CLINICAL STUDY REPORT – 48 WEEKS ANALYSIS

A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP COMPARATIVE BIOEQUIVALENCE TRIAL OF MABIONCD20 (MABION SA) COMPARED TO MABTHERA (RITUXIMAB, ROCHE) IN PATIENTS WITH RHEUMATOID ARTHRITIS

1 TITLE PAGE

Name of test drug/ investigational product(s):	MabionCD20®[1] MabThera® (rituximab)
Indication studied:	Rheumatoid Arthritis
Study design:	Multicenter, randomized, double-blind, parallel-group, active-control, clinical equivalence study
Name and address of sponsor:	Mabion S.A. Langiewicza str. 60, 95-050 Konstantynów Łódzki, Poland
Protocol identification	MabionCD20-001RA (MABRA) (MB01)
EudraCT-Number	2012-003194-25
Development phase of study	Phase III
Study initiation date:	14-May-2013 (screening of first patient)
Date of early study termination (if applicable):	Not applicable
Study completion date (last subject completed):	15-May-2017 (last patient last visit for 24 Weeks Analysis) 26-Oct-2017(last patient last visit for 48 Weeks Analysis)
Name and affiliation of Coordinating / Principal Investigator(s) or sponsor's responsible medical officer (SRMO):	Mariusz Korkosz, MD, PhD, Assoc. Prof. Małopolskie Centrum Medyczne s.c. Rejtana str. 2 30-510 Kraków, Poland
Sponsor's contact person:	Sławomir Jaros, PhD Chief Scientific Officer, Chief Operational Officer
Date of report:	28-Mar-2019 (version 2.0, 48 weeks) (final)

[1] Throughout this document, symbols indicating proprietary names (®, ™) may not be displayed for ease of readability; the appearance of product names without these symbols does not imply that these names are not protected.

2 SYNOPSIS

Name of Sponsor/Company: Mabion S.A.	**Individual Study Table Referring to Study Report:**	**(For National Authority Use only)**
Name of Finished Product: MabionCD20®		
Name of Active Ingredient: Recombinant mouse/human glycosylated IgG1-k immunoglobulin against CD20		

Study title:
A Randomized, Double-blind, Parallel-group Comparative Bioequivalence Trial of MabionCD20® (Mabion SA) Compared to MabThera® (rituximab, Roche) in Patients with Rheumatoid Arthritis

Sponsor's study number:	MabionCD20-001RA (MABRA) (MB01)
EudraCT number:	2012-003194-25
Sponsor:	Mabion S.A. (Langiewicza str. 60, 95-050 Konstantynów Łódzki, Poland)

Investigators:
Mariusz Korkosz, MD, PhD, Assoc. Prof. (Małopolskie Centrum Medyczne s.c., Rejtana str. 2, 30-510 Kraków, Poland)

Study center(s):
The study was initiated in 7 countries (Croatia, Bosnia and Herzegovina, Georgia, Lithuania, Poland, Serbia and Ukraine) and conducted at 50 study centers in 6 countries, as no patients were enrolled in Croatia.

Publication (reference):
Not applicable.

Studied period (years):		**Phase of development:**
First patient, first visit:	14-May-2013	Phase III
Last patient, last visit (24 Weeks):	15-May-2017	
Last patient, last visit (48 Weeks):	26-Oct-2017	

