover the complete elimination phase of rituximab, as the time from last rituximab administration to the last PK sampling is longer than 5 times of the terminal half-life of rituximab.

PK and PD parameters were solely determined in a sub-population of patients enrolled at selected medical centers. Primary ($AUC_{(0\text{-}t)}$ and $C_{max\text{-}second}$) and secondary PK endpoints ($AUC_{(0\text{-}inf)}$, $C_{max\text{-}first}$, $C_{trough}$, $T_{1/2}$, $V_D$ and CL) were analysed for the PK-PP and PK-ITT population. Descriptive statistics revealed that the results of the analysed PK parameters were comparable between the MabionCD20 and MabThera treatment groups. The ANOVA analysis of the primary and secondary PK endpoints demonstrated that MabionCD20 and MabThera can be considered biosimilar; since the ratio of the LS means was close to 100% and respective 90% CIs were contained within the predefined bioequivalence margin of 80 – 125%.

In **Study MabionCD20-002NHL** patients with CD20-positive DLBCL received 375 mg/m² MabionCD20 or MabThera every 3 weeks for 8 cycles in parallel to CHOP chemotherapy. The provided clinical study report contains data for the double-blind treatment period up to Week 26, while an updated CSR including data from the follow-up period until Week 46 was provided.

Results from descriptive statistics and ANOVA analysis of the primary PK endpoints $AUC_{(1\text{-}4)}$ and $AUC_{(13\text{-}26)}$ revealed that MabionCD20 and MabThera can be considered biosimilar, as LS mean ratios were close to 100% and respective 90% CIs were contained within the pre-defined equivalence margin of 70 – 143%. Of note, the 90% CIs also met the 80 – 125% equivalence margin as generally applied for demonstration of PK similarity and which was recommended by CHMP during a preceding scientific advice. Still, a trend towards slightly increased rituximab exposure in the MabionCD20 vs. MabThera treatment group was observed (Estimated geometric LS mean ratio for $AUC_{(1\text{-}4)}$=104.06% and for $AUC_{(13\text{-}26)}$=106.11% in the PP population).

The analysis of secondary PK endpoints ($AUC_{(1\text{-}26)}$, $C_{trough}$, $C_{max}$, $K_{el}$, $T_{1/2}$, CL) mainly supported the results of the primary analysis. Secondary PK endpoints have only been analysed in the PP population.

**Pharmacodynamics**

Effect on Circulating CD19+ B-Cells

The magnitude of B-cell depletion was investigated as pharmacodynamic marker. Due to the similar expression profile of CD19 and CD20 on peripheral B-cells and taking into account that the presence of rituximab in serum interferes with detection of CD20, CD19+ peripheral B-cells were measured as a surrogate for peripheral CD20+ B-cells via FACS analysis.

In study **MabionCD20-001RA**, pharmacodynamic endpoints were only determined in a sub-population of patients. The minimum level of circulating CD19+ B-cells ($C_{min\ B\ cell}$) was zero in the majority of patients (median $C_{min\ B\ cell}$=0 in both treatment groups). The ANOVA analysis demonstrated that the LS mean ratios for $C_{min\ B\ cell}$ and $AUC_{0\text{-}t\ B\text{-}cell}$ largely deviated from 100% in both the PD-PP and the PD-ITT population. Conclusively, the 95% CI were not contained within the 80 – 125% equivalence margin and biosimilarity in PD endpoints could not be confirmed. This result was not considered a concern of clinical relevance given the overall low numbers of residual CD19+ B-cells after treatment with rituximab. In fact, the primary PD analysis confirms the mode of action and suggests that a complete and durable B-cell depletion after both treatment with MabionCD20 and MabThera was achieved.

In study **MabionCD20-002NHL**, the pharmacodynamic endpoint investigated was $AUC_{(1\text{-}26)\ B\text{-}cell}$. Complete and sustained reduction in MFI was shown for both MabionCD20 and MabThera after exclusion of 11 patients identified as outliers using post-hoc statistical methods.

Similar to the PD analysis in study MabionCD20-001RA, PD parameters in study MabionCD20-002NHL failed to meet the equivalence criteria and PD similarity between MabionCD20 and MabThera could not be confirmed statistically. The area under the circulating CD19+ B cell level versus time curves ($AUC_{0\text{-}t\ B\text{-}cell}$) did not seem to be comparable for both groups, even when outliers are excluded ($AUC_{1\text{-}26weeks\ B\text{-}cell}$: 120.76 in MabionCD20 and 249.20 in MabThera). It is further noted that the estimated mean of $AUC_{(1\text{-}26)\ B\text{-}cell}$ (outliers only) was higher in the MabionCD20 than in the MabThera treatment group.

Immunogenicity

In general, the assessment of immunogenicity in both MabionCD20-001RA and MabionCD20-002NHL was in accordance with the recommendations received during CHMP scientific advice (EMEA/H/SA/2237/1/2011/SME/III).

In study **MabionCD20-001RA**, the incidence of patients with treatment emergent ADA up to Visit 10 (Week 24) was comparable between MabionCD20 (12.1%) and MabThera (11.1%). Neutralizing antibodies were only detected in 2 patients in each treatment group. However, the presence of NAb did not seem to have an impact on efficacy.

In study **MabionCD20-002NHL**, ADA incidence was generally lower as compared to study MabionCD20-001RA which most likely relates to the CHOP-induced immunosuppression in NHL patients. Only 3% of patients in the MabionCD20 arm vs. 0% of patients in the MabThera arm were identified to be ADA positive. None of the ADA-positive patients experienced serious adverse events, infusion related reactions or immune mediated AEs. All samples confirmed positive for ADA were tested negative for NAb. However, the reliability of NAb results is still questionable considering the low drug tolerance level of the NAb assay.

The effect of the presence of ADA on PK exposure was explored in the ANOVA analysis of primary PK parameters grouped by ADA status. In ADA-positive patients, the values determined for the primary PK parameters appeared to be higher in the MabionCD20 group and lower in the MabThera group, suggesting a difference in ADA characteristics. However, given the low numbers of ADA-positive patients, no meaningful conclusion can be drawn.

## 3.3.4. Conclusions on clinical pharmacology

The analysis of pharmacokinetic endpoints revealed that bioequivalence criteria were met and thus, PK similarity of MabionCD20 and the reference product MabThera was demonstrated.

Immunogenicity in both pivotal studies was largely comparable between MabionCD20 and MabThera.

Overall from PD/PK point of view the MAA for Rituximab Mabion is considered approvable.

## 3.3.5. Clinical efficacy

## Dose-response studies and main clinical studies

**Main study**

**Study MabionCD20-001RA - A phase 3, multicentre, randomised, double-blind, parallel-group active-control trial to compare the clinical efficacy, safety, and the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of MabionCD20 and MabThera in patients with rheumatoid arthritis (RA).**

The trial was divided into 2 periods; a double-blind period up to 24 Weeks and an open-label period up to 48 Weeks. Data from the open-label period were submitted with the D120 responses.

**Figure** Visit chart MabionCD20-001RA

| | Schedule | Week | Day | Visit | |
|---|---|---|---|---|---|
| | Screening | -4 | -28 to -8 | V0 | |
| Treatment Period | | 1 | 1 | V1 | Infusion |
| | | | 2 | V1a | |
| | | | 3 | V1b | |
| | | | 7 | V2 | |
| | | 2 | 15 | V3 | Infusion |
| Observation Period | | | 16 | V3a | |
| | | | 17 | V3b | |
| | | 4 | 22 | V4 | |
| | | | 28 | V5 | |
| | | 8 | 56 | V6 | |
| | | 12 | 84 | V7 | |
| | | 16 | 112 | V8 | |
| | | 20 | 140 | V9 | |
| | | 24 | 168 | V10 | Early Termination |
| | | 32 | 224 | V11 | |
| | | 40 | 280 | V12 | |
| | | 48 | 336 | V13 | |

| Re-treatment | | | | |
|---|---|---|---|---|
| Schedule | Week | Day | Visit | |
| Re-treatment Period | 24 | 168 | V10 | Infusion |
| | 25 | 175 | V10a | |
| | 26 | 182 | V10b | Infusion |
| Re-treatment observation Period | 27 | 189 | V10c | |
| | 28 | 196 | V10d | |
| | 32 | 224 | V11 | |
| | 40 | 280 | V12 | |
| | 48 | 336 | V13 | |

## Methods

***Study Participants***

Main inclusion criteria:

1. Caucasian male or female ≥ 18 up to 80 years old (inclusive);
2. Body Surface Area (BSA) between 1.5–2.2 $m^2$ calculated according to the DuBois & DuBois formula: BSA in m2 = (Weight (kg)0.425 x Height (cm)0.725) x 0.007184;
3. Patients with active RA diagnosed according to revised 1987 American Rheumatism Association criteria, with disease duration minimum 6 months prior to screening visit, who are naive to tumor necrosis factor (TNF) antagonists or any other monoclonal antibody therapies and who have had an inadequate response to an adequate regimen of MTX or/and other DMARDs;
4. Patients with currently moderate to severe active RA defined as the presence of the following:
   - ≥8 swollen joints and ≥8 tender joints, observed by a physician;
   - radiographic evidence of ≥1 joint with defined erosion attributable to RA;
   - and two or more of the following: serum C-reactive protein (CRP) ≥6 mg/L; erythrocyte sedimentation rate (ESR) ≥28 mm/hr; morning stiffness in and around joints lasting longer than 45 minutes;

5. Patients on MTX treatment receiving 10–25 mg/week for at least 12 weeks, with the last 4 weeks at a stable dose.

Main exclusion criteria

1. History of or current rheumatic autoimmune disease other than RA, e.g. Juvenile Idiopathic Arthritis (except concurrent Sjogren's syndrome);
2. History of or current inflammatory joint disease other than RA;
3. American College for Rheumatology Functional Class IV disease;
4. History of significant systemic involvement secondary to RA like severe vasculitis, pulmonary fibrosis, Felty's syndrome or other immunological disorders e.g. systemic lupus erythematosus (SLE), scleroderma, inflammatory bowel disease;
5. Subject with known positive tests for Human Immunodeficiency Virus Type (HIV), hepatitis B surface antigen (HBsAg), anti-HBc antibodies, or hepatitis C antibody;
6. Serious and uncontrolled co-existing diseases which, in the investigator's opinion, would preclude subject participation;
7. Prior treatment of RA with rituximab, other anti-CD20 mAb, anti-TNF-α drug or other monoclonal antibodies;
8. Use of systemic glucocorticoids at dose higher than 10 mg prednisolone daily or equivalent, within 2 weeks prior to screening and between screening and Day 1;
9. Major surgery (including joint surgery) within 8 weeks prior to screening or planned surgery within 12 months after baseline;
10. Recent vaccination, especially live viral vaccinations (<4 weeks prior to study drug infusion on Day 1).

***Treatments***

Patients were randomized to receive 2 intravenous infusions at a dose of 1000 mg/infusion of MabionCD20 (Group 1) or MabThera (Group 2) as study medication on Day 1 and on Day 15 of a 24-week treatment and observation period. Dose modifications were not allowed.

Patients who experienced a clinical relapse at Week 24 (defined as an increase in the disease activity score (DAS)28- erythrocyte sedimentation rate (DAS28-ESR) $\geq$0.6) and residual disease activity (DAS28-ESR >3.2), received a second open-label course of study drug if they still fulfilled all the inclusion and exclusion criteria and had a clinical response to first course of treatment (defined as at least a 1.2-point decrease in the DAS28-ESR starting from the 16th week after the first infusion, with low disease activity [defined as a DAS28-ESR $\leq$3.2]).

Re-treatment was planned to be a second course of study drug treatment administered as 2 infusions of 1000mg two weeks apart, as in the first course of study drug treatment. According to the original protocol, all patients qualifying for re-treatment should receive MabionCD20. By protocol amendment 2, to compensate for production delays, the protocol was changed to allow open-label treatment with MabThera depending on the sponsor's decision, as second course of treatment. This resulted in 4 treatment groups, 2 continuing with the study medication originally randomized to, and 2 who switched treatments (see Patient disposition diagram below).

***Objectives***

The primary objective was to demonstrate biosimilarity between test product MabionCD20 and the reference product MabThera in patients with active RA, based on the percentage of patients in each treatment group achieving the primary efficacy endpoint of a ≥20% improvement on the American College of Rheumatology score (ACR20) at Week 24.

Secondary objectives were:

1. To evaluate biosimilarity between test product MabionCD20 and reference product MabThera;
    - based on efficacy and response scores: percentage of patients achieving ACR20, ACR50, ACR70, Changes in Disease Activity Score (DAS28-ESR), percent of patients with moderate and good response on the European League Against Rheumatism (EULAR) scale at weeks: 4, 8, 12, 16, 20, 24 (except for ACR20 as it is the primary objective), and 48;
    - based on pharmacodynamic endpoints;
2. To demonstrate comparative safety and tolerability of a single course of treatment (2 infusions spaced 2 weeks apart) of MabionCD20 and MabThera in patients with moderate to severe active RA and to demonstrate safety of MabionCD20 as second cycle treatment after initial MabThera treatment;
3. To demonstrate bioequivalence in pharmacokinetic (PK) characteristics between MabionCD20 and MabThera.

***Outcomes/endpoints***

The primary endpoint was the proportion of patients with a ≥20% improvement versus baseline of the American College of Rheumatology (ACR) score (ACR20 response) at Week 24.

Secondary endpoints included the ACR20 response at weeks 4; 8; 12; 16; 20; and 48, the proportion of patients with a ≥50% and ≥70% improvement versus baseline of the ACR score (ACR50 and ACR70 response, respectively) at weeks 4; 8; 12; 16; 20; 24; and 48, the change from baseline in DAS28-ESR; and the proportion of patients with a moderate or good European League Against Rheumatism (EULAR) response. In addition, the individual components of ACR criteria were analysed (tender and swollen joint count, patient's assessment of pain, patient's and physician's assessment of global disease activity, patient's assessment of physical functions based on the Health Assessment Questionnaire Disability Index score, and evaluation of the ESR).

***Results***

**Introductory Note**

There is a relevant change in the number of patients included in the efficacy and safety analysis sets of study MabionCD20-001RA since the CHMP D120 List of Questions.

A total of 993 patients were screened and 709 subjects were randomized into the study.
However, in response to the GCP inspection findings at the Bosnian site as well as the fact that all Bosnian sites were monitored by the same CRA, the Applicant decided to exclude data of patients from all Bosnian clinical sites from the analysis reported in the updated version of the MabionCD20-001RA CSR.
Thus, 80 patients (11.3% out of 709 enrolled) in Bosnia and Herzegovina were excluded from the efficacy, safety and immunogenicity data presented in the MabionCD20-001RA CSR Version 2.0 in accordance with the recommendation of the GCP inspectors.

Subsequent sections of this document have therefore been updated and reflect the data of the re-analysis.

**Participant flow**

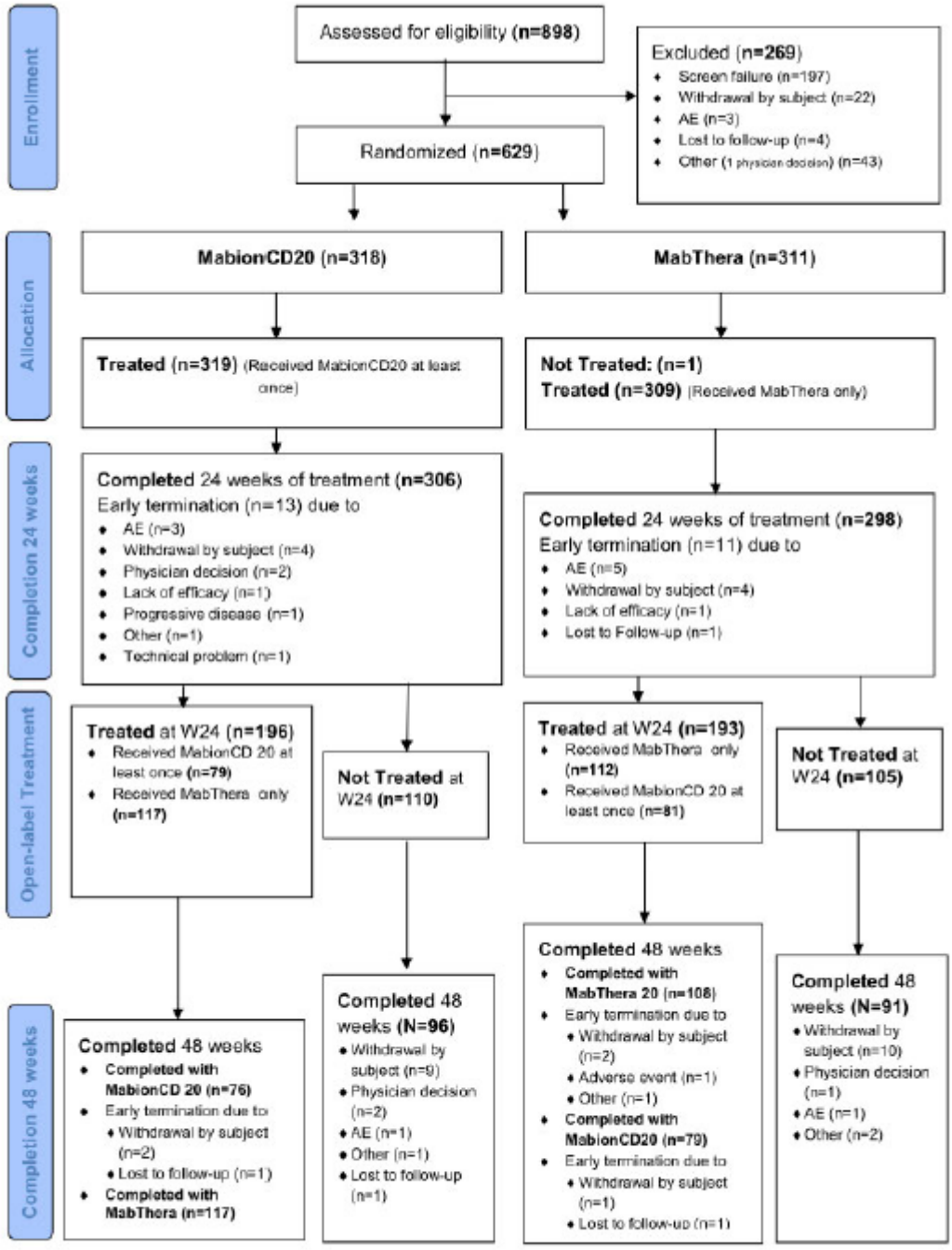



**Figure 9-1 Patient disposition diagram, whole study period**

Source: Tables 14.1.1, 14.1.4.1.1, and 14.1.4.2.1. 14.1.4.2.2, Appendices 16.2.1 and 16.2. 5
n = number of patients, AE = adverse event, D = day, PD = disease progression, ACR = American College of Rheumatology

**Numbers analysed**

The ITT set comprised 629 patients; 318 patients were analyzed in the MabionCD20 group according to the randomized treatment of MabionCD20 and 311 patients were analyzed in the MabThera group according to the randomized treatment of MabThera. This population was used for the sensitivity of the main clinical efficacy analyses.

In total, 39 randomized patients were excluded from the PP set, 21 patients randomized to receive MabionCD20 and 18 patients randomized to receive MabThera.

One patient was not excluded from the per-protocol population as recommended by the GCP inspectors. However, a sensitivity analysis, which excluded this patient, was performed for primary endpoint, ACR20.

As regards to the safety set (SAF), total of 629 patients were randomized, but 628 patients were analyzed in the SAF because 1 patient did not receive the randomized study medication (MabThera) (Table 10-3).

**Table 10-3 Analysis sets – Safety population (excl. Bosnia), displayed according to treatment received (double-blind study period)**

| | MabionCD20 | | MabThera | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Patients in the safety set (SAF) | 319 | (100.0%) | 309 | (100.0%) | 628 | (100.0%) |

Source: Table 14.1.2.2.
Treatment groups are displayed according to treatment received.

In the open-label study period, efficacy data were analyzed according to the randomized treatment in the ITT, and the safety data of all patients were analyzed in the safety set (SAF), according to the treatment that they had actually received (Table 10-4).

**Table 10-4 Analysis sets – Safety population (excl. Bosnia), displayed according to treatment received (open-label study period)**

| | Received a second course of treatment | | | | | Did not receive a second course of treatment | | |
|---|---|---|---|---|---|---|---|---|
| | MabionCD20 after MabThera | MabThera after MabionCD20 | MabionCD20 constantly | MabThera constantly | Total | MabionCD20 | MabThera | Total |
| | n | n | n | n | n | n | | |
| Patients in the safety set (SAF) | 81 | 117 | 79 | 112 | 389 | 110 | 105 | 215 |

Source: Tables 14.1.4.2.1, 14.1.4.2.2

**Summary of main efficacy results**

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: Summary of efficacy for trial MabionCD20-001RA**

| | |
|---|---|
| **Title:** A randomized, double-blind, parallel-group comparative bioequivalence trial of MabionCD20 (Mabion SA) compared to Mabthera (Rituximab, Roche) in patients with rheumatoid arthritis | |
| Study identifier | MabionCD20-001RA |
| Design | Parallel group design |

| | | | |
|---|---|---|---|
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 24 weeks<br>not applicable<br>not applicable |
| Hypothesis | Equivalence | | |
| Treatments groups based on safety population | MabionCD20 | | 1000 mg iv Mabion CD20 on day 1 and 15, n = 319 excluding Bosnian sites* |
| | Mabthera | | 1000 mg iv MabThera on day 1 and 15, n = 309 excluding Bosnian sites* |
| Endpoints and definitions | Primary endpoint | ACR20 | ACR20 Response according to the American College of Rheumatology score at week 24 |
| | Secondary endpoints | ACR50 | ACR50 Response according to the American College of Rheumatology score at week 24 |
| | | ACR70 | ACR70 Response according to the American College of Rheumatology score at week 24 |
| | | DAS28 | Change in Disease Activity Score from baseline to week 24 |
| | | EULAR | percent of patients with good response on the European League Against Rheumatism (EULAR) scale at week 24 |
| Database lock | 16-08-2017 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Per Protocol Population at week 24 | | |
| Descriptive statistics and estimate variability | Treatment group | MabionCD20 | MabThera |
| | Number of subject | 298 | 292 |
| | ACR20 | 226/298 (79.2%) | 248/292 (84.9%) |
| | 95%-CI | (74.1%, 83.7%) | (80.3%, 88.8%) |
| Effect estimate per comparison | Primary endpoint | Comparison groups | MabionCD20 - Mabthera |
| | | Difference in incidences | -5.7% |
| | | 95%-CI | (-12.0%, 0.5%) |
| | | Equivalence margin | (-13%, 13%) |
| Notes | Equivalence has been shown with regard to the pre-specified equivalence range. The same holds true for the analysis based on the ITT population: the 95%-CI for the difference in incidences (-11.3%, 1.1%) falls into the pre-specified equivalence range. The Applicant justified the model sensitivity with respect to the high response rates of about 80% based on the analysis of data from historical MabThera studies. However, further justification is needed. (LoOI) | | |
| **Analysis description** | **Secondary analysis** | | |
| Analysis population and time point description | Per Protocol Population at week 24 | | |
| | Treatment group | MabionCD20 | MabThera |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Number of subject | 298 | 292 |
| | ACR50 | 137/298 (46.0%) | 142/292 (48.6%) |
| | 95%-CI | (40.2%, 51.8%) | (42.77, 54.5%) |
| Effect estimate per comparison | ACR50 | Comparison groups | MabionCD20 - Mabthera |
| | | Difference in incidences | -2.7% |
| | | 95%-CI | (-10.7, 5.5%) |
| | | Equivalence margin | N/A |
| Descriptive statistics and estimate variability | Treatment group | MabionCD20 | MabThera |
| | Number of subject | 298 | 292 |
| | ACR70 | 33/298 (11.1%) | 36/292 (12.3%) |
| | 95%-CI | (7.8%, 15.2%) | (8.8, 16.7%) |
| Effect estimate per comparison | ACR70 | Comparison groups | MabionCD20 - Mabthera |
| | | Difference in incidences | -1.3% |
| | | 95%-CI | (-6.6, 4.0%) |
| | | Equivalence margin | N/A |
| Descriptive statistics and estimate variability | Treatment group | MabionCD20 | MabThera |
| | Number of subject | 298 | 292 |
| | DAS28-ESR<br><br>Mean (SD) | -2.43 (1.21) | -2.49 (1.13) |
| | LS-Mean (ANCOVA model) | -2.47 | -2.52 |
| Effect estimate per comparison | DAS28-ESR | Comparison groups | MabionCD20 - Mabthera |
| | | Difference in incidences | 0.05% |
| | | 95%-CI | (-0.077%, 0.184) |
| | | Equivalence margin | N/A |
| Descriptive statistics and estimate variability | Treatment group | MabionCD20 | MabThera |
| | Number of subject | 298 | 292 |
| | EULAR | 20/298 (6.7%) | 19/292 (6.5%) |
| | 95%-CI | (4.1, 10.2%) | (4.0, 10.0%) |
| Effect estimate per comparison | EULAR | Comparison groups | MabionCD20 - Mabthera |
| | | Difference in incidences | 0.2% |
| | | 95%-CI | (-4.0, 4.4%) |
| | | Equivalence margin | N/A |

* Analyses including the 80 patients from Bosnia provided consistent results.

## Clinical studies in special populations

N/A

## Supportive study (MabionCD20-002-NHL)

Supportive efficacy data were obtained from study MabionCD20-002NHL, a PK/PD bioequivalence trial in adult patients with (Ann Arbor stages I, II, III, IV) CD20 positive DBLCL.

Patients with DLBCL were randomly assigned (ratio 5:2) to MabionCD20 (375 mg/m², intravenous [IV], or MabThera (375 mg/m² IV) given every 3 weeks for 8 cycles until Day 148 (Week 22). All patients concomitantly received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy.

The study consisted of a screening period (Visit 0, Day -28 to Day – 8 prior to Visit 1). The active treatment period extended from Visit 1 (Day 1, Week 1) with randomization and first study drug administration until Visit 13 (Day 176 ±4, Week 26).

The primary objective was to assess the PK bioequivalence between MabionCD20 and MabThera in combination with CHOP. Secondary objectives included tumor response, evaluated on Day 176 (Week 26), 4 weeks after last study drug administration, as efficacy parameter.

**Table 11-18 Efficacy assessment (PP [W13-W26] population)**

| Response | MabionCD20 N=74 | MabThera N=29 | Response Rate difference (95% CI) |
|---|---|---|---|
| Complete or partial, n (%) | 66 (89.2) | 27 (93.1) | -3.91 (-15.54–7.71) |
| Complete, n (%) | 33 (44.6) | 12 (41.4) | |
| Partial, n (%) | 33 (44.6) | 15 (51.7) | |
| Stable disease, n (%) | 6 (8.1) | 2 (6.9) | |
| Progressive disease, n (%) | 2 (2.7) | 0 (0) | |

Source: Table 14.2.1.11

## 3.3.6. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

**MabionCD20-001RA** is a randomised, active-controlled, double-blind, multicentre, 2-arm, parallel-group confirmatory study to compare the efficacy, safety, PK, and pharmacodynamics of MabionCD20 vs. MabThera in adult patients with moderate to severe active (≥ 6 months' diagnosis) RA, who had to had an inadequate response to an adequate regimen of MTX or/and other DMARDs and were untreated with anti-TNF or any other monoclonal antibody therapies.

The patient population chosen, TNF inhibitor naïve RA patients not responding adequately to therapy with MTX or other DMARDs, is outside of the approved indication of the reference product. In its scientific advice, the CHMP agreed with the patient population chosen by the Applicant (EMEA/CHMP/SAWP/698133/2012).

The study was divided into two periods; a double-blind period up to week 24 (6 months), in which patients received one first course of treatment (two infusions of 1000 mg of either MabionCD20 or MabThera on Days 1 and 15) and an open-label period up to week 48. After the initial 24 weeks period, patients who had a clinical response, could receive a second course of treatment with MabionCD20 or MabThera in case of relapse (defined by an increase in DAS28-ESR and residual disease activity).

The second course of treatment was originally planned with MabionCD20, but to compensate for production delays, the protocol was changed to allow open-label treatment with MabThera depending on the sponsor's decision, as second course of treatment.

629 patients were randomized in a 1:1 ratio to receive the first course of study medication (a 1000 mg i.v. infusion of MabionCD20 or MabThera on two separate occasions, two weeks apart (i.e., on Day 1 and on Day 15). The majority of randomized, treated and evaluable patients (682 of 707 [96.5%]) completed the study up to 24 weeks, 344 [96.1%] in the MabionCD20 treatment group vs 338 [96.8%] in the MabThera treatment group. The PP population comprised 664 patients; 334 patients received MabionCD20 and 330 MabThera.

In total, 247 patients, 129 in the MabionCD20 group and 118 in the MabThera group, qualified for and received re-treatment. Further 142 patients, 66 in the MabionCD20 group and 76 in the MabThera group, received re-treatment, although they did not qualify for re-treatment. Thus, in total 389 of 629 patients received re-treatment.

The primary objective was to demonstrate comparable efficacy between MabionCD20 and MabThera in combination with MTX in patients with active RA using ACR20 at week 24 as the primary efficacy parameter.

The secondary efficacy endpoints were:

- Percentage of patients achieving ACR20, ACR50, ACR70;
- Changes in Disease Activity Score (DAS28-ESR);
- Percent of patients with moderate and good response on the EULAR scale at weeks: 4, 8, 12, 16, 20, 24 (except for ACR20 as it is the primary endpoint), and 48.

**MabionCD20-002NHL** is a randomised, active-controlled, double-blind, multicentre, 2-arm, parallel-group study to compare PK, PD safety and efficacy of MabionCD20 plus CHOP vs MabThera plus CHOP in adult patients with (Ann Arbor stages I, II, III, IV) CD20-positive DBLCL.

143 patients were randomized in a 5:2 ratio to either MabionCD20 (n=102) or MabThera (n=41) treatment group. 3 patients did not receive the allocated treatment (MabionCD20 n=2 and Mabthera n=1). The majority of 140 patients (n=120, 85.7%) completed the study up to 26 weeks.

The primary objective was to demonstrate the biosimilarity in terms of PK between MabionCD20 and MabThera using (AUC(1-4) and (AUC(13-26)) as the primary PK parameters. Efficacy was a secondary endpoint in this study. It was assessed by evaluation of tumor response (complete response, partial response, stable disease, and progressive disease) at Week 26 (after 8 treatment cycles of 21 days). No statistical analysis was performed for the efficacy endpoint.

### *Efficacy data and additional analyses*

#### MabionCD20-001RA (pivotal efficacy trial)

The demographics were largely similar between treatment arms in terms of age, gender, enrolment by country and other demographic parameters and with regard to the efficacy variables, duration of rheumatoid arthritis at baseline and dose of methotrexate at baseline and Week 24.

The proportions of patients which completed the double-blind period were similar between treatment groups, MabionCD20 95.9 % vs. MabThera 96.4%.

The primary efficacy endpoint was met.

ACR20 at Week 24 was 79.2% in the MabionCD20 arm and 84.9% in the MabThera arm and the difference in ACR20 was - 5.7% (95% CI [-12.0; 0.5%]) in the PP set. Equivalence was concluded by the Applicant as the entire 95% CI for the difference between the 2 treatments was within the pre-specified margin of ± 13%.

In the ITT set, ACR20 at Week 24 was 79.0% in the MabionCD20 arm and 84.1% in the MabThera arm. The difference in ACR20s was -5.1% (95% CI [-11.3; 1.1%]). However, the ACR20 results in the PP and ITT populations are considerably higher than the effect size of 50% assumed in the sample size calculation.

The secondary efficacy objective based on efficacy and response scores up to Week 24 was met. The observed 95% CIs of differences of endpoints ACR 20, ACR 50, ACR 70 and EULAR response at Weeks 4, 8, 16, 20 and 24 were at maximum ±12.0 % (borders included) in the PP set and supported by the results of the ITT sensitivity analyses. Treatment had no influence on DAS28-ESR at any time point as analysed per ANCOVA model. The 95% CIs for the difference of LS-means between MabionCD20 and MabThera were small, all between - 0.252 and 0.148.

Kaplan-Meier analyses of the time to first onset of ACR20 response and, in particular, of the time to first good EULAR response appear to indicate that the treatment effect on MabionCD20 sets in earlier compared to MabThera, whereas when comparing the Kaplan-Meier curves themselves the treatment effect of a combined good or moderate EULAR response sets in earlier on MabThera. Overall, the differences are small and not considered clinically relevant. Differences in ACR20, ACR50 and ACR70 and Good EULAR responses at Week 48 (end of open-label period) between the MabionCD20 and MabThera groups of patients not re-treated, ranged from approximately 4.8% to 11.2% (no CIs were provided). These differences are all in favor of MabionCD20.

With regard to the long-term efficacy data for the patients who were retreated with a second course of MabionCD20 or MabThera, the possible selection bias introduced by protocol amendment 2 an analysis was conducted to evaluate any possible occurrence of selection bias for the retreatment groups and impact on the efficacy data at week 48 in the MabionCD20-001RA study. The analysis revealed that the retreatment groups were balanced for baseline demographic or disease characteristics, efficacy at Week 24, immunogenicity at Week 24 and time until the patients were on treatment.

Overall, ACR 20, ACR 50, ACR 70 and EULAR responses showed the highest degree of similarity between the 2 groups of patients who switched treatment. These are, however, the groups of least importance from a regulatory perspective since interchangeability is not part of a marketing authorization in the EU.

Predefined subgroup analyses were performed for the primary efficacy endpoint, the ACR20 at Week 24, using the Mantel-Haenszel risk difference method for the ITT population. Subgroups were gender, baseline sero-positivity for either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-ACPA antibody), duration of RA (comparing patients < and> median in the ITT) and baseline DAS28-ESR (comparing patients < and> median in the ITT), but not for age.

Most subgroup analyses indicated a slight numerical advantage for Mabthera over MabionCD20 in ACR20 response at Week 24.

The subgroup of seronegative patients comprised 14.8% of the ITT population, 43 of 318 [13.5%] patients in the MabionCD20 group compared to 50 of 311 [16.1%] patients in the MabThera group. The ACR20 response rates at Week 24 were comparable between seronegative and seropositive patients in the MabionCD20 arm, 76.7% versus 79.9%, whereas in the MabThera arm more seronegative patients, 92.0%, achieved an ACR20 response compared to 83.1% of seropositive patients. This resulted in a difference of 15.3%, 95% CI [0.6; 30.0%] between treatment groups in the subgroup of seronegative patients at baseline. Results of this subgroup analysis contradict the findings of previous studies with MabThera. According to the MabThera SmPC the probability of achieving an ACR20 response at Week 24 was significantly less in the group of seronegative patients. As regards to disease activity at baseline (DAS28-ESR) there was a difference of 16.2% in ACR20 response rates in patients treated with MabionCD20 with lower (≤median) disease activity, 71.1% as

compared to patients with higher (> median) disease activity, 87.3%, whereas no such difference was observed for patients treated with MabThera, 85.4% versus 83.3%. The resulting difference between both treatment groups in the patient subgroup with lower (≤median) disease activity was 14.3%, 95% CI [5.0; 23.6%].

Subgroup differences for ACR20 response as observed in the subgroup analyses are replicated in adjusted multivariable ANOVA models with treatment interactions for baseline sero-positivity, duration of RA, baseline disease severity (DAS28-ESR), gender and age group. Sero-positivity showed a pronounced differential effect between treatment arms (OR = 0.606 vs 0.216; p = 0.132). In the same model, i.e., taking sero-positivity and other prognostic effects into account baseline disease severity showed an even more pronounced and significant differential effect (OR = 0.201 vs 0.652; p = 0.009). Furthermore, age group had a pronounced differential effect between treatment arms (OR = 0.607 vs 0.216; p = 0.114). Arguments of the Applicant around three-way interaction models cannot be followed. It is stressed once more that non-significant effects do not proof that there is no effect. This is especially true for this rather small trial and with Bosnian sites further excluded. Hence, observed subgroup effects, both from the multivariable interaction model and the simple subgroup analyses presented previously show a possible signal which needs to be taken into consideration. Overall, the interaction models show that the differences in treatment effects observed between MabThera and MabionCD20 are most likely not only based on differences in prognostic factors of the population but are due to differences in the originator and biosimilar product.