Objectives:
Primary:
To demonstrate biosimilarity between test product (MabionCD20®) and reference product (MabThera®, rituximab) in patients with active Rheumatoid Arthritis (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:
1. To evaluate biosimilarity between test product (MabionCD20®) and reference product (MabThera®, rituximab)
   - based on efficacy and response scores: percentage of patients achieving ACR20, ACR50, ACR70, Changes in Disease Activity Score (DAS28-ESR), and 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 was the primary objective), and 48
   - based on pharmacodynamic endpoints: Minimum level (C_{min} B-cell) and time to reach the minimum level (T_{min} B-cell) of circulating CD19+ B-cells, area under the circulating CD19+ B-cell level versus time curve from the first administration to final time point at Week 24 (AUC_{0-t} B-cell), duration of B cell depletion (T B-cell), i.e. time interval over which the level of circulating CD19+ B-cells was <30 cell/µL or below the detection limit, and follow-up of levels of circulating CD19+ B-cells until re-treatment or up to 48 Weeks
2. To demonstrate comparative safety and tolerability of a single course of treatment (two infusions spaced two Weeks apart) of MabionCD20® and MabThera® (rituximab) in patients with moderate to severe active RA
   - based on safety endpoints: Adverse Events, Clinical Laboratory Assessments, Vital signs, and Electrocardiograms (ECG)
3. To demonstrate bioequivalence in pharmacokinetic (PK) characteristics between MabionCD20® and MabThera® (rituximab)
   - based on primary PK endpoints: area under the plasma concentration-time curve from the first administration to final time point at Week 24 (AUC_{0-t}) and maximum measured plasma concentration after the second infusion of the treatment course (C_{max} second)
   - based on secondary PK endpoints: maximum measured plasma concentration after the first infusion of the treatment cycle (C_{max}-first), plasma concentration just before next study treatment infusion on Day 15 (C_{trough}), $t_{½}$ after the second infusion, Volume distribution at steady state (VD), and Clearance (CL)
4. To demonstrate safety of MabionCD20® as second cycle treatment after initial MabThera® (rituximab) treatment

Design:
Multicenter, randomized, double-blind, parallel-group, active control study
Methodology:
Eligible patients were randomized strictly sequentially (ratio 1:1) to 1 of 2 available double-blind treatments:
- Group 1 with investigational product (MabionCD20®; test product)
- Group 2 with active-control treatment (MabThera®, rituximab; reference product)

Treatment in both groups consisted of 2 intravenous infusions of MabionCD20® or MabThera® (rituximab), at a dose of 1000 mg/infusion, on Days 1 and 15.
Patients were allowed to re-enter the study for the second time if they were screening failures.
Patients were allowed to be treated again (re-treatment) when they had a clinical response which was followed by a clinical relapse and if assessments at Week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20® or MabThera® (rituximab) was then provided under open-label conditions as two infusions of 1000 mg each, separated by two weeks.
Re-treatment could be started at least 24 Weeks after first course of treatment and if a patient met the following criteria:
- Response to first course of treatment with at least a 1.2-point decrease in DAS28-ESR score starting from the 16th Week after

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the first infusion, with low disease activity (defined as a DAS28-ESR score ≤3.2)

- Negative history for adverse events that contraindicated rituximab therapy
- Reactivation of the disease by Week 24 with an increase in DAS28-ESR score ≥0.6 and residual disease activity with a DAS28-ESR score >3.2

Study endpoints were evaluated in the PP (Per-Protocol) population for the main analyses and in the ITT (Intent-to-Treat) population as sensitivity analyses. Safety parameters were evaluated in all patients who received at least a portion of one infusion. Pharmacokinetic (PK) and pharmacodynamic (PD) parameters were determined only in patients enrolled at selected medical centers.

Interim analysis:

This clinical study was a comparative bioequivalence trial and included a PK sub-study. One formal blinded interim analysis and one final analysis were foreseen for the study.

The final analysis of the study was performed in two steps: the main results were presented first and comprise the final data until and including Week 24 (database lock 16-Aug-2017), whereas study visits later than Week 24 (open-label period, second course of study medication, re-treatment) were included in this updated clinical study report after database lock of the data collected in the open-label period (database lock on 29-Jan-2018).