With view on missing data multiple imputation was done separately for each of the underlying components of ACR and DAS28. Values were only imputed based on treatment arm and results in the component at previous visits. No further covariate information is used. 500 data sets were imputed to derive the final analyses. As multiple imputation has a random component, results depend on the random seed, which should be pre-specified at the time of planning the trial (in the protocol or SAP). The Applicant only referred to a seed which would for example be appropriate. This is not considered sufficient. As the Applicant explains, the amount of missing data was rather small (only 3.8% to 4.2%) and the PP set is usually considered more sensitive and relevant.

With regard to the proposed similarity margin of ±13% for ACR20 a meta-analysis was performed with three studies 'Emery et al 2010 (SERENE)', 'Emery et al 2006 (DANCER)', and 'Cohen et al 2006 (REFLEX)', using both fixed and random effects model, and then the analysis is repeated by including the data from Edwards et al, N Engl J Med 2004; 350:2572-81. The methods for fixed and random effects meta-analysis were explained including derived quantities such as $I^2$ and $\tau^2$. Both estimates for $I^2$ and $\tau^2$ are very imprecise with very wide confidence intervals. With regard to the proposed similarity margin of ±13% for ACR20 meta-analysis were performed with three studies using both fixed and random effects model, and then repeated with four studies. Both analysis showed similar results and support the proposed similarity margin. It is noted (as raised previously) that response rates with rituximab + MTX are in the range of 50.6% to 62.5% and thus much lower in all studies than in the biosimilarity study. Hence, the assay sensitivity with such high response rates is questioned.

**MabionCD20-002NHL (supportive efficacy trial)**

Data on previous treatment for DLBCL were not collected in the eCRF. As per eligibility criteria patients enrolled in the study had no immunotherapy for DLBCL within 1.5 years prior to screening and did not have any chemotherapy or radiotherapy for treatment of lymphoma within 28 days prior to treatment.

Demographic characteristics were in general well balanced between treatment groups. Patients included in the study were white, half of them male and with a median age of 53.5 years (range: 19 - 78).

Characteristics of disease status at baseline were generally comparable between the MabionCD20 and the MabThera treatment groups with the exception of the age adjusted IPI.

The percentage of patients classified as high-intermediate was 19% in the MabionCD20 group, and 32.5% in the MabThera group; the percentage of patients classified as high risk was 8% in the MabionCD20 group, and 2.5% in the MabThera group. In accordance, the percentage of patients with elevated serum lactate dehydrogenase levels was higher in the MabThera group.

Numbers and frequencies of patients who completed all 8 cycles of CHOP chemotherapy were comparable between the two treatment arms.

Adverse events and withdrawal by subject led to treatment discontinuation more frequently in the MabionCD20 treatment group than in the MabThera treatment group even taking the unequal randomization ratio (5:2) into consideration. Overall, the frequencies of discontinuation of treatment were comparable between MabionCD20 and MabThera treatment groups, 15% versus 12.2%.

Apart from evaluation of tumor response at Week 26, no other secondary efficacy endpoints were defined and evaluated in the study.

There are slight numerical differences in the objective response rates (ORR; complete and partial response combined) at Week 26 between the 2 treatment groups, both in the PP population (MabionCD20 89.2% versus MabThera 93.1%) , a modified ITT population (MabionCD20 79.2% versus MabThera 84.2%) and an ITT population including randomized patients with lack of assessment (MabionCD20 74.5% versus MabThera 78.0%) in favour of MabThera.

These differences in response rates (complete and partial response combined) of 3.5% [95% CI -18.77; 11.69] (new ITT set) and 3.9% [95% CI – 15.54; 7.71) (PP set) between MabionCD20 and MabThera are considered comparable and not clinically relevant. The sample size (especially in the MabThera arm) is too small to base any sound conclusions neither in favour nor in disfavour of the biosimilar.

## 3.3.7. Conclusions on clinical efficacy

Similar efficacy can be concluded in study MabionCD20-001RA in patients with active RA as regards ACR20 at Week 24. This is supported by the secondary efficacy parameters of ACR 20, 50 and 70, EULAR response, and DAS28-ESR from Week 4 to Week 24. Most subgroup analyses indicated a slight numerical advantage for Mabthera over MabionCD20 in ACR20 response at Week 24. Subgroup differences for ACR20 response as observed in the subgroup analyses are replicated in adjusted multivariable ANOVA models with treatment interactions for baseline sero-positivity, duration of RA, baseline disease severity (DAS28-ESR), gender and age group. Sero-positivity showed a pronounced differential effect between treatment arms (OR = 0.606 vs 0.216; p = 0.132). In the same model, i.e., taking sero-positivity and other prognostic effects into account baseline disease severity showed an even more pronounced and significant differential effect (OR = 0.201 vs 0.652; p = 0.009). Furthermore, age group had a pronounced differential effect between treatment arms (OR = 0.607 vs 0.216; p = 0.114). Arguments of the Applicant around three-way interaction models cannot be followed. It is stressed once more that non-significant effects do not proof that there is no effect. This is especially true for this rather small trial and with Bosnian sites further excluded. Hence, observed subgroup effects, both from the multivariable interaction model and the simple subgroup analyses presented previously show a possible signal which needs to be taken into consideration. Overall, the interaction models show that the differences in treatment effects observed between MabThera and MabionCD20 are most likely not only based on differences in prognostic factors of the population but are due to differences in the originator and biosimilar product.

Study MabionCD20-002NHL provided supportive efficacy data.

Results of tumour response at Week 26 do not raise a concern regarding similarity; however, the significance of this data is limited by study design and low numbers of treated patients.

## 3.3.8. Clinical safety

## Patient exposure

In total, 419 patients were randomized and treated with MabionCD20 in the double-blind parts of studies MabionCD20-001RA and MabionCD20-002NHL excluding 80 patients from Bosnia.

In study **MabionCD20-001RA**, 315 of the 319 patients in the MabionCD20 group (98.7%) and 304 of the 309 patients in the MabThera group (98.4%) received a complete course of infusions (see Table below). The median infusion duration was similar in both treatment groups (4.3 and 3.3 hours for infusion 1 and 2 respectively).

**Table: Exposure to study medication: number and duration of infusion, and dose (double-blind study period) – SAF (excl. Bosnia)**

| Parameter<br>Category/ Statistics | MabionCD20<br>(N=319) | MabThera<br>(N=309) | Total<br>(N=628) |
|---|---|---|---|
| **Number of infusions [n (%)]** | | | |
| 1 | 4 (1.3%) | 5 (1.6%) | 9 (1.4%) |
| 2 | 315 (98.7%) | 304 (98.4%) | 619 (98.6%) |
| **Duration of infusion 1 [h]** | | | |
| N | 319 | 309 | 628 |
| Missing | 0 | 0 | 0 |
| Mean (SD) | 4.48 (0.541) | 4.45 (0.520) | 4.47 (0.531) |
| Median | 4.30 | 4.25 | 4.28 |
| Range (min-max) | 2.3-8.7 | 1.0-6.9 | 1.0-8.7 |

| Parameter<br>Category/ Statistics | MabionCD20<br>(N=319) | MabThera<br>(N=309) | Total<br>(N=628) |
|---|---|---|---|
| **Duration of infusion 2 [h]** | | | |
| N | 315 | 304 | 619 |
| Missing | 4 | 5 | 9 |
| Mean (SD) | 3.50 (0.593) | 3.52 (0.651) | 3.51 (0.621) |
| Median | 3.33 | 3.31 | 3.32 |
| Range (min-max) | 1.5-6.5 | 1.5-6.6 | 1.5-6.6 |
| **Total dose of study medication [mg]** | | | |
| N | 318 | 309 | 627 |
| Missing | 1 | 0 | 1 |
| Mean (SD) | 1987.4 (111.62) | 1980.9 (156.02) | 1984.2 (135.26) |
| Median | 2000.0 | 2000.0 | 2000.0 |
| Range (min-max) | 1000-2000 | 100-2000 | 100-2000 |

Source: Table 14.3.1
SD = Standard deviation, min = Minimum, max = Maximum
Patients were analyzed according to the treatment that they actually received.

Of the 389 patients who received a second course of treatment during the open-label study period, 385 (99.0%) received 2 infusions of treatment as in the first course of treatment, irrespective of the type of treatment. Four patients overall (1.0%) received only 1 infusion. The median infusion duration was similar in across treatment groups.

**Table: Exposure to study medication: number and duration of infusion, and dose (open-label study period, patients who received a second course of treatment) – SAF (excl. Bosnia)**

| Parameter Category/ Statistics | MabionCD20 after MabThera (N=81) | MabThera after MabionCD20 (N=117) | MabionCD20 constantly (N=79) | MabThera constantly (N=112) | Total (N=389) |
|---|---|---|---|---|---|
| **Number of infusions [n (%)]** | | | | | |
| 3 | 1 (1.2%) | 0 (0.0%) | 2 (2.5%) | 1 (0.9%) | 4 (1.0%) |
| 4 | 80 (98.8%) | 117 (100.0%) | 77 (97.5%) | 111 (99.1%) | 385 (99.0%) |
| **Duration of infusion 3 [h]** | | | | | |
| N | 81 | 116 | 79 | 112 | 388 |
| Missing | 0 | 1 | 0 | 0 | 1 |
| Mean (SD) | 3.71 (0.533) | 3.81 (0.722) | 3.71 (0.627) | 3.79 (0.781) | 3.76 (0.686) |
| Median | 3.33 | 3.53 | 3.38 | 3.50 | 3.50 |
| Range (min-max) | 3.0-4.5 | 2.3-6.4 | 1.7-5.6 | 2.0-6.7 | 1.7-6.7 |
| **Duration of infusion 4 [h]** | | | | | |
| N | 80 | 117 | 77 | 111 | 385 |
| Missing | 1 | 0 | 2 | 1 | 4 |
| Mean (SD) | 3.31 (0.179) | 3.51 (0.790) | 3.31 (0.192) | 3.56 (0.826) | 3.44 (0.641) |
| Median | 3.25 | 3.33 | 3.25 | 3.33 | 3.25 |
| Range (min-max) | 3.0-4.3 | 1.5-7.2 | 3.0-4.5 | 1.5-6.7 | 1.5-7.2 |
| **Total dose of study medication [mg]** | | | | | |
| N | 81 | 117 | 79 | 112 | 389 |
| Missing | 0 | 0 | 0 | 0 | 0 |
| Mean (SD) | 1987.7 (111.11) | 1991.5 (65.09) | 1974.7 (158.09) | 1991.1 (94.49) | 1987.1 (106.92) |
| Median | 2000.0 | 2000.0 | 2000.0 | 2000.0 | 2000.0 |
| Range (min-max) | 1000-2000 | 1500-2000 | 1000-2000 | 1000-2000 | 1000-2000 |

Source: Table 14.3.4
SD = Standard deviation, min = Minimum, max = Maximum
Patients were analyzed according to the treatment that they actually received.

In study **MabionCD20-002NHL**, 100 patients in the MabionCD20 group (100%) and 40 patients in the MabThera group (100%) received the first infusion (see Table below). The majority of patients (120 [85%]) completed the 8-cycle treatment schedule (85% in the MabionCD20 group and 87.5% in MabThera group). 70.7% (99 of 140) patients treated completed the Week 46 follow-up (70% in the MabionCD20 group and 72.5% in the MabThera group).

**Table: Exposure to study medication: Number of infusions, duration of infusion (min)**

| Visit | Cycle | Parameter | Total | MabionCD20 | Mabthera |
|---|---|---|---|---|---|
| V1 | 1 | Number of Infusions, n (%) | 140 (100.0) | 100 (100.0) | 40 (100.0) |
| | | Mean duration (SD), min | 222.6 (42) | 226.2 (43.7) | 213.5 (36.6) |
| | | Median duration (min-max), min | 214.5 (60-420) | 215 (136-420) | 210 (60-303) |
| V4 | 2 | Number of Infusions, n (%) | 137 (97.9) | 98 (98.0) | 39 (97.5) |
| | | Mean duration (SD), min | 160.1 (26.5) | 159.3 (25.6) | 161.9 (28.8) |
| | | Median duration (min-max) | 154 (120-240) | 155 (120-240) | 152 (128-230) |
| V5 | 3 | Number of Infusions, n (%) | 135 (96.4) | 96 (96.0) | 39 (97.5) |
| | | Mean duration (SD), min | 158.4 (26.3) | 157.1 (23.9) | 161.6 (31.6) |
| | | Median duration (min-max), min | 152 (109-240) | 153.5 (109-240) | 150 (125-240) |
| V6 | 4 | Number of Infusions, n (%) | 133 (95.0) | 94 (94.0) | 39 (97.5) |
| | | Mean duration (SD), min | 157.4 (24.7) | 156.5 (22.1) | 159.7 (30.2) |
| | | Median duration (min-max), min | 151 (120-240) | 152 (120-232) | 150 (125-240) |
| V8 | 5 | Number of Infusions, n (%) | 130 (92.9) | 93 (93.0) | 37 (92.5) |
| | | Mean duration (SD), min | 155.3 (20.9) | 156.1 (21.1) | 153.2 (20.5) |
| | | Median duration (min-max), min | 151 (122-235) | 152 (122-235) | 150 (125-210) |
| V9 | 6 | Number of Infusions, n (%) | 126 (90.0) | 90 (90.0) | 36 (90.0) |
| | | Mean duration (SD), min | 156 (22.4) | 155.9 (21.4) | 156.2 (25.2) |
| | | Median duration (min-max), min | 151 (125-240) | 153 (125-225) | 150 (127-240) |
| V10 | 7 | Number of Infusions, n (%) | 120 (85.7) | 86 (86.0) | 34 (85.0) |
| | | Mean duration (SD), min | 158 (26.9) | 157.7 (26) | 158.9 (29.4) |
| | | Median duration (min-max), min | 152.5 (121-270) | 153.5 (125-270) | 150 (121-240) |
| V11 | 8 | Number of Infusions, n (%) | 119 (85.0) | 85 (85.0) | 34 (85.0) |
| | | Mean duration (SD), min | 154.5 (22.2) | 154.4 (22.2) | 154.6 (22.6) |
| | | Median duration (min-max), min | 150 (90-238) | 153 (90-238) | 150 (121-210) |

## Adverse events

### MabionCD20-001RA

Completeness of AE data

When assessing the adverse event data AE underreporting needs to be taken into account. AE underreporting was noted as major findings during the GCP inspections of two sites (see section 3.3.3 of the Integrated Inspection Report). This included an infusion reaction at one site, individual events of pain at the other site and clinically significant laboratory events at both sites.

TEAE rates recorded during the double-blind study period by country and treatment arm vary from 30% and 20.0%, Serbia, to 55.9% and 56.3%, Ukraine (Table 1 below). TEAE rates recorded during the double-blind study period by site vary considerably more, from 0.0% to 100%, partially due to low numbers of patients per site. Numbers and percentages of recorded AEs are unexpectedly low in certain sites when compared to other sites of the respective countries (Table 1 below). The 5 sites enrol 49 of 628 (7.8%) patients of the SAF population Bosnian sites excluded.

Even when taking into account the lower overall TEAE incidences during the open-label study period, it is of note that certain sites did not record a single TEAE in 8 and 6 patients, respectively, over the study period of 48 Weeks. For comparison, the third Serbian site reported AEs in 10 of 26 patients during the double-blind period alone. A country-specific effect seems therefore rather unlikely.

Table 1 TEAEs by country and site (double-blind study period) - SAF updated

| | Treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | MabionCD20 | | | | MabThera | | | |
| Country/Site | N | AE n | Patient n | Patient % | N | AE n | Patient n | Patient % |
| ALL COUNTRIES | 359 | 261 | 146 | (40.7%) | 349 | 269 | 143 | (41.0%) |
| BOSNIA AND HERZEGOVINA | 40 | 15 | 10 | (25.0%) | 40 | 32 | 13 | (32.5%) |
| [redacted] | 4 | 1 | 1 | (25.0%) | 5 | 1 | 1 | (20.0%) |
| | 18 | 4 | 2 | (11.1%) | 18 | 3 | 3 | (16.7%) |
| | 6 | 5 | 5 | (83.3%) | 6 | 16 | 5 | (83.3%) |
| | 8 | 0 | 0 | (0.0%) | 7 | 1 | 1 | (14.3%) |
| | 4 | 5 | 2 | (50.0%) | 4 | 11 | 3 | (75.0%) |
| GEORGIA | 86 | 39 | 28 | (32.6%) | 86 | 43 | 30 | (34.9%) |
| [redacted] | 13 | 2 | 2 | (15.4%) | 12 | 3 | 2 | (16.7%) |
| | 8 | 4 | 3 | (37.5%) | 8 | 3 | 3 | (37.5%) |
| | 10 | 14 | 8 | (80.0%) | 11 | 14 | 8 | (72.7%) |
| | 17 | 6 | 5 | (29.4%) | 17 | 5 | 5 | (29.4%) |
| | 20 | 3 | 3 | (15.0%) | 21 | 5 | 4 | (19.0%) |
| | 12 | 7 | 4 | (33.3%) | 12 | 10 | 5 | (41.7%) |
| | 6 | 3 | 3 | (50.0%) | 5 | 3 | 3 | (60.0%) |
| LITHUANIA | 2 | 0 | 0 | (0.0%) | 2 | 2 | 1 | (50.0%) |
| [redacted] | 2 | 0 | 0 | (0.0%) | 2 | 2 | 1 | (50.0%) |
| POLAND | 140 | 116 | 62 | (44.3%) | 133 | 116 | 57 | (42.9%) |
| [redacted] | 2 | 5 | 2 | (100.0%) | 2 | 12 | 2 | (100.0%) |
| | 11 | 6 | 4 | (36.4%) | 10 | 4 | 2 | (20.0%) |
| | 6 | 13 | 3 | (50.0%) | 6 | 4 | 3 | (50.0%) |
| | 1 | 0 | 0 | (0.0%) | 2 | 4 | 2 | (100.0%) |
| | 3 | 0 | 0 | (0.0%) | 2 | 1 | 1 | (50.0%) |
| | 21 | 7 | 5 | (23.8%) | 21 | 4 | 3 | (14.3%) |
| | 5 | 1 | 1 | (20.0%) | 4 | 1 | 1 | (25.0%) |
| | 9 | 5 | 4 | (44.4%) | 9 | 5 | 3 | (33.3%) |
| | 19 | 18 | 13 | (68.4%) | 19 | 16 | 10 | (52.6%) |
| | 9 | 12 | 7 | (77.8%) | 9 | 12 | 6 | (66.7%) |
| | 2 | 5 | 2 | (100.0%) | | | | |
| | 5 | 0 | 0 | (0.0%) | 5 | 1 | 1 | (20.0%) |
| | 7 | 0 | 0 | (0.0%) | 8 | 1 | 1 | (12.5%) |
| | 12 | 16 | 9 | (75.0%) | 12 | 31 | 10 | (83.3%) |
| | 15 | 13 | 6 | (40.0%) | 15 | 14 | 8 | (53.3%) |
| | 3 | 0 | 0 | (0.0%) | 1 | 2 | 1 | (100.0%) |
| | 3 | 2 | 1 | (33.3%) | 4 | 1 | 1 | (25.0%) |
| | 1 | 1 | 1 | (100.0%) | | | | |
| | 2 | 0 | 0 | (0.0%) | 2 | 0 | 0 | (0.0%) |
| | 3 | 11 | 3 | (100.0%) | 2 | 3 | 2 | (100.0%) |
| | 1 | 1 | 1 | (100.0%) | | | | |

| | Treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | MabionCD20 | | | | MabThera | | | |
| Country/Site | N | AE n | Patient n | Patient % | N | AE n | Patient n | Patient % |
| SERBIA | 20 | 13 | 6 | (30.0%) | 20 | 5 | 4 | (20.0%) |
| [redacted] | 12 | 13 | 6 | (50.0%) | 14 | 5 | 4 | (28.6%) |
| [redacted] | 4 | 0 | 0 | (0.0%) | 4 | 0 | 0 | (0.0%) |
| [redacted] | 4 | 0 | 0 | (0.0%) | 2 | 0 | 0 | (0.0%) |
| UKRAINE | 71 | 78 | 40 | (56.3%) | 68 | 71 | 38 | (55.9%) |
| [redacted] | 4 | 5 | 4 | (100.0%) | 3 | 3 | 2 | (66.7%) |
| [redacted] | 4 | 2 | 2 | (50.0%) | 5 | 1 | 1 | (20.0%) |
| [redacted] | 4 | 1 | 1 | (25.0%) | 6 | 0 | 0 | (0.0%) |
| [redacted] | 9 | 16 | 7 | (77.8%) | 8 | 15 | 8 | (100.0%) |
| [redacted] | 12 | 30 | 9 | (75.0%) | 12 | 20 | 6 | (50.0%) |
| [redacted] | 10 | 11 | 8 | (80.0%) | 12 | 13 | 11 | (91.7%) |
| [redacted] | 3 | 3 | 2 | (66.7%) | 3 | 5 | 2 | (66.7%) |
| [redacted] | 8 | 4 | 2 | (25.0%) | 7 | 5 | 2 | (28.6%) |
| [redacted] | 9 | 3 | 2 | (22.2%) | 8 | 5 | 3 | (37.5%) |
| [redacted] | 2 | 1 | 1 | (50.0%) | 1 | 2 | 1 | (100.0%) |
| [redacted] | 2 | 1 | 1 | (50.0%) | | | | |
| [redacted] | 4 | 1 | 1 | (25.0%) | 3 | 2 | 2 | (66.7%) |

Double-blind study period

Generally, very small and non-significant differences (ranging from -0.6% to 1.3%) between the MabionCD20 and MabThera groups were found for all TEAEs, severe/life threatening TEAEs, related TEAEs, and related severe/life threatening TEAEs, TEAEs leading to reduction of dose, treatment emergent SAEs (TESAEs), TEAEs leading to interruption of dose, TEAEs leading to permanent discontinuation (withdrawal) of trial medication, related TEAEs leading to permanent discontinuation of trial medication (see Table below).The overall rates of all treatment-emergent adverse events (TEAEs) that started after the first infusion of study drug and occurred during the course of the double-blind study period were 42.6% in the MabionCD20 group (136/319 patients experiencing 246 TEAEs) and 42.1% in the MabThera group (130/309 patients experiencing 237 TEAEs).

The 5 SOCs with the highest frequencies of patients with TEAEs in descending order were

- Infections and infestations 13.8%, investigations 9.1%, general disorders and administration site conditions 6.6%, blood and lymphatic system disorders 5.0% and skin and subcutaneous tissue disorders 4.4% in the MabionCD20 group, and
- Infections and infestations 14.9%, general disorders and administration site conditions 7.4%, investigations 6.1%, and blood and lymphatic system disorders and skin and subcutaneous tissue disorders 5.5% each in the MabThera group.

The 5 most common TEAEs in descending order were

- Infusion related reaction 4.7 %, Upper respiratory tract infection 2.8%, UTI, Hypertension, Leukopenia and Low density lipoprotein increased 2.2% each in the MabionCD20 group, and
- Infusion related reaction 3.6%, Influenza and Headache 2.9% each, UTI and Leukopenia 2.3% each in the MabThera group.

**Table: Overview of adverse events (double-blind study period) – SAF (excl. Bosnia)**

| | MabionCD20 (N=319) | | | MabThera (N=309) | | | Difference | |
|---|---|---|---|---|---|---|---|---|
| | AE n | Patient n | Patient (%) | AE n | Patient n | Patient (%) | % | 95% CI * |
| All AEs | 251 | 140 | (43.9%) | 247 | 133 | (43.0%) | -0.8% | [-8.6% ; 6.9%] |
| Pre-treatment AEs | 5 | 4 | (1.3%) | 10 | 9 | (2.9%) | 1.7% | [-0.7% ; 4.0%] |
| Treatment emergent AEs (TEAEs) | 246 | 136 | (42.6%) | 237 | 130 | (42.1%) | -0.6% | [-8.3% ; 7.1%] |
| Severe TEAEs[a] | 4 | 4 | (1.3%) | 7 | 6 | (1.9%) | 0.7% | [-1.4% ; 2.8%] |
| Related TEAEs[b] | 136 | 90 | (28.2%) | 138 | 88 | (28.5%) | 0.3% | [-6.8% ; 7.3%] |
| Related severe TEAEs[a,b] | 2 | 2 | (0.6%) | 5 | 4 | (1.3%) | 0.7% | [-1.1% ; 2.4%] |
| Serious AEs (SAEs) (including pre-treatment SAEs) | 7 | 7 | (2.2%) | 6 | 6 | (1.9%) | -0.3% | [-2.6% ; 2.1%] |
| Treatment emergent SAEs (TESAEs) | 7 | 7 | (2.2%) | 6 | 6 | (1.9%) | -0.3% | [-2.6% ; 2.1%] |
| Severe TESAEs[a] | 2 | 2 | (0.6%) | 2 | 2 | (0.6%) | 0.0% | [-1.5% ; 1.5%] |
| Related TESAEs[b] | 1 | 1 | (0.3%) | 2 | 2 | (0.6%) | 0.3% | [-1.0% ; 1.7%] |
| TEAEs leading to reduction of dose | 6 | 6 | (1.9%) | 8 | 8 | (2.6%) | 0.7% | [-1.7% ; 3.2%] |
| TEAEs leading to interruption of dose | 11 | 9 | (2.8%) | 12 | 11 | (3.6%) | 0.7% | [-2.1% ; 3.6%] |
| TEAEs leading to permanent discontinuation (withdrawal) of study medication | 4 | 3 | (0.9%) | 8 | 7 | (2.3%) | 1.3% | [-0.8% ; 3.5%] |
| Related TEAEs leading to permanent discontinuation of study medication[b] | 0 | 0 | (0.0%) | 7 | 6 | (1.9%) | 1.9% | [0.2% ; 3.7%] |
| AEs leading to death (i.e. outcome of AE is fatal) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0.0% | [-0.9% ; 0.9%] |
| TEAEs leading to death | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0.0% | [-0.9% ; 0.9%] |
| Related TEAEs leading to death[b] | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0.0% | [-0.9% ; 0.9%] |

Source: Table 14.4.1.1
CI = confidence interval; Diff. = Difference Patient % (MabThera – MabionCD20)
[a] Severity of AEs was classified as 1=mild, 2=moderate, 3=severe, 4=life-threatening
[b] A TEAE was analyzed as related to study medication (i.e. as adverse drug reaction, ADR) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite', or if the relationship to study treatment was missing
* Two-sided 95% CI for the difference in proportions based on the Agresti-Caffo method [38].
Treatment groups are displayed according to treatment received.

In 28.2% of patients in the MabionCD20 and 28.5% in the MabThera group, TEAEs were suspected to be related to study medication. In the MabionCD20 group, most frequently recorded drug-related PTs were infusion related reaction (15 of 319 patients [4.7%]), and pruritus and leukopenia (6 patients) and in the MabThera group infusion related reaction (11 of 309 patients [3.6%]) and leukopenia (6 patients). There were no clinically meaningful differences in the incidences and qualitative profile of related adverse events by MedDRA SOC between the two treatment groups.

Most TEAEs were mild or moderate; only few were severe/life threatening (4 TEAEs in 4 patients in the MabionCD20 and 7 TEAEs in 6 patients in the MabThera group).

Adverse events after Week 24 before the third infusion

Nine patients who received a second course of treatment reported at least one AE after the Week 24 visit but before the third infusion of MabionCD20 or MabThera. These 15 AEs are not included in the AE tables for the open-label study period.

Open-label study period – patients who received a second treatment course (N=389)

The overall rates of all TEAEs that started after the first infusion of study drug of the second course of treatment and occurred during the course of the open-label study period were 21.0% in the MabionCD20 after MabThera group (17/81 patients experiencing 30 TEAEs), 32.5% in the MabThera after MabionCD20 group (38/117 patients experiencing 66 TEAEs), 24.1% in the group receiving MabionCD20 constantly (19/79 patients experiencing 36 TEAEs), and 38.4% in the group receiving MabThera constantly (43/112 patients experiencing 67 TEAEs) (see Table below). Thus, there is an imbalance, difference > 10.0%, between respective treatment groups, in disfavor of MabThera. TEAEs most commonly affected the SOCs infections and infestations, investigations, blood and lymphatic system disorders, and general disorders and administration site conditions as during the double-blind study period. However, differences in frequencies of AEs in SOCs general disorders and administration site conditions (mainly infusion related and infusion site reactions) and investigations contributed to the imbalance noted between treatment groups.

Adverse events occurring in 3 or more patients were:

- Infusion related reaction (3.8%), bronchitis and influenza (3.8%) in the MabionCD20 constantly group, and
- Infusion site reaction (6.3%), hypersensitivity, sinusitis and blood triglycerides increased (2.7% each) in the MabThera constantly group.

**Table: Overview of adverse events (open-label study period, patients who received a second course of treatment) – SAF (excl. Bosnia)**

| | MabionCD20 after MabThera (N=81) | | | MabThera after MabionCD20 (N=117) | | | MabionCD20 constantly (N=79) | | | MabThera constantly (N=112) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AE n | Pat. n | Pat. % | AE n | Pat. n | Pat. % | AE n | Pat. n | Pat. % | AE n | Pat. n | Pat. % |
| Treatment emergent AEs (TEAEs) | 30 | 17 | (21.0%) | 66 | 38 | (32.5%) | 36 | 19 | (24.1%) | 67 | 43 | (38.4%) |
| Severe TEAEs[a] | 3 | 2 | (2.5%) | 1 | 1 | (0.9%) | 1 | 1 | (1.3%) | 1 | 1 | (0.9%) |
| Related TEAEs[b] | 15 | 10 | (12.3%) | 45 | 26 | (22.2%) | 18 | 13 | (16.5%) | 41 | 29 | (25.9%) |
| Related severe TEAEs[a,b] | 2 | 2 | (2.5%) | 0 | 0 | (0.0%) | 1 | 1 | (1.3%) | 0 | 0 | (0.0%) |
| Treatment emergent SAEs (TESAEs) | 2 | 2 | (2.5%) | 0 | 0 | (0.0%) | 1 | 1 | (1.3%) | 0 | 0 | (0.0%) |
| Severe TESAEs[a] | 1 | 1 | (1.2%) | 0 | 0 | (0.0%) | 1 | 1 | (1.3%) | 0 | 0 | (0.0%) |
| Related TESAEs[b] | 1 | 1 | (1.2%) | 0 | 0 | (0.0%) | 1 | 1 | (1.3%) | 0 | 0 | (0.0%) |
| TEAEs leading to reduction of dose | 0 | 0 | (0.0%) | 3 | 3 | (2.6%) | 0 | 0 | (0.0%) | 8 | 8 | (7.1%) |
| TEAEs leading to interruption of dose | 0 | 0 | (0.0%) | 2 | 2 | (1.7%) | 2 | 2 | (2.5%) | 2 | 2 | (1.8%) |
| TEAEs leading to permanent discontinuation (i.e. withdrawal) of study medication | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 1 | 1 | (0.9%) |
| Related TEAEs leading to permanent discontinuation of study medication[b] | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 1 | 1 | (0.9%) |
| TEAEs leading to death | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) |
| Related TEAEs leading to death[b] | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) | 0 | 0 | (0.0%) |

Source: Table 14.4.3.1
Pat. = Patient
[a] severity of AEs was classified as 1=mild, 2=moderate, 3=severe, 4=life-threatening
[b] A TEAE was analyzed as related to study medication (i.e. as adverse drug reaction, ADR) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite', or if the relationship to study treatment was missing

Open-label study period – patients not re-treated (N=215)

In comparison, overall rates of all TEAEs that occurred during the course of the open-label study period in those 215 patients who did not receive a second course of treatment were low, 11.8% in the MabionCD20 group (13/110 patients experiencing 21 TEAEs) and 9.5% in the MabThera group (10/105 patients experiencing 17 TEAEs).

**MabionCD20-002NHL**

Overall, there were differences > 5 to >10% in 8 of 12 TEAE categories with the higher frequencies reported for the MabionCD20 treatment group compared to the MabThera treatment group (see Table below).

69.3% of the patients experienced 1 or more TEAE, 71.0% in the MabionCD20 group and 65.0% in the MabThera group. TEAEs were mostly recorded during the double-blind period. 619 TEAEs were recorded in 69.3% of patients treated with either MabionCD20 or MabThera over the whole study period up to Week 46 compared to 608 recorded in 68.8% of patients during the double-blind period.

On average, patients in the MabionCD20 group experienced slightly more TEAEs than patients in the MabThera group, 6.5 TEAEs (463 TEAEs in 71 patients) in the MabionCD20 group compared to 5.8 (145 TEAEs in 25 patients) in the MabThera group during the double-blind period.

The 5 SOCs with the highest frequencies of patients with TEAEs in descending order were:

- Blood and lymphatic system disorders 46%, infections and infestations 24%, investigations and skin and subcutaneous tissue disorders 16% each, and general disorders 15 % in the MabionCD20 group, and
- Blood and lymphatic system disorders 35.0%, investigations 17.5%, and gastrointestinal disorders, infections and infestations, and skin and subcutaneous tissue disorders 15% each in the MabThera group.

There was no individual AE contributing with a difference of ≥ 5% to the overall difference of 11.0% in frequencies between the MabionCD20 treatment group and the MabThera treatment group in the SOC blood and lymphatic system disorders, whereas the AE pneumonia (8% in MabionCD20 vs 0% in MabThera group) contributed to the overall difference of 9.0% in frequencies between the MabionCD20 treatment group and the MabThera treatment group in the SOC infections and infestations.

11.0% of patients experienced cardiac AEs in the MabionCD20 treatment group as compared to 5.0% of patients in the MabThera treatment group. Except for cardiac failure and supraventricular tachycardia cardiac AEs occurred only once in the MabionCD20 treatment group. The number of patients with cardiac or vascular disorders at baseline was slightly higher in the MabionCD20 group (28% each) compared to the MabThera group (22.5% each).

The proportion of patients experiencing ≥1 related TEAE was higher in the MabionCD20 than in the MabThera group (53.0% vs 42.5%).

The 4 SOCs with the highest frequencies of patients with related TEAEs in descending order were

- Blood and lymphatic system disorders 33.0%, skin and subcutaneous tissue disorders 16.0%, investigations 12.0%, and infections and infestations 11.0% in the MabionCD20 group, and
- Blood and lymphatic system disorders 32.5%, investigations 17.5%, skin and subcutaneous tissue disorders 12.5% and infections and infestations 7.5% in the MabThera group.

Differences between the two treatment groups exceeded 5% for 2 of the SOCs:

- 6% of the patients in MabionCD20 group had cardiac AEs compared to none in MabThera group,
- 12% of the patients in MabionCD20 group had related AEs in the SOC investigations compared to 17.5% in MabThera group.

Overall, the proportion of patients experiencing one or more severe TEAE was higher in the MabionCD20 group compared to the MabThera group (40% vs 22.5%), the difference being 17.5% (95%CI 1.39; 33.61). This difference was most apparent in the SOC Blood and Lymphatic Disorders with higher frequencies for severe neutropenia and leukopenia in the MabionCD20 group. Frequencies of severe infections were low in both treatment groups.

**Table: Overview of adverse events up to Week 46 – SAF**

| | Total N=140 | MabionCD20 N=100 | MabThera N=40 | |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | % difference (95% CI)* |
| All AEs | 98 (70.0) | 71 (71.0) | 27 (67.5) | 3.5 (-13.52–20.52) |
| Pre-treatment AEs | 5 (3.6) | 3 (3.0) | 2 (5.0) | -2 (-9.54–5.54) |
| Serious AEs (SAEs) (including pre-treatment SAEs) | 24 (17.1) | 19 (19.0) | 5 (12.5) | 6.5 (-6.31–19.31) |
| Treatment emergent AE | 97 (69.3) | 71 (71.0) | 26 (65.0) | 6 (-11.25–23.25) |
| Treatment emergent SAEs (TESAEs) | 24 (17.1) | 19 (19.0) | 5 (12.5) | 6.5 (-6.31–19.31) |
| Severe TEAEs[a] | 49 (35.0) | 40 (40.0) | 9 (22.5) | 17.5 (1.39–33.61) |
| Related TEAEs[b] | 70 (50.0) | 53 (53.0) | 17 (42.5) | 10.5 (-7.68–28.68) |
| Related severe TEAEs | 38 (27.1) | 29 (29.0) | 9 (22.5) | 6.5 (-9.2–22.2) |
| Related serious TEAEs | 15 (10.7) | 13 (13.0) | 2 (5.0) | 8 (-1.44–17.44) |
| TEAEs leading to reduction of dose | 1 (0.7) | 0 (0.0) | 1 (2.5) | -2.5 (-7.34–2.34) |
| TEAEs leading to interruption of dose | 9 (6.4) | 6 (6.0) | 3 (7.5) | -1.5 (-10.9–7.9) |
| TEAEs leading to permanent discontinuation (i.e., withdrawal) of study medication | 10 (7.1) | 9 (9.0) | 1 (2.5) | 6.5 (-0.91–3.91) |
| Related TEAEs leading to permanent discontinuation of study medication | 4 (2.9) | 3 (3.0) | 1 (2.5) | 0.5 (-5.38–6.38) |
| AEs leading to death (i.e., outcome of AE is fatal) | 8 (5.7) | 8 (8.0) | 0 (0.0) | 8 (2.68–13.32) |
| TEAEs leading to death | 8 (5.7) | 8 (8.0) | 0 (0.0) | 8 (2.68–13.32) |
| Related TEAEs leading to death | 2 (1.4)[1] | 2 (2.0) | 0 (0.0) | 2 (-0.74–4.74) |

Source: Tables 14.3.1
AE = adverse event; TEAEs =treatment emergent adverse events; CI = confidence interval
[a] At least severe. Severity of AEs was classified as 1=mild, 2=moderate, 3=severe, 4=life-threatening.
[b] A TEAE was analysed as related to study medication (i.e., as adverse drug reaction) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite', or if the relationship to study treatment was missing
* Two-sided 95% CI for the difference in proportions based on the Clopper-Pearson method [7].
[1]unlikely related, see Section 12.3

## Serious adverse events and deaths

### MabionCD20-001RA

There were 7 serious TEAEs reported in 7 patients (2.2%) of the MabionCD20 group and 6 serious TEAEs in 6 patients (1.9%) of the MabThera group during the double-blind study period of the first 24 weeks.
3 of the 14 were classified as related to drug treatment (1 SAE of "neutrophil count decreased" in 1 patient in the MabionCD20 group and 1 SAE of "gastroenteritis" and 1 SAE of "squamous cell carcinoma of the lung" in 2 patients in the MabThera group). All but 2 patients recovered (1 patient with Squamous cell carcinoma of lung in MabThera group and 1 patient with Breast cancer in MabionCD20 group).

There were only 4 SAEs reported in 4 patients during the open-label study period resulting in an incidence of 0.67% (4 of overall 604 patients). These were SAEs of UTI and nephrolithiasis in 2 patients who received Mabthera after MabionCD20, 1 SAE of pleurisy in a patient who received

MabionCD20 for both treatment courses, and 1 SAE of knee operation in a patient who did not receive a second course.

No patient died during the course of the 24-week double-blind phase of the study and during the open-label study period up to 48 weeks.

**Table: Incidence of serious TEAEs by SOC and PT (double-blind study period) – SAF (excl. Bosnia)**

| | MabionCD20 (N=319) | | | MabThera (N=309) | | | Total (N=628) | | |
|---|---|---|---|---|---|---|---|---|---|
| MedDRA SOC, MedDRA PT | AE n | Patient n | Patient % | AE n | Patient n | Patient % | AE n | Patient n | Patient % |
| **Any** | **7** | **7** | **(2.2%)** | **6** | **6** | **(1.9%)** | **13** | **13** | **(2.1%)** |
| **Blood and lymphatic system disorders** | **1** | **1** | **(0.3%)** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.2%)** |
| Anaemia | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Infections and infestations** | **1** | **1** | **(0.3%)** | **2** | **2** | **(0.6%)** | **3** | **3** | **(0.5%)** |
| Chronic sinusitis | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |
| Gastroenteritis | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |
| Pneumonia | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Injury, poisoning and procedural complications** | **1** | **1** | **(0.3%)** | **1** | **1** | **(0.3%)** | **2** | **2** | **(0.3%)** |
| Humerus fracture | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |
| Joint injury | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Investigations** | **1** | **1** | **(0.3%)** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.2%)** |
| Neutrophil count decreased | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **1** | **1** | **(0.3%)** | **1** | **1** | **(0.3%)** | **2** | **2** | **(0.3%)** |
| Breast cancer | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| Squamous cell carcinoma of lung | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |
| **Renal and urinary disorders** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.3%)** | **1** | **1** | **(0.2%)** |
| Renal colic | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |
| **Respiratory, thoracic and mediastinal disorders** | **1** | **1** | **(0.3%)** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.2%)** |
| Idiopathic pulmonary fibrosis | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Surgical and medical procedures** | **1** | **1** | **(0.3%)** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.2%)** |
| Cataract operation | 1 | 1 | (0.3%) | 0 | 0 | (0.0%) | 1 | 1 | (0.2%) |
| **Vascular disorders** | **0** | **0** | **(0.0%)** | **1** | **1** | **(0.3%)** | **1** | **1** | **(0.2%)** |
| Cerebral ischaemia | 0 | 0 | (0.0%) | 1 | 1 | (0.3%) | 1 | 1 | (0.2%) |

Source: Table 14.4.1.4
SOC=system organ class, PT=preferred term
TEAEs by SOC are presented in alphabetical order
Patients were analyzed according to the treatment they actually received.

**MabionCD20-002NHL**

There is a numerical imbalance (>5% difference) in frequencies of SAEs in the MabionCD20 group (19.0%) compared to the Mabthera treatment group (12.5%).

SAEs occurred most commonly in the SOCs Cardiac Disorders (MabionCD20 5.0% vs. MabThera 0.0%) and Infections and infestations (MabionCD20 5.0% vs. MabThera 2.5%), followed by Gastrointestinal Disorders (MabionCD20 3.0% vs. MabThera 0.0%) and Neoplasms, malignant, benign and unspecified (MabionCD20 3.0% vs. MabThera 0.0%). There are also 2 SAEs of "hypotension" in the MabionCD20 group.

The spectrum of SAEs reported generally reflects both the established adverse reaction profile of rituximab, the adverse events associated with the underlying disease and the chemotherapy.

There were 8 (8.0%) fatal SAEs in the MabionCD20 treatment group versus none (0.0%) in the MabThera treatment group, the difference being 8.0% (95%CI 2.68; 13.32).

Preferred Terms of the 8 fatal SAEs were Non-Hodgkin's lymphoma (n=3), hypotension (n=2), and death, cardiovascular insufficiency and pancreatic necrosis (n=1 each). Investigator's assessment of causal relationship to study drug treatment was "not related" for all fatal SAEs with the exception of the fatal SAEs of pancreatic necrosis and death, which had been assessed as "unlikely related".

Death due to progressive disease is plausibly documented for 2 subjects. Causes of death due to progressive disease, pulmonary embolism and pulmonary oedema and of pulmonary embolism with "acute pulmonary heart" and "diffusion" of Non-Hodgkin's lymphoma, respectively, were established by autopsy in 2 patients. An alternative explanation of fatal drug-induced pancreatitis unrelated to MabionCD20 and /or progression of disease may be considered in one patient. No information is available on the course of disease after hospital admission in 2 patients, (PT terms of fatal SAEs of hypotension and cardiovascular insufficiency, resp.). Death of unknown reason occurred 103 days after last cycle of treatment with preceding symptoms of stroke of unknown temporal relationship to death in one patient.

**Table: Number of patients experiencing one or more treatment-emergent serious adverse events by SOC and PT**

| SOC[1] | PT[2] | Total N=140 n (%) | MabionCD20 N=100 n (%) | MabThera N=40 n (%) |
|---|---|---|---|---|
| All TESAEs | | 24 (17.1) | 19 (19.0) | 5 (12.5) |
| Blood and lymphatic system disorders | | 3 (2.1) | 2 (2.0) | 1 (2.5) |
| | Anaemia | 2 (1.4) | 1 (1.0) | 1 (2.5) |
| | Febrile neutropenia | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| Cardiac disorders | | 5 (3.6) | 5 (5.0) | 0 (0.0) |
| | Atrial fibrillation | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Atrial flutter | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Cardiac failure | 2 (1.4) | 2 (2.0) | 0 (0.0) |
| | Cardiovascular insufficiency | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Myocardial infarction | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| Gastrointestinal disorders | | 3 (2.1) | 3 (3.0) | 0 (0.0) |
| | Nausea | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Pancreatic necrosis | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Pancreatitis acute | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| General disorders and administration site conditions | | 2 (1.4) | 1 (1.0) | 1 (2.5) |
| | Death | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Disease progression | 1 (0.7) | 0 (0.0) | 1 (2.5) |
| Infections and infestations | | 6 (4.3) | 5 (5.0) | 1 (2.5) |
| | Bronchitis | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Lung infection | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Pneumonia | 3 (2.1) | 3 (3.0) | 0 (0.0) |
| | Sepsis | 1 (0.7) | 0 (0.0) | 1 (2.5) |
| Injury, poisoning and procedural complications | | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Brain contusion | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| | Patella fracture | 1 (0.7) | 1 (1.0) | 0 (0.0) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | 3 (2.1) | 3 (3.0) | 0 (0.0) |
| | Non-Hodgkin's lymphoma | 3 (2.1) | 3 (3.0) | 0 (0.0) |
| Nervous system disorders | | 1 (0.7) | 0 (0.0) | 1 (2.5) |
| | Haemorrhagic stroke | 1 (0.7) | 0 (0.0) | 1 (2.5) |
| Respiratory, thoracic and mediastinal disorders | | 3 (2.1) | 2 (2.0) | 1 (2.5) |
| | Bronchospasm | 1 (0.7) | 0 (0.0) | 1 (2.5) |
| | Pulmonary embolism | 2 (1.4) | 2 (2.0) | 0 (0.0) |
| Vascular disorders | | 2 (1.4) | 2 (2.0) | 0 (0.0) |
| | Hypotension | 2 (1.4) | 2 (2.0) | 0 (0.0) |

Source: Table 14.3.1.8

SOC = system organ class; PT = preferred term; TEAEs = treatment emergent adverse events

[1]Different related treatment emergent serious adverse events within the same preferred term and system organ class and involving the same patient have been counted as one. A single patient could appear in multiple classes.

[2] PT with a frequency lower than 2% are pooled and displayed as 'other' for more than 5% of patients reporting an TEAE allocated to a SOC. Otherwise individual PTs are not displayed as other with the infusion related reactions.

**Table Listing of fatal treatment emergent serious adverse events (adapted)**

| Subject | Sex | Age (yrs) | AA | IPI[3] | Preferred term | SAE term | Duration (days) | Related-ness[1] | Cycle (inf. day) | Timing of onset[2] (days) | Treatment | Response at Week 11 (Day 71) | Dose at time of event [mg/m2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | | 3 | 3 | Cardiovascular insufficiency | Cardiovascular insufficiency | 19 | None | 5 (85) | 10 | MabionCD20 | Complete | 379.9 |
| [redacted] | | | 3 | 2 | Non-Hodgkin's lymphoma | Death due to progression of the disease | 0 | None | 5 (85) | 6 | MabionCD20 | Progressive | 399.6 |
| [redacted] | | | 4 | 4 | Hypotension | Hypotension with fatal outcome | 0 | None | 1 (1) | 10 | MabionCD20 | Not assessed | 375.2 |
| [redacted] | | | 4 | 3 | Hypotension | Hypotension with fatal outcome | 3 | None | 5 (85) | 9 | MabionCD20 | Partial | 375.5 |
| [redacted] | | | 4 | 3 | Non-Hodgkin's lymphoma | Sudden death due to progression of Non-Hodgkin's Lymphoma, IV st. | 0 | None | 1 (1) | 12 | MabionCD20 | Not assessed | 375.2 |
| [redacted] | | | 3 | 3 | Pancreatic necrosis | Acute pancreatic necrosis | 4 | Unlikely | 6 (106) | 4 | MabionCD20 | Complete | 393.0 |
| [redacted] | | | 4 | 3 | Non-Hodgkin's lymphoma | Progression of NHL | 0 | None | 4 (64) | 41 | MabionCD20 | Partial | 377.9 |
| [redacted] | | | 4 | 4 | Death | Unknown reason | 0 | Unlikely | 8 (256) | 103 | MabionCD20 | Partial | 374.9 |

Source: Appendix 14.3.2.1
AA = Ann Arbor staging score; BSA = Body Surface Area; conc = concentration; F = female; inf = infusion; IPI = International Prognostic Index; M = male; yrs = years
[1]A TESAE was analysed as related to study medication (i.e., as adverse drug reaction) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite', or if the relationship to study treatment was missing
[2]Timing of onset of the adverse event in relation to the last dose of MabionCD20 or MabThera
[3] 2 = low intermediate risk, 3 = high intermediate risk, 4 = high risk


| Preferred term | SAE term | Duration (days) | Related-ness[1] | Cycle (inf. day) | Timing of onset[2] (days) | Treatment | Response at Week 11 (Day 71) | Dose at time of event [mg/m2] |
|---|---|---|---|---|---|---|---|---|
| Cardiovascular insufficiency | Cardiovascular insufficiency | 19 | None | 5 (85) | 10 | MabionCD20 | Complete | 379.9 |
| Non-Hodgkin's lymphoma | Death due to progression of the disease | 0 | None | 5 (85) | 6 | MabionCD20 | Progressive | 399.6 |
| Hypotension | Hypotension with fatal outcome | 0 | None | 1 (1) | 10 | MabionCD20 | Not assessed | 375.2 |
| Hypotension | Hypotension with fatal outcome | 3 | None | 5 (85) | 9 | MabionCD20 | Partial | 375.5 |
| Non-Hodgkin's lymphoma | Sudden death due to progression of Non-Hodgkin's Lymphoma, IV st. | 0 | None | 1 (1) | 12 | MabionCD20 | Not assessed | 375.2 |
| Pancreatic necrosis | Acute pancreatic necrosis | 4 | Unlikely | 6 (106) | 4 | MabionCD20 | Complete | 393.0 |
| Non-Hodgkin's lymphoma | Progression of NHL | 0 | None | 4 (64) | 41 | MabionCD20 | Partial | 377.9 |
| Death | Unknown reason | 0 | Unlikely | 8 (256) | 103 | MabionCD20 | Partial | 374.9 |


Source: Appendix 14.3.2.1

1 TESAE was analysed as related to study medication (i.e., as adverse drug reaction) if the relationship to study treatment was documented as 'unlikely', 'possible', 'probable', or 'definite', or if the relationship to study treatment was missing

2 Timing of onset of the adverse event in relation to the last dose of MabionCD20 or MabThera

## Laboratory findings

### MabionCD20-001RA

No clinically relevant changes were apparent in the haematology and serum chemistry assessments (mean values and ranges, at baseline and each visit, and the corresponding mean changes, and shift analyses) between both treatment groups during the 24 week double-blind part of the study. Generally, the documented mean changes in any of the hematology and serum chemistry parameters from baseline through week 24 or week 48 appeared to be small and similar between the treatment groups, irrespective of a second course of treatment after 24 weeks.

Slight differences in the time course of mean ESR and CRP were noted between treatment groups which do not appear to be clinically relevant during the 24 week double-blind part of the study. Both ACPA and RF values decreased during the double-blind period of the study and further during the open-label study period in the patient groups that received a second course of treatment. In patients who did not receive a second course of treatment, the mean ACPA and RF values increased again between Week 24 and Week 48 of the study.

As regards to immunoglobulins, there was a tendency to lower mean values over time in both treatment arms during the 24 week double-blind part of the study, which continued further during the double-blind period of the study for the patient groups that received a second course of treatment.

Generally, proportions of patients with IgG and IgM values below the Lower Limit of Normal (ULN) were comparable between respective treatment groups at Week 24 and Week 48, proportions of patients with IgM below ULN at Week 48 being slightly higher in patients who received a second course of treatment compared to patients who did not receive a second course of treatment.

The assessments of vital signs did not reveal any clinically significant findings, with no considerable differences between the two treatment groups.

**MabionCD20-002NHL**

No clinically meaningful differences (mean counts/concentrations and number of patients outside the normal range) in laboratory parameters, haematology and serum chemistry, were apparent between both treatment groups.

Analysis of the shift in laboratory values did not reveal major differences between the treatment groups. In general, the number of patients with normal haematological parameters dropped with patient shifting to low values at Week 26, this was in particular the case for WBC count and more pronounced in the MabThera group. For platelet counts no clear shifts occurred.

The assessments of vital signs did not reveal any clinically significant findings and no considerable differences between the two treatment groups.

## Immunological events

**MabionCD20-001RA**

ADA-positive incidences were comparable between treatment groups at Week 24, MabionCD20 group 16.5% versus MabThera group 15.3%.

Frequencies of treatment-induced ADA (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA) at Week 24 were 14.2 % (45 of 316) in the MabionCD20 group and 13.4% (41 of 306) in the MabThera group.

In the MabThera group, NAb were solely detected at baseline, whereas in the MabionCD20 group 2 patients were found to be positive for NAb also at V3, V5 and V10 until Week 24. In both patients no immune related AE were identified. In the subset of patients who did not receive a second course of treatment, one patient in each treatment group was found to be NAb-positive during the whole study period of 48 weeks and was not NAb-positive at baseline.

Frequencies of preferred terms associated with infusion reactions or hypersensitivity were comparable between both treatment arms up to Week 24.

For patients who did not receive a second treatment course, ADA-positive incidences were comparable between treatment groups at Week 24, MabionCD20 group 12.1% versus MabThera group 11.8%, but higher in the MabThera group at Week 48, MabionCD20 group 18.8% versus MabThera group 25.8%.In the same subset of patients, frequencies of treatment-induced ADA were 21.8% (24 of 110 patients) in the MabionCD20 group and 23.8% % (25 of 105 patients) in the MabThera group over the whole study period.

Analysis of PTs of infusion reactions or immune-mediated events by ADA-status did not show differences considered clinically relevant.

Likewise, analysis of ADA and NAb testing and of associations between ADA-status and infusion-reactions or potential immune-mediated AEs performed for patients who received a second course of treatment did not show differences considered clinically relevant.

However, absolute number of patients per treatment group were comparatively small. To this purpose, the applicant conducted a pooled analysis of subjects who were not re-treated (110 in MabionCD20 and 105 in MabThera) and subjects who were re-treated with the same treatment they were randomised to, (did not switch the treatment at Week 24 - 79 in MabionCD20 constantly and 112 in MabThera constantly). The proportion of patients with ADA positive response was 18.5% and 22.1% respectively under MabionCD20 and MabThera groups. The proportion of patients with persistently

positive ADA response was slightly lower for MabionCD20 (11.6%) group as compared to the MabThera group (15.2%).