To address the limited availability of literature data on variability of PK parameters for rituximab in patients with active RA, a blinded interim analysis was performed. Full PK profiles were obtained in at least 106 patients (53 per group) who had completed their Week-4 assessments. If the intra-subject coefficient of variation in primary PK endpoints C_{max} or AUC_{0-t} was ≥35%, the sponsor could enroll additional patients to reach sufficient power to evaluate PK-related secondary study objectives. The parameters C_{max}-second and AUC_{0-t} had coefficients of variation <35%, therefore it was not necessary to increase the sample size for PK and PD analyses. The final PK analysis for the entire study was performed after completion of the Week-24 assessments.

Number of patients:

Planned: 734 randomized patients (367 in each group)

Assuming that 85% of randomized patients complete the study according to protocol, but less patients could be included in case the drop-out rate was less than expected. Necessary for statistical evaluation of clinical equivalence hypothesis on primary objective at 80% power: 624 patients (312 in each group).

Analyzed: For safety: 628 randomized and treated patients in the safety set (319 in the MabionCD20® group and 309 in the MabThera® group)

For efficacy: 629 patients in the intention-to-treat set: (318 in the MabionCD20® group and 311 in the MabThera® group)

590 in the per-protocol set: (298 in the MabionCD20® group and 292 in the MabThera® group)

Due to EMA inspection findings at a Bosnian site (BOS05), as a matter of abundant caution, Mabion decided to exclude all data of patients from all Bosnian clinical sites from the analysis reported in the updated version of the clinical study report. This decision was taken to ensure the high quality of the underlying data and will constitute an additional check to the validity of overall study conclusions.

Indication: Rheumatoid Arthritis (RA)

Diagnosis and main criteria for inclusion:

Adult male and female patients aged 18–80 years with a body surface area (BSA) between 1.5–2.2 m^2 suffering from moderate to severe, active RA (diagnosed according to 1987 American Rheumatism Association (ARA) criteria), despite treatment with methotrexate (at 10–25 mg/Week for at least 12 Weeks with the last 4 Weeks at a stable dose) or other DMARDs, with a minimum disease duration of 6 months prior to screening were eligible for enrollment. Eligible patients were also naïve to TNF-antagonist treatment and to any other biological therapy with monoclonal antibodies, had no history of or current other rheumatic autoimmune or inflammatory joint disease than RA, and had no functional class IV disease according to American College of Rheumatology.

Test product:	MabionCD20®
Batch numbers:	0101113; 0101114; 0101115; 0101213; 0101214; 0101312; 0101314; 0101315; 0101412; 0101413; 0101415; 0101514; 0101615;
Dose:	1000 mg MabionCD20® in 1 intravenous infusion Posology was based on SmPC of MabThera® (rituximab) for treatment of patients with RA
Mode of administration:	Intravenous infusion
Reference product:	MabThera® (rituximab)
Batch numbers:	H0148B03; H0625B02; H0636B03; H0710B03; H0720B02; H0725B04; H0751B01; N3498B02; N3511B03; N7005B03; N7011B02; N7014B07; N7025B04; N7032B04; N7035B06; N7042B06; N7052B08; N7076B06; N7089B05; N7098B05; N7103B06; N7108B02; N7115B07; N7119B03; N7120B02; N7127B13; N7136B02;
Dose:	1000 mg MabThera® (rituximab) in 1 intravenous infusion First infusion of each course: The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it could be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Second infusion of each course: Subsequent doses of MabThera® (rituximab) could be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
Mode of administration:	Intravenous infusion

Duration of treatment: Two intravenous infusions of MabionCD20® or MabThera® (rituximab) at 1000 mg/infusion were administered on

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Day 1 and Day 15 of a 24-Week treatment and observation period, after which the need for a second course (re-treatment) was evaluated. Patients could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at Week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera (rituximab) was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks. During the observation period, assessments of efficacy, laboratory values, and safety were conducted at regular intervals up to 48 Weeks.

Background treatment:

All eligible patients had background treatment with methotrexate at 10–25 mg/Week for at least 12 Weeks with the last 4 Weeks at a stable dose. To counter any undesired effects of methotrexate, folic acid (5–15 mg/Week orally) could be used.