**MabionCD20-002NHL**

Frequencies of immunological adverse events were low and comparable.

None of the ADA positive patients had infusion related reactions or allergic or immune mediated AEs.

Frequencies of treatment induced ADAs up to Week 46 (i.e., not ADA positive at baseline but positive after treatment) were low, 6.1% (6 patients) in the MabionCD20 group and 1 (2.5%) in the MabThera group. Persistent ADA response was reported in 4 (4.0%) patients in the MabionCD20 group compared to 1 (2.5%) patient in the MabThera group. None of the ADA positive patients had neutralising antibodies (NAb).

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

N/A

## Discontinuation due to AEs

**MabionCD20-001RA**

12 TEAEs (4 in 3 [0.9%] MabionCD20-001RA patients in the MabionCD20 and 8 in 7 [1.3%] patients in the MabThera group) led to permanent discontinuation of the study medication during the double-blind period of the study. Three of these events were serious and 6 events (in 5 patients) were assessed as probably or possibly related to the trial drug (infusion site reaction, urticaria, leukopenia, haemoglobin decreased, cough, and rhinorrhoea).

Among patients who received a second course of treatment there was one AE (hemoglobin decreased) in a patient on MabThera which led to permanent discontinuation of treatment after the first infusion of the second treatment course.

**MabionCD20-002NHL**

There were 9 (9%) AEs leading to permanent discontinuation of study medication in the MabionCD20 treatment group versus 1 (2.5 %) in the MabThera treatment group.

Frequencies of related AEs leading to permanent discontinuation of study medication were similar (n=3 [3%] in the MabionCD20 group vs. n=1 [2.5%] in the MabThera group).

## 3.3.9. Discussion on clinical safety

The safety of MabionCD20 was evaluated in two clinical studies conducted in adult patients with RA (study MabionCD20-001RA) and DLBCL (study MabionCD20-002NHL); the EU-authorized reference product MabThera was used as comparator in both studies.

In total, 458 patients were treated with MabionCD20 during the double-blind parts of studies MabionCD20-001RA (N=358) and MabionCD20-002NHL (N=100).

In response to the GCP inspection findings and the recommended acceptability criteria all patients from Bosnian sites were excluded from the data sets of study MabionCD20-001RA and safety analyses repeated. Thus, safety data are presented for overall 419 patients treated with MabionCD20 during the double-blind parts of studies MabionCD20-001RA (N=319) and MabionCD20-002NHL (N=100).

The safety data submitted in the MAA cover the double-blind periods of both studies, i.e. 24 weeks and 26 weeks, respectively, and the open-label periods up to Weeks 48 and 46, respectively.

Long-term safety data up to 1 year are available for less than 200 patients treated with MabionCD20 in study MabionCD20-001RA, namely for 79 patients who received MabionCD20 for the first and the second course of treatment and for 110 patients who did not receive a second course of treatment. In this context, the possible selection bias introduced by protocol amendment 2 needs to be taken into account as the retreatment was selected in a non-randomized fashion based on the availability of MabionCD20 during the open-label period of the study; However, an analysis provided by the applicant demonstrates that overall the 4 retreatment groups were generally balanced for baseline demographic or disease characteristics, efficacy at Week 24, immunogenicity at Week 24 and time until the patients were on treatment.

**MabionCD20-001RA**

In the Safety Analysis Set (628 patients), 319 patients (50.6%) were analysed in the MabionCD20 group and 309 patients (49.2%) were analysed in the MabThera group. Exposure to study drug was similar between MabionCD20 and Mabthera treatment groups by number of infusions, duration of infusion and total dose of study medication and exposure to methotrexate. Key baseline demographic, disease (RA) characteristics, incidence of past and current medical conditions and the use of past medication seemed to be similar for the two treatment groups.

Adverse events

- Double-blind study period

The incidence of AEs was similar in both treatment groups (MabionCD20: 42.6%; MabThera: 42.1%).

The most commonly affected primary SOCs were infections and infestations, investigations, general disorders and administration site conditions, blood and lymphatic system disorders and skin and subcutaneous tissue disorders. The frequency of AEs reported for the SOC Musculoskeletal and connective tissue disorders were low in both treatment groups, MabionCD20 1.3% and MabThera 2.3%.

The 3 most common AEs (each < 5%) reported in the MabionCD20 group were infusion-related reaction, urinary tract infection and upper respiratory tract infection in the MabionCD20 group and infusion-related reaction, influenza and headache in the MabThera group.

No meaningful differences by SOC were observed for AEs considered as study drug-related.

Frequencies of severe and life-threatening adverse events were low and comparable between the treatment arms.

The frequency of AEs requiring dose interruption was slightly lower in the MabionCD20 arm. AEs leading to dose reduction were recorded at one study center, UKR11, with similar frequencies for both treatment arms.

The frequency of SAEs was similar for the MabionCD (2.2%) and MabThera (1.9%) arms. None of the SAEs occurred more than once per treatment arm. There were no deaths.

The incidences of IRR assessed as related to study drug were 4.7% in the MabionCD20 arm and 3.6% in the MabThera arm.

In summary, the AE profile of MabioncD20 appears to be similar to the AE profile of MabThera for the double-blind part of study MabionCD20-001RA.

- Open-label study period – patients not re-treated (N=215)

Assessment of comparability is limited due to the low numbers of TEAEs reported during the course of the open-label study period in those 215 patients who did not receive a second course of treatment. AE rates were comparable between treatment groups.

- Open-label study period – patients who received a second course of treatment (N=389)

Assessment of the comparability of the AE profiles of the four treatment groups is limited by the non-randomized administration of study medication after protocol amendment 2.

Overall rates of all TEAEs that occurred during the course of the open-label study period in those patients who received a second course of treatment showed imbalances (difference > 10.0%) between the four treatment groups in disfavour of MabThera in contrast to the similar rates recorded during the double-blind study period. Frequencies of TEAEs by SOC across treatment groups did not show meaningful differences except for the SOCs Investigations, and General disorders and site administration conditions which were slightly higher in the 2 MabThera treatment groups.

Completeness of AE data

Underreporting of AEs was noted during the GCP inspections of 2 sites.

According to an analysis provided by the applicant, overall AE and SAE incidences in the MabionCD20-001RA study were lower compared to four other biosimilar studies (AE incidence: 43.9% vs. 54.8% to 61.9% and SAE incidence: 2.1% vs. 4.5% to 8.7%9) whilst incidences of related AEs and discontinuations due to AE were comparable (28.3% vs. 25.9% to 43.1%, and 1.6% vs. 1.8% to 4.2%). The applicant discusses geographic factors, the "subjective nature of AE reporting" and psychological factors as possible explanations.

Nonetheless, lower overall AE and SAE incidences limit the sensitivity to detect differences between MabionCD20 and the reference product.

Laboratory parameters

No clinically meaningful differences in laboratory parameters were apparent between both treatment groups. Changes in ACPA and RF factors and in immunoglobulins over time were consistent with the mechanism of action of rituximab.

Frequencies of treatment-induced ADA were comparable, 14.2% (45/316) patients) in MabionCD20 and 13.4% (41/306 patients) MabThera treatment arms, at Week 24. In the subset of patients who did not receive a second treatment course frequencies of treatment-induced ADA were also comparable, 21.8% (24/110 patients) in MabionCD20 and 23.8% (25/105 patients) MabThera treatment arms.

Analysis of PTs of infusion reactions or immune-mediated events by ADA-status did not show differences considered clinically relevant but numbers were low.

In the MabionCD20 group, 2 of 316 patients were positive for NAb after baseline, while in the MabThera groups none of the 306 patients were positive for NAb after baseline until Week 24.

The Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006) asks for ADA data from a controlled clinical trial for one year, unless a shorter follow-up can be justified. Approximately 220 patients per treatment arm who do not undergo switching were to represent the minimal amount of patients required for the long-term safety and immunogenicity study based upon the expected frequency of ADA development of MabThera according to the Scientific Advice given (EMA/CHMP/SAWP/666672/2015). To this purpose the applicant conducted a pooled analysis of subjects who were not re-treated (110 in MabionCD20 and 105 in MabThera) and subjects who were re-treated with the same treatment they were randomised

to, (did not switch the treatment at Week 24 - 79 in MabionCD20 constantly and 112 in MabThera constantly). Nonetheless, data are available only for 79 patients re-treated with Mabion CD20.

**MabionCD20-002NHL**

In the Safety Analysis Set, 100 patients in the MabionCD20 group (100%) and 40 patients in the MabThera group (100%) received the first infusion. Exposure to study drug was similar between MabionCD20 and Mabthera treatment groups by duration of treatment and number of infusions received at each visit. The majority of patients (120 [85%]) completed the 8-cycle treatment schedule (85% in the MabionCD20 group and 87.5% in MabThera group). Mean and median dose at each visit were comparable, though numerically somewhat higher for MabionCD20 in comparison to MabThera at Cycles 7 and 8. Exposure of both treatment groups to concomitant CHOP chemotherapy was similar.

The population included in this study was younger than the population included in the pivotal study for the authorization of this indication for MabThera and also younger than the overall target population of this indication.

AEs were not graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) affecting the comparability of severe AEs such as neutropenia.

Relevant imbalances were observed between both groups in several baseline characteristics or medical history in safety set population:

- Relevant imbalance was observed for the age-adjusted International Prognostic Index (IPI). The percentage of patients classified as high-intermediate risk was 19% in the in the MabionCD20 group, and 32.5% in the MabThera group, while high risk was 8% in the MabionCD20 group, and 2.5% in the MabThera group;
- Elevated LDH was 42% in the MabionCD20 group, and 55% in the MabThera group;
- Higher percentage of patients had neoplasms (benign, malignant and unspecified) history at baseline in MabThera group (6% in MabionCD20 vs 20.0% in MabThera group);
- Higher percentage of patients had metabolism history at baseline in MabionCD20 group (metabolism and nutrition disorders: 12.0% in MabionCD20 vs 0% in MabThera group);
- Slightly higher percentage of patients had cardiac or vascular history at baseline in MabionCD20 group (cardiac and vascular disorders, respectively: 28% each in MabionCD20 vs 22.5% each in MabThera group).

However, no relevant differences were observed in systolic blood pressure, diastolic blood pressure, pulse, ECG, ECG abnormalities at baseline. Moreover, transthoracic echocardiography was abnormal in 55.0% of patients in the MabionCD20 group and 65.0% of patients in the MabThera group (without being clinically significant: 53% for MabionCD20 and 62.5% for MabThera; clinically significant: 2% for MabionCD20 and 2.5% for MabThera).

Taking all together, these differences do not appear to reveal a consistent explanation for the observed trend for worse safety profile observed in MabionCD20 group as compared to MabThera group.

<u>Adverse events</u>

There were differences > 5 to >10% in 8 of 12 AE categories with the higher frequencies reported for the MabionCD20 treatment group compared to the MabThera treatment group. As regards to the numerical imbalances, the unequal randomization (5:2) and the low numbers of treated patients (MabionCD20: 100 vs. MabThera: 40) need to be taken into consideration.

Overall, 71.0% of patients in the MabionCD20 treatment group and 65.0% of patients in the MabThera treatment group experienced 1 TEAE or more, mostly during the double-blind period (608 of 619 TEAEs). Patients in the MabionCD20 group experienced slightly more AEs, on average 6.5 TEAEs per patient, compared to on average 5.8 TEAEs per patient in the MabThera group during the double-blind period.

Analysis of AEs regardless of causality by frequency and severity showed imbalances in the SOC Blood and Lymphatic System Disorders with higher frequencies for severe neutropenia and leukopenia in the MabionCD20 group. The higher frequency of all AEs in the SOC infection and infestations in the MabionCD20 group with a higher frequency of pneumonia (MabionCD20 8% vs. MabThera 0%) was not seen when the analysis was restricted to severe AEs.

Clinically, neutropenia is manageable by prophylaxis and treatment with G-CSF. Proportions of patients receiving treatment with G-CSF were comparable between MabionCD20 and MabThera treatment groups, 49.0% vs. 45.0%.

Cardiac events were twice as common in the MabionCD group compared to the MabThera group, 11% vs. 5% . Except for cardiac failure and supraventricular tachycardia cardiac AEs occurred only once in the MabionCD20 treatment group. The number of patients with cardiac or vascular disorders at baseline was slightly higher in the MabionCD20 group (28% each) compared to the MabThera group (22.5% each) as pointed out by the Applicant, however as described above, other cardiac baseline characteristics did not show imbalances.

Overall, the profile of TEAEs appears clinically comparable between treatment groups with the exception of cardiac events.

The proportion of patients experiencing ≥1 AE assessed as drug-related was higher in the MabionCD20 than in the MabThera group (53.0% vs 42.5%). Differences between the two treatment groups exceeded 5% for 2 of the SOCs; 6% of the patients in MabionCD20 group had cardiac AEs compared to none in MabThera group. 12% of the patients in MabionCD20 group had related AEs in the SOC investigations compared to 17.5% in MabThera group.

The profile of related TEAEs was clinically comparable between treatment groups except for cardiac events.

Frequencies of AEs leading to dose interruption were comparable in the MabionCD20 group compared to the MabThera group, 6.0% vs. 7.5%, respectively.

Frequencies of AEs leading to permanent discontinuation of study drug were higher in the MabionCD20 group than in the MabThera group, 9.0% vs. 2.5%.

Deaths and other serious adverse events

There was a slight imbalance in the frequency of SAEs reported for MabionCD20 as compared to MabThera, 19% vs. 12.5%.

The spectrum of SAEs reported generally appeared to reflect both the established adverse reaction profile of rituximab, the adverse events associated with the underlying disease and the chemotherapy.

There were 8 (8.0%) fatal SAEs in the MabionCD20 treatment group versus none (0.0%) in the MabThera treatment group the difference being 8.0% (95%CI 2.68; 13.32).

Preferred Terms of the 8 fatal SAEs were Non-Hodgkin's lymphoma (n=3), hypotension (n=2), and death, cardiovascular insufficiency and pancreatic necrosis (n=1 each). Investigator's assessment of causal relationship to study drug treatment was "not related" for all fatal SAEs with the exception of the fatal SAEs of pancreatic necrosis and death, which had been assessed as "unlikely related".

None of the deaths was due to documented severe infections such as septicaemia or pneumonia. Whilst the spectrum of causes of death does not reveal new safety signals, the lack of pertinent information in 3 of 8 cases is considered high.

The Applicant provided two main justifications, namely that trial design and small sample size as well as higher risks associated with baseline scores observed in the patients who died would explain the higher death rate in the MabionCD20 group.

Applying the first justification of trial design with unequal randomization (5:2) and small sample size of altogether 140 patients, the difference between treatment arms would be attributed to chance as only one death in the MabThera group would have led to a proportion of 2.5% instead of 0%. The attribution to chance alone seems, however, not fully plausible, as the probability of a chance finding is less than 5.0% and the other imbalances in AE categories also disfavor MabionCD20.

With regard to the second justification, Ann Arbor staging scores ≥ 3 were quite similar in both groups (60% in MabionCD20 group vs. 55% in MabThera group). Likewise, though the proportion of patients with high risk age-adjusted IPI was slightly higher in the MabionCD20 group (8% vs. 2.5%), the proportion of patients with a high-intermediate risk score was considerably higher in the MabThera group (19% vs. 32.5 %).

Thus, unequivocal reasons for the imbalance in deaths between the treatment groups are not apparent.

Laboratory parameters

No clinically meaningful differences in laboratory parameters were apparent between both treatment groups. Data on neutrophil counts were not collected in the eCRF which precludes an assessment whether the higher frequencies of severe neutropenia events in the MabionCD20 group are paralleled by a respective difference in neutrophils counts between treatment groups or otherwise.

Frequencies of treatment induced ADAs up to Week 46 (i.e., not ADA positive at baseline but positive after treatment) were low, 6.1% (6 patients) in the MabionCD20 group and 1 (2.5%) in the MabThera group. Impact of ADA on safety did not seem to be relevant. None of the ADA positive patients had NAb.

## 3.3.10. Conclusions on clinical safety

Overall, the safety profile of MabioncD20 appears to be similar to the AE profile of MabThera for the double-blind part of study MabionCD20-001RA, even though underreporting of AEs may have limited the sensitivity to detect differences between treatment arms.

The AE data for study MabionCD20-002NHL showed differences > 5% and imbalances in AE and SAE incidences, severity and deaths:

- The proportion of patients experiencing one or more TEAE was slightly higher in the MabionCD20 group compared to the MabThera group (71.0% vs. 65.0%);
- The proportion of patients experiencing one or more TESAEs was slightly higher in the MabionCD20 group compared to the MabThera group (19.0% vs. 12.5%);
- The proportion of patients experiencing ≥1 related TEAE was higher in the MabionCD20 than in the MabThera group (53.0% vs. 42.5%);
- The proportion of patients experiencing one or more severe TEAE was higher in the MabionCD20 group compared to the MabThera group (40.0% vs. 22.5%);

- Seven patients (7.0%) died during the double-blind part of the study in the MabionCD20 group, none in the MabThera group. 6 of the 7 deaths were assessed as not related and 1 as unlikely related to the treatment. An additional death of unknown cause occurred in the MabionCD20 group during the open-label study period, and none in the MabThera group. Of note, completion rates of follow-up until Week 46 were similar between treatment groups.

Some AEs were observed more frequently in the MabionCD20 arm, severe neutropenia, pneumonia, and cardiac events.
In order evaluate imbalance in fatal events in the MabionCD20-002NHL study, the Applicant conducted several analyses including independent medical reviews of all eight fatal adverse events, computation and comparison of survival rate observed in the MabionCD20-002NHL study with recently published survival data for DLBCL patients; evaluation of analytical comparability of batches used across the MabionCD20 MABRA and MADILYM clinical trials an evaluation of correlation between quality attributes of the IMP batches and clinical safety data. Overall the applicant considered that the unequal randomization ratio and the low sample size a reasonable cause for the imbalance in the incidence of fatal serious adverse events. The same arguments are provided by the applicant with regard to the increased incidence of cardiovascular events is reported after MabionCD20 administration including two events, which have occurred within 24 hours of the IMP infusion in the MabionCD20 study arm. Even when considering the unequal randomisation there is a remaining imbalance between both arms being 0 and 3.3 events in the Mabthera arm and MabionCD20 arm respectively. Regarding the cardiovascular events arguing with the uneven randomization ratio is not agreed as the difference is 11% in the MabionCD20 treatment arm in comparison to 5% in the reference MabThera arm. Although no clear cause of the differences in safety between Mabthera and MabionCD20 could be identified and the findings might indeed be chance findings there are numerous uncertainties.

Therefore, biosimilarity is currently not considered demonstrated for study MabionCD20-002NHL.

## *3.4. Risk management plan*

## Summary of safety concerns

The applicant proposed the following summary of safety concerns in the updated RMP Version number 1.2 dated 10-Oct-2019:

**Table: Summary of the Safety Concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | **NHL/CLL**<br>• Infusion-related reactions<br>• Infections (including serious)<br>• Progressive multifocal leukoencephalopathy<br>• Hepatitis B reactivation<br>**RA**<br>• Infusion-related reactions<br>• Infections (including serious)<br>• Progressive multifocal leukoencephalopathy<br>• Hepatitis B reactivation<br>• Hypogammaglobulinemia<br>**GPA/MPA**<br>• Infusion-related reactions<br>• Infections (including serious)<br>• Progressive multifocal leukoencephalopathy<br>• Hepatitis B reactivation<br>• Hypogammaglobulinemia |
| Important potential risks | **NHL/CLL**<br>• Off label use in paediatric patients<br>• Administration route error<br>**RA**<br>• Malignant events<br>• Impact on cardiovascular disease<br>• Off label use in paediatric patients<br>**GPA/MPA**<br>• Off label use in paediatric patients<br>• Malignant events |

| Summary of safety concerns | |
|---|---|
| | • Impact on cardiovascular disease<br>• Relapses |
| Missing information | **NHL/CLL**<br>• Use in pregnancy and lactation<br>**RA**<br>• Use in pregnancy and lactation<br>**GPA/MPA**<br>• Use in pregnancy and lactation<br>• Long term use in GPA/MPA patients |

## 3.4.1. Discussion on safety specification

**Populations not studied in clinical trials**

No data for MabionCD20 in children, pregnant or breastfeeding women, hepatic and renal impaired are available. This is considered acceptable given that the MabionCD20 is developed as biosimilar to MabThera and data can be retrieved from the originator.

**Potential for medication errors**

A risk for potential medication errors exist as meanwhile MabThera has also been authorized for subcutaneous administration (1400mg for patients with NHL, FL and DLBCL; 1600mg for patients with CLL). Administration route error is included as important potential risk in the indication NHL/CLL.

**Specific paediatric issues**

There is a potential for off-label use in pediatric oncological indications. This applies also to the reference product MabThera.

Off label use in pediatric patients is included as important potential risk in the indications NHL/CLL and in the indications RA and GPA/MPA. Off label use in autoimmune disease is included as important potential risk in the indications RA and GPA/MPA.

Further aspects

Evaluation of the provided safety data did not reveal any major safety concerns. However, some safety issues are addressed in the LoOI. Therefore, at the time being a final conclusion on possible modifications of the proposed summary of safety concerns is not possible.

## 3.4.2. Conclusions on the safety specification

Having considered the data in the safety specification the Rapporteur notes that the RMP has been updated and aligned with the originator MabThera's RMP (version 19.2).

Further modifications to the RMP may be necessary depending on the Applicant's response to the LoOI.

## 3.4.3. Pharmacovigilance plan

### *Routine pharmacovigilance activities*

The Applicant proposed specific adverse reaction follow-up (FU) questionnaires for the following safety concerns:

- Posterior multifocal leukoencephalopathy;
- Malignant events;
- Off Label Use in Paediatric Patients.

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

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

***Summary of additional PhV activities***

**Table 1 Part III.3: On-going and planned additional pharmacovigilance activities**

| **Study Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| None | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| None | | | | |
| **Category 4** - Stated additional pharmacovigilance activities | | | | |
| | | | | |
| German Biologics Register – Rheumatoid Arthritis (**RABBIT**): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new | To evaluate the long-term safety profile of rituximab in rheumatoid arthritis patients in comparison to RA patients with similar disease activity receiving biologics and standard disease- | Long-term safety in RA with emphasis on:<br>Infections (including serious infections)<br>Infusion-related reactions<br>PML | Protocol finalised | Q2 2020 |
| | | | Study start | Q2 2020 |
| | | | Study finish | Q4 2036 |
| | | | Final report available | Q4 2037 |

| | | | | |
|---|---|---|---|---|
| advanced targeted therapies<br><br>Planned | modifying anti-rheumatic drugs (DMARD) | Liver-related events<br><br>Malignant events<br><br>Impact on cardiovascular disease<br><br>Use in pregnancy and lactation | | |

The applicant included RABBIT register study as category 4 activity.

For the reference product MabThera, three category 4 register studies (ARTIS, RABBIT and BSRBR) are in place. The applicant is encouraged to join all registers in place for the reference product.

During the assessment the applicant was reminded that category 4 studies should not be included in the pharmacovigilance plan as per GVP V rev 2. At the time of the report the applicant was requested that the RMP needed to be revised accordingly.

***Overall conclusions on the PhV Plan***

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

## 3.4.4. Plans for post-authorisation efficacy studies

N/A

## 3.4.5. Risk minimisation measures

***Routine Risk Minimisation Measures***

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

***Additional Risk Minimisation Measures***

V.2. Additional Risk Minimisation Measures

**Educational materials for healthcare professionals and patients and patient alert card**

Objectives:

To address the important identified risk of Infections and PML and the important identified risk of Administration route error, the MAH proposes educational materials for HCPs and for patients to provide information about these reactions, their early symptoms and the best course of action to be taken when they appear, beyond the recommendation contained in the Product Information.

To address the risk of PML and infections, the MAH proposes Patient Alert Card to ensure that special information regarding the patient's current therapy and its important risks is held by the patient at all times and reaches the relevant HCP as appropriate. It contains the minimum necessary information to convey the key minimization message(s) and the required mitigating action, in any circumstances, including emergency.

All physicians who are expected to prescribe Rituximab Mabion are provided with educational materials and Patient Alert Card, however, they are instructed to use them just for patients who use the product for non-oncology indications (RA, GPA/MPA and PV).

Rationale for the additional risk minimisation activity:

Rituximab Mabion is a biosimilar medicinal product. As a biosimilar, Rituximab Mabion are provided with educational materials and Patient Alert Card, however, they are instructed to use them just for patients who use the product for non-oncology indications (RA, GPA/MPA and PV).

Rationale for the additional risk minimisation activity:

Rituximab Mabion is a biosimilar medicinal product. As a biosimilar, Rituximab Mabion has the same risks and hence needs to follow the same risk minimization measures as the reference product. To provide information to HCPs and patients on the possible risk of occurrence of Infections, PML and Administration Route Error and to provide appropriate management, beyond the recommendation contained in the Product Information.

Target audience and planned distribution path:

Healthcare professionals and patients. Appropriate method of distribution of educational material and target group will be agreed with national competent authorities.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of risk minimisation measures will be measured by routine pharmacovigilance activities.

Criteria for success: reduction in the frequency/no occurrence act of Infections, PML and Administration route error in relation to patients' exposure to Rituximab Mabion. Planned dates for assessment: during PSUR preparation, as per the EURD list (if applicable) and signal detection activity as per internal procedures. Effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

The applicant was requested that the section V.2. Additional Risk Minimisation Measures and Annex 6 need further revision to be in line with reference product RMP. It should be clear which indications aRMMs are targeting. For Rexeful RMP and product information, there are currently discrepancies between information provided in V.2. Additional Risk Minimisation Measures, Annex 6 and Product information Annex II.D. All these three sections should be aligned to include clear information on which aRMMs are targeting non-oncology indications (RA, GPA/MPA and PV) and which oncology indications (NHL/CLL).

Additionally, the applicant at the time this report was adopted was reminded that The Patient information pack should also include Patient information leaflet as per Guidance on the format of the risk management plan Rev.2.0.1.

***Summary of additional risk minimisation measures***

**Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Infusion Related reactions (All Indication) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of SmPC contains information of necessity of premedication administration before infusion of Rituximab Mabion in order to reduce the frequency and severity of infusion related reactions and appropriate monitoring and treatment.<br><br>PL section 4 contains information on the need to report immediately occurrence of any symptom of infusion related reaction to the person giving the infusion in order to slow or stop the infusion or administer additional treatment.<br><br>The pack size (50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>None | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |
| Infections (including Serious Infections) (All Indications) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of SmPC contains information about risk of serious (even fatal) infections during therapy with rituximab and contraindications taking into account increased risk of Infections in patients with an active, severe infection.<br><br>PL section 2 and 4 contains information on the need to tell the doctor about all infections the patient had and may have (in particular hepatitis infection) before the treatment with Rituximab Mabion<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly. | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>• *Patient Alert Card (PAC)*<br><br>• *Educational material for patients and HCP* | |
| Progressive Multifocal Leukoencephalopathy<br>(All Indications) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of SmPC contains information of necessity of monitoring patients at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.<br><br>Package leaflet section 4 includes information about possibility of PML occurrence and the need of immediate reporting to the doctor if the patient gets specific signs of a PML.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>• *Patient Alert Card (PAC)*<br><br>• *Educational material for patients and HCP* | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*Targeted follow up questionnaire*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |
| Hepatitis B reactivation<br>(All Indications) | Routine risk minimisation measures:<br><br>Section 4.4 and 4.8 of SmPC states that HBV screening should be performed in all patients before treatment with rituximab. Active hepatitis B disease is contraindication for rituximab treatment. | Routine pharmacovigilance activities |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | PL section 2 and 4 contains information of necessity to inform a doctor about the history of hepatitis infection or active hepatitis infection as well as the need to check carefully for signs of the infection before Rituximab Mabion administration.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>*None* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |
| Hypogammaglobulinemia (non-oncology indications) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of the SmPC states that the risk of hypogammaglobulinemia may increase the risk of serious infection. Therefore Immunoglobulin level should be checked before rituximab treatment. There was no increased rate in overall infections or serious infections in patients with low IG.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>*None* | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*None* |
| **Important Potential Risks** | | |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Malignant Events (non-oncology indications) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of the SmPC states that Immunomodulatory drugs may increase the risk of malignancy and possible risk for the development of solid tumours cannot be excluded.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>*None* | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*Targeted follow up questionnaire*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |
| Impact on cardiovascular disease (non-oncology indications) | Routine risk minimization measures:<br><br>Section 4.4 and 4.8 of the SmPC states that safety of rituximab in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease has not been established well. The occurrence of pre-existing ischemic cardiac conditions has been observed during rituximab therapy. Therefore, the risk of cardiovascular complications should be considered before treatment. Monitoring of patients during administration should be performed.<br><br>PL section 2 and 4 contains information of the need to inform the doctor about any heart problem in past or current.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | resuscitation facilities are immediately available.<br>Additional risk minimization measures:<br>*None* | |
| Relapses (GPA/MPA) | Routine risk minimization measures:<br>Section 5.1 of the SmPC states that there are limited data to make conclusions regarding the efficacy of subsequent courses of rituximab in patients with GPA/MPA.<br>Additional risk minimization measures:<br>*None* | Routine pharmacovigilance activities<br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>*None*<br>Additional pharmacovigilance activities:<br>*None* |
| Off label use in paediatric patients (All Indications) | Routine risk minimization measures:<br>Section 4.1 and 4.2 of the SmPC states that the safety and efficacy of l Rituximab Mabion in children below 18 years has not been established.<br>PL section 2 contains information that there is not much information about the use of Rituximab Mabion in children and young people.<br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br>Additional risk minimization measures:<br>*None* | Routine pharmacovigilance activities<br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>*Targeted follow up questionnaire*<br>Additional pharmacovigilance activities:<br>*None* |
| Administration route error (NHL/CLL) | Routine risk minimization measures: | Routine pharmacovigilance activities |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Section 1 of the SmPC states name of the medicinal product and section 4.2 states Posology and method of administration.<br><br>The pack size (one 50 ml vial) limits the risk of mistake in dosing and overdosing while solution for infusion is being prepared and ensures that the medicine is used correctly.<br><br>Prescription medicinal product only subject to administration in a hospital under close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available.<br><br>Additional risk minimization measures:<br><br>• *Educational material for HCP* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*None* |
| **Missing information** | | |
| Use in pregnancy and lactation (All Indications) | Routine risk minimization measures:<br><br>SmPC Section 4.6 states that there are no adequate and well-controlled data from studies in pregnant women, therefore Rituximab Mabion should not be administered to pregnant women unless the possible benefit outweighs the potential risk.<br><br>PL section 2 includes information that Rituximab Mabion should can affect a baby and the possibility of being pregnant or plan to become pregnant should be reported to doctor. Is also informs about the necessity to use contraception while treatment with Rituximab Mabion and 12 months after.<br><br>Additional risk minimization measures:<br><br>*None* | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>*None*<br><br>Additional pharmacovigilance activities:<br><br>*participation to RABBIT* |
| Long term use in GPA/MPA patients (GPA/MPA) | Routine risk minimization measures:<br><br>Section 5.1 of the SmPC states that the efficacy and safety of rituximab in maintenance therapy has not been established.<br><br>Additional risk minimization measures:<br><br>*None* | Routine pharmacovigilance activities<br><br>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | | *None*<br>Additional pharmacovigilance activities:<br>*None* |

The Part V.3 need revision in accordance with the comments on the PhV plan that category 4 studies should not be included in the pharmacovigilance plan as per GVP V rev 2.

***Overall conclusions on risk minimisation measures***

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

### 3.4.6. Summary of the risk management plan

The public summary of the RMP may require revision:

a) Section I. 'The medicine and what it is used for' should be updated to include all proposed indications (from Table Part I.1), including Pemphigus vulgaris, (PV) which was included as indication in the current RMP v.1.2;

b) The applicant should ensure that reference to MabionCD20 in the RMP summary is in all cases replaced by the product name Rexeful unless explained;

c) Annex 8 should be included in the RMP.

The RMP summary and annexes should be further revised in accordance with comments to other parts of the RMP, as necessary.

### 3.4.7. Conclusion on the RMP

Only minor issues remain which need to be addressed based on the PRAC assessment of the RMP. The CHMP and PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report.

## *3.5. Pharmacovigilance system*

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

***Periodic Safety Update Reports submission requirements***

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

# 4. Orphan medicinal products

N/A

# 5. Benefit risk assessment

## *5.1. Therapeutic Context*

### 5.1.1. Disease or condition

MabionCD20 is developed as a biosimilar medicinal product to MabThera. 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):

Oncology indications:

- Non-Hodgkin's lymphoma (NHL: diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL));
- Chronic lymphocytic leukemia (CLL).

Immunology indications:

- Rheumatoid arthritis (RA);
- Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

### 5.1.2. Available therapies and unmet medical need

N/A

### 5.1.3. Main clinical studies

- A pivotal efficacy and safety study in 629 patients after exclusion of Bosnian sites with active (≥ 6 months' diagnosis) RA not responding adequately to an adequate regimen of MTX or/and other DMARDs and untreated with anti-TNF or any other monoclonal antibody therapies (study MabionCD20-001RA), powered to demonstrate equivalence of ACR20 response at Week 24 as the primary endpoint between MabionCD20 and MabThera and to provide data on PK/PD and safety including immunogenicity assessments;
- A supportive PK/PD equivalence study in 140 patients with CD20 positive DLBCL (study MabionCD20-002NHL) powered to demonstrate equivalence of PK parameters at Week 26 as the primary endpoint between MabionCD20 and MabThera and to provide data on PK, PD, efficacy and safety including immunogenicity assessments.

## *5.2. Favourable effects*

**MabionCD20-001RA (Clinical aspects)**

PK/PD

Similarity in primary PK endpoints ($AUC_{(0\text{-}t)}$ and $C_{max\text{-}second}$) between MabionCD20 and MabThera was adequately demonstrated. Immunogenicity was shown to be comparable between the treatment groups.

Efficacy

In the PPS all patients, ACR20 at Week 24 was 77.8% in the MabionCD20 arm and 83.0% in the MabThera arm and the difference in ACR20s was -5.2% (95% CI [-0.8; 11.2%]). The entire 95% CI for the difference between the 2 treatments was within the pre-specified margin of ± 13%.

In the PPS excluding patients from Bosnia, ACR20 at Week 24 was 79.3% in the MabionCD20 arm and 85.1% in the MabThera arm and the difference in ACR20s was -5.8% (95% CI [-0.3; 12.0%]). The entire 95% CI for the difference between the 2 treatments was within the pre-specified margin of ± 13%.

In the ITT set, ACR20 at Week 24 was 79.0% in the MabionCD20 arm and 84.1% in the MabThera arm. The difference in ACR20 was -5.1% (95% CI [-11.3; 1.1%]).

The secondary efficacy objective based on efficacy and response scores, ACR 50, ACR 70, DAS28-ESR and EULAR, up to Week 24 was met and supported by the ITT sensitivity analyses.

Differences in ACR20, ACR50 and ACR70 and Good EULAR responses at Week 48 (end of open-label period) between the MabionCD20 and MabThera groups of patients not re-treated, ranged from approximately 4.8% to 11.2% (no CIs were provided). These differences are all in favor of MabionCD20.

Overall, **ACR 20, ACR 50, ACR 70 and EULAR responses showed a high degree of similarity between the 2 groups of patients who switched treatment.**

**MabionCD20-002NHL (Clinical aspects)**

PK/PD

Similarity in primary PK endpoints ($AUC_{(1-4)}$ and $AUC_{(13-26)}$) between MabionCD20 and MabThera was adequately demonstrated. Immunogenicity was shown to be comparable between the treatment groups.

Efficacy

ORR at Week 26 was 89.2% for the MabionCD20 group compared to 93.1% for the MabThera group% in the PP set, 79.2% for the MabionCD20 group compared to 84.2% for the MabThera group in a modified ITT set, and 74.5% for the MabionCD20 group compared to 78.0% for the MabThera group in an ITT population including randomized patients with lack of assessment as missing.

Complete response rate at Week 26 was 44.6% for the MabionCD20 treatment group in comparison to 41.1 % for the Mabthera treatment group in the PP set. CR rate was similar in the modified ITT set, MabionCD20 35.4% versus MabThera 36.8%.

## *5.3. Uncertainties and limitations about favourable effects*

**MabionCD20-001RA (Clinical aspects)**

Efficacy

The ACR20 results in the PP and ITT populations were considerably higher than the effect size of 50% assumed in the sample size calculation.

Differences noted in the Kaplan-Meier analyses of the time to first onset of ACR 20 response and of EULAR response, are small and not considered relevant.

Most subgroup analyses indicated a slight numerical advantage for MabThera over MabionCD20 in ACR20 response at Week 24.

As regards to the prespecified subgroup analysis of disease activity at baseline (DAS28-ESR), there was a difference of 16.2% in ACR20 response rates in patients treated with MabionCD20 with lower (≤ median) disease activity, 71.1% as compared to patients with higher (> median) disease activity, 87.3%, whereas no such difference was observed for patients treated with MabThera, 85.4% versus 83.3%. The resulting difference between both treatment groups in the patients with lower (≤median) disease activity was 14.3%, 95% CI [5.0; 23.6%].

The subgroup of seronegative patients comprised 14.8% of the ITT population, 43 of 318 [13.5%] patients in the MabionCD20 group compared to 50 of 311 [16.1%] patients in the MabThera group. The ACR20 response rates at Week 24 were comparable between seronegative and seropositive patients in the MabionCD20 arm, 76.7% versus 79.9%, whereas in the MabThera arm more seronegative patients, 92.0%, achieved an ACR20 response compared to 83.1% of seropositive patients. This resulted in a difference of 15.3%, 95% CI [0.6; 30.0%] between treatment groups in the subgroup of seronegative patients at baseline.

Subgroup differences for ACR20 response as observed in the subgroup analyses are replicated in adjusted multivariable ANOVA models with treatment interactions for baseline sero-positivity, duration of RA, baseline disease severity (DAS28-ESR), gender and age group.

The interaction models show that the differences in treatment effects observed between MabThera and MabionCD20 are most likely not only based on differences in prognostic factors of the population but are due to differences in the originator and biosimilar product.

GCP compliance of the sponsor's performance and systems cannot be fully confirmed in the light of numerous findings observed during the routine GCP inspection.

The clinical data were not generated with the commercial product.

**MabionCD20-002NHL (Clinical aspects)**

Efficacy

The study was not powered to evaluate efficacy. The sample size (especially in the MabThera arm) is too small to base any sound conclusions neither in favour nor in disfavour of the biosimilar.

As regards to the age-adjusted IPI, the percentage of patients classified as high-intermediate was 19% in the MabionCD20 group, and 32.5% in the MabThera group; the percentage of patients classified as high risk was 8% in the MabionCD20 group, and 2.5% in the MabThera group.

The clinical data were not generated with the commercial product.

## *5.4. Unfavourable effects*

**Quality**

The current MAA is not considered approvable from a quality point of view since major concerns are raised regarding biosimilarity to the reference product Mabthera.

**Non-Clinical**

N/A

**Clinical aspects**

**Study MabionCD20-001RA**

Safety

The safety profile of MabionCD20 was similar to MabThera with regards to the incidence of overall adverse events, related AEs and SAEs during the double-blind period. There were no deaths. The frequencies of AEs requiring dose interruption and of AEs leading to permanent discontinuation were slightly lower in the MabionCD20 arm.

The incidences of infusion-related reactions (MabionCD20 4.7% vs. MabThera 3.6%) and of treatment-induced ADAs (MabionCD20 14.2% vs. MabThera 13.4%) were comparable. Incidences of neutralizing antibodies were low and not associated with immunological events.

No clinically meaningful differences in laboratory parameters were apparent between both treatment groups.

There were no new safety concerns.

AE rates of patients not re-treated with a second treatment course were low and overall comparable during the open-label period.

**Study MabionCD20-002NHL**

Safety

There were differences > 5 to >10% in 8 of 12 AE categories with the higher frequencies reported for the MabionCD20 treatment group compared to the MabThera treatment group.

Analysis of AEs regardless of causality by frequency and severity showed imbalances in the SOC Blood and Lymphatic System Disorders with higher frequencies for severe neutropenia and leukopenia in the MabionCD20 group. The higher frequency of all AEs in the SOC infection and infestations in the MabionCD20 group with a higher frequency of pneumonia was not seen when the analysis was restricted to severe AEs.

Cardiac events were twice as common in the MabionCD20 group compared to the MabThera group, 11% vs. 5%.

The proportion of patients experiencing ≥1 AE assessed as drug-related was higher in the MabionCD20 than in the MabThera group (53.0% vs 42.5%). Differences between the two treatment groups exceeded 5.0% for 2 of the SOCs; 6.0% of the patients in MabionCD20 group had cardiac AEs compared to none in MabThera group. 12.0% of the patients in MabionCD20 group had related AEs in the SOC investigations compared to 17.5% in MabThera group.

Frequencies of AEs leading to permanent discontinuation of study drug were higher in the MabionCD20 group than in the MabThera group, 9.0% vs. 2.5%.

There was an imbalance in the frequency of SAEs reported for MabionCD20 as compared to MabThera, 19.0% vs. 12.5%.

There were 8 (8.0%) fatal SAEs in the MabionCD20 treatment group versus none (0.0%) in the MabThera treatment group. Preferred Terms of the 8 fatal SAEs were Non-Hodgkin's lymphoma (n=3), hypotension (n=2), and death, cardiovascular insufficiency and pancreatic necrosis (n=1 each). Investigator's assessment of causal relationship to study drug treatment was "not related" for all fatal

SAEs with the exception of the fatal SAEs of pancreatic necrosis and death, which had been assessed as "unlikely related".

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

**Quality**

Uncertainty remains on the retrospective approach taken by the company, which is not compliant with GMP principles and ICH Q5E.

Selection of clinical lots for retrospective comparability and similarity evaluations analyses.

Based on the data provided full comparability of the clinical and the proposed commercial batches which were not used in the clinical trials is not considered demonstrated.

Uncertainties remain with regards to the developmental approach as a QTPP was not established based extensive characterization of the reference medicinal product. QTPP report provided was basically extracted from the overall biosimilarity study (2018), hence, it was generated retrospectively.

Uncertainty remains with regard to the validity of the QTPP. Some uncertainty remains with regard to reliability of the data presented in the dossier as multiple inconsistencies and errors were identified during review of the MAA.

Although recent improvements in the quality system are acknowledged, these cannot resolve for the previous concerns raised.

Most importantly, a reasonable uncertainty remains with regard to biosimilarity as MabionCD20 exhibits lower (below min-max) levels in afucosylated species than the reference medicinal product Mabthera. The observed difference preclude a positive conclusion on biosimilartiy as the difference might impact potency/efficacy of the product. This is supported by structure function correlation using a sensitive ADCC activity assay.

**Non-Clinical**

N/A, see quality

**Clinical aspects**

**MabionCD20-001RA**

Safety

Due to issues identified at one site as well as the fact that all Bosnian sites were monitored by the same CRA, the applicant decided to exclude the data of all patients included in Bosnian clinical sites from the analysis reported in the updated version of the CSR.

The clinical data were not generated with the commercial product.

**MabionCD20-002NHL (Clinical aspects)**

Safety

Unequal randomization ratio (5:2).

Low numbers of treated patients (MabionCD20: 100 vs. MabThera: 40).

As regards to the age-adjusted IPI, the percentage of patients classified as high-intermediate was 19% in the MabionCD20 group, and 32.5% in the MabThera group; the percentage of patients classified as high risk was 8% in the MabionCD20 group, and 2.5% in the MabThera group.

The number of patients with cardiac or vascular disorders at baseline was slightly higher in the MabionCD20 group (28% each) compared to the MabThera group (22.5% each). However, no relevant differences were observed in systolic blood pressure, diastolic blood pressure, pulse, ECG, ECG abnormalities and results of transthoracic echocardiography at baseline.

Unequivocal reasons for the imbalance in deaths between treatment groups are not apparent.

The clinical data were not generated with the commercial product.

## *5.6. Effects Table*

N/A

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

### 5.7.1. Importance of favourable and unfavourable effects

This is an application for a biosimilar rituximab, MabionCD20. The purpose of this biosimilar application is not to demonstrate a positive benefit risk balance, but to demonstrate similarity of the test product to reference product MabThera with regard to quality, non-clinical and clinical aspects.

**Quality, Non-clinical aspects**

According to the guidance (EMA/CHMP/BWP/247713/2012) the development and documentation for biosimilars should cover two distinct aspects:

i. molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product;

ii. performance and consistency of the manufacturing process of the biosimilar on its own.

Based on the data provided with the MAA both aspects are currently questioned.

**Clinical aspects**

The clinical data were not generated with the commercial product and comparability is currently not considered demonstrated.

**MabionCD20-001RA**

Biosimilarity in PK/PD is considered adequately demonstrated.

GCP compliance of the sponsor's performance and systems cannot be fully confirmed in the light of numerous findings observed during the routine GCP inspection of this study. Due to issues identified at one site as well as the fact that all Bosnian sites were monitored by the same CRA, the applicant decided to exclude the data of all patients included in Bosnian clinical sites from the analysis reported in the updated version of the CSR.

Equivalence was demonstrated for the primary efficacy endpoint and is supported by the ITT sensitivity analyses and the secondary endpoints.

The high response rates in ACR20 at Week 24 observed in both treatment arms are considered clinically re-assuring and may reflect both effects of shorter treatment duration at enrolment and improved background treatment of RA patients as compared to the populations enrolled in historical rituximab trials.

From the perspective of the similarity approach, however, the high response rates appear less favourable as they limit the sensitivity of the model to detect differences between the test product and

the reference product. The equivalence margin of ±13% was implicitly accepted with the assumption of a 50 to 60% effect size during the EMA scientific advice procedure in 2011.

Results of the secondary efficacy parameters, ACR 50, ACR 70, DAS28-ESR, and EULAR response at Week 24, were similar for both treatment groups and supported by the ITT sensitivity analyses. Differences noted in the Kaplan-Meier analyses of the time to first onset of ACR 20 response and of EULAR response, are small and not considered relevant.

Differences observed in pre-defined subgroup analyses in particular of seronegative patients and of patients with lower disease activity at baseline require further analyses and could be regarded as clinically relevant. Results of the subgroup analysis in seronegative patients contradict the findings of previous studies with MabThera. According to the MabThera SmPC the probability of achieving an ACR20 response at Week 24 was significantly less in the group of seronegative patients.

Subgroup differences for ACR20 response as observed in the subgroup analyses are replicated in adjusted multivariable ANOVA models with treatment interactions for baseline sero-positivity, duration of RA, baseline disease severity (DAS28-ESR), gender and age group.

The interaction models show that the differences in treatment effects observed between MabThera and MabionCD20 are most likely not only based on differences in prognostic factors of the population but are due to differences in the originator and biosimilar product. Generally, the safety profile of MabionCD20 appears to be similar to the safety profile of MabThera for the double-blind part of study MabionCD20-001RA. However, underreporting of AEs casts doubt on the completeness and reliability of the AE data thereby interfering with the similarity assessment.

The size of the long-term safety database for MabionCD20 is small, less than 200 patients including 79 patients re-treated with a second course of MabionCD20 and 115 patients not re-treated. In addition, as for the efficacy data, the reliability of the long-term safety data in re-treated patients is currently unclear. Analyses of immunogenicity data up to 1 year were not provided for re-treated patients.

Study MabionCD20-001RA was a confirmatory study to compare the efficacy, safety and PK/PD of MabionCD20 vs. MabThera. Whereas the issues and uncertainties concerning efficacy and safety do not constitute a major objection to the similarity assessment themselves, the totality of the remaining issues and uncertainties surrounding the acceptability of the data constitute a major objection. These clinical issues are, however, addressed in the LoOI along with further questions which, at present, preclude a positive benefit-risk balance.

**MabionCD20-002NHL**

Biosimilarity in PK/PD can be considered adequately demonstrated.

Generally, the assessment of the safety data is limited by the unequal randomization (5:2) and the low numbers of treated patients (MabionCD20 100 vs. MabThera 40).

There was a slight numerical difference in the ORR at Week 26 between the 2 treatment groups, in the PP population (MabionCD20 89.2% versus MabThera 93.1%) in favour of MabThera which was also noted in the ITT sensitivity analyses. This difference of 3.9% (95% CI –15.54; 7.71) is considered comparable and not clinically relevant.

The AE data for study MabionCD20-002NHL showed numerical imbalances in AE and SAE incidences, severity and deaths. These imbalances were in disfavour of MabionCD20. Some AEs were observed more frequently in the MabionCD20 arm, severe neutropenia, pneumonia, cardiac events, and deaths.

Overall, the profile of TEAEs appears clinically comparable between treatment groups with the exception of cardiac events which were twice as common in the MabionCD20 group compared to the MabThera group. Although the proportion of patients with cardiac or vascular disorders were slightly

higher in the MabionCD20 group, no relevant differences were observed in systolic blood pressure, diastolic blood pressure, pulse, ECG, ECG abnormalities and results of transthoracic echocardiography at baseline.

Of importance and concern is the imbalance in deaths, 8.0% in the MabionCD20 group vs. none in the MabThera group which persisted over the open-label follow-up period.

Given that study MabionCD20-002NHL is a PK/PD bioequivalence trial and efficacy and safety data were assessed as secondary parameters, results of tumour response do not raise a concern regarding similarity. The sample size (especially in the MabThera arm) is too small to base any sound conclusions neither in favour nor in disfavour of the biosimilar.

This is in contrast to the safety data, where in particular the imbalance in deaths is seen as a safety signal which constitutes a major objection. The totality of the efficacy and safety data precludes a positive benefit-risk balance. At the time of the adoption of this report, the safety outstanding issues are raised to the applicant together with additional questions.

### 5.7.2. Balance of benefits and risks

***Quality***

Biosimilarity on a quality level and on functional biological activity is currently not considered demonstrated.

***Non-clinical***

N/A

***Clinical***

Clinically, equivalence of MabionCD20 has been demonstrated for PK in 2 trials and two different indications (rheumatoid arthritis and diffuse large B-cell lymphoma). Despite the fact that there were numerically differences between the treatment arms, the tumour responses in the Study MabionCD20-002NHL were comparable between the treatment arms.

Equivalence has been demonstrated for the main efficacy parameters in the confirmatory trial in the indication in rheumatoid arthritis with supportive evidence from the trial in diffuse large B-cell lymphoma. However, the results that deviate considerably from the initial assumptions question sensitivity of the clinical model and results from (pre-specified) subgroup analyses cast doubt on the consistency of effects.

Overall, at the time of adoption of this report, biosimilarity is currently not considered demonstrated since several uncertainties have been detected on efficacy and safety and the potential impact on results is unknown.

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

None

## *5.8. Conclusions*

The overall B/R of MabionCD20 is currently negative.

# 6. Extrapolation of safety and efficacy

The Applicant is requesting for MabionCD20 the same indications that are authorized for the reference medicinal product, MabThera, and provided a deep discussion on extrapolation of indications.

To sum up, one study in each category of indications: B-cell malignancies (CLL and NHL) or diseases of elevated immune activity (RA, GPA and MPA) have been conducted. Mechanism of action, pharmacokinetics, pharmacodynamics, safety (including immunogenicity) can be considered at least similar for indications included in the same category. Therefore, extrapolation of indications from NHL (supportive study) and RA (pivotal study) patients to the rest of authorized indications seems to be feasible, provided that issues on quality, bioequivalence and clinical studies can be resolved.

# 7. Recommended conditions for marketing authorisation and product information

## *7.1. Proposed list of post-authorisation measures*

N/A

## *7.2. Conditions for the marketing authorisation*

N/A

## *7.3. Other Conditions*

The PRAC Rapporteur considers that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

An educational material for healthcare professionals to address the risk(s) of

- Infections (including serious infections)
- Progressive multifocal leukoencephalopathy (PML)
- Administration route error

An educational material for patients to address the risk(s) of

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

A patient alert card to address the risk(s) of

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

## *7.4. Summary of product characteristics (SmPC)*

See commented version attached separately. In order to avoid further variations after MA of the biosimilar product, we propose to bring the content in line with current guidance documents during this application procedure. In this context it is requested that the SmPC of the originator should also reflect current guidelines/ recommendations with the next forthcoming variation affecting the content of the SmPC.

### *7.5. Package leaflet (PL)*

See point mentioned above.

### *User consultation*

According to the articles 59(3) and 61(1) of Directive 2001/83/EC as amended, it is required that consultations with target patient groups shall be carried out in order to demonstrate the readability and usefulness of the package leaflet to patients.

With regard to biosimilars a bridging report could also be provided to demonstrate that the package leaflet is well written and designed to be clear and understandable, enabling the users to act appropriately. The applicant proposed to perform a bridging report at a later stage during the clock stop phase (D120) but in contrast to the bridging a full user testing was carried out by the consultant and included in the response package. This readability test demonstrated excellent results, therefore the outstanding point is fulfilled.

### *Conclusion from the checklist for the review of user consultation*

The success criteria are demonstrated

### Quick Response (QR) code

N/A

## 8. QRD checklist for the review of user testing results

### *PRODUCT INFORMATION*

| | |
|---|---|
| **Name of the medicinal product:** | **Rituximab Mabion** |
| **Name and address of the applicant:** | **Mabion S.A.** |
| **Name of company which has performed the user testing:** | [redacted] |
| **Type of Marketing Authorisation Application:** | **NA** |
| **Active substance:** | **rituximab** |
| **Pharmaco-therapeutic group**<br>**(ATC Code):** | **antineoplastic agents, monoclonal antibodies, (L01X C02)** |
| **Therapeutic indication(s):** | **Biosimilar medicinal product (see reference medicinal product MabThera)**<br>**Indications proposed by the applicant:**<br>**Non-Hodgkin's lymphoma (NHL)**<br>MabionCD20 is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.<br>MabionCD20 maintenance therapy is indicated for the treatment of follicular lymphoma patients responding |

| Name of the medicinal product: | Rituximab Mabion |
|---|---|
| | to induction therapy.<br><br>MabionCD20 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.<br><br>MabionCD20 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.<br><br>**Chronic lymphocytic leukaemia (CLL)**<br><br>MabionCD20 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.<br><br>See section 5.1 for further information.<br><br>**Rheumatoid arthritis**<br><br>MabionCD20 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.<br><br>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.<br><br>**Granulomatosis with polyangiitis and microscopic polyangiitis**<br><br>MabionCD20, 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). |