Premedication before each infusion:

To decrease incidence and severity of infusion-related reactions, patients received premedication with 100 mg intravenous methylprednisolone to be completed 30 ± 10 minutes prior to the MabionCD20® or MabThera® (rituximab) infusions. According to the special warnings and precautions for use in the SmPC of MabThera® (rituximab), premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol) and an anti-histamine (e.g., diphenhydramine) was administered before each infusion of MabionCD20® or MabThera® (rituximab). The premedication schedule and concomitant treatments were the same for the first and second courses of treatment.

Criteria for evaluation:

Efficacy / clinical pharmacology:

Efficacy and response scores:

1. The American College of Rheumatology (ACR) core population of disease-activity measures included:
   - tender joint count (of 68 joints)
   - swollen joint count (of 66 joints)
   - patient's assessment of pain
   - patient's global assessment of disease activity
   - physician's global assessment of disease activity
   - patient's assessment of physical functions using the Health Assessment Questionnaire Disability Index (HAQ-DI) score
   - evaluation of erythrocyte sedimentation rate (ESR)

   A patient achieved ACR20 if the following criteria were satisfied:
   - percent improvement from baseline was ≥ 20% in tender joint count and
   - percent improvement from baseline was ≥ 20% in swollen joint count and
   - percent improvement from baseline was ≥ 20% in 3 of the 5 remaining ACR core population measures including
     - patient's assessment of pain,
     - patient's global assessment of disease activity,
     - physician's global assessment of disease activity,
     - patient's assessment of physical functions HAQ-DI
     - laboratory evaluation of acute phase reactant (erythrocyte sedimentation rate, ESR)

     (a patient achieved ACR50 or ACR70 if the above criteria were satisfied, replacing 20% with 50% or 70%, respectively)
2. The disease activity score (DAS28-ESR) is a composite disease activity index of 4 clinical variables involving:
   - tender joint count (up to 28 joints, tender28),
   - swollen joint count (up to 28 joints, swollen28),
   - erythrocyte sedimentation rate (ESR, in mm/h),
   - the patient's assessment of global disease activity using a 10-cm Visual Analog Scale (VAS) with range 0–100, with 0 being no disease activity and 100 being maximal disease activity

   The percentage of patients with each level of EULAR response (good, moderate or no response):
   - good EULAR response: the patient demonstrated a significant change from baseline (<-1.2) and reached low disease activity (DAS28-ESR ≤ 3.2).
   - moderate EULAR response: the patient demonstrated a minimum change from baseline in DAS28-ESR of >-0.6 to <-1.2 and achieved an endpoint DAS28-ESR ≤ or >5.1.
3. Patient's Global Assessment of Disease Activity using a VAS
4. Physician's Global Assessment of Disease Activity using a VAS
5. Health Activities Questionnaire (HAQ-DI)

Pharmacodynamic endpoints:

Blood sampling and determination of circulating CD19+ B-cell, and for CD3+, CD4+, and CD8+ T-cell levels was performed at selected study centers, for the same patients also having the PK sampling.

The time points were: within 60 min before the first infusion (Day 1), 24 h (Day 2) and 48 h (Day 3) after first infusion, within 60 min before the second infusion (Day 15), 24 h (Day 16) and 48 h (Day 17) after the second infusion, and on Day 28 (Week 4), Day 112 (Week 16) and Day 168 (Week 24) after the first infusion. For patients receiving only one course of treatment, additional blood samples were collected on Day 224 (Week 32), Day 280 (Week 40) and Day 336 (Week 48).

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Pharmacokinetic endpoints:

Serum concentration of MabThera® (rituximab) or MabionCD20® was measured in serum of patients enrolled at selected study centers using a validated direct-antigen enzyme-linked immunosorbent assay (ELISA) at the Research and Development Centre of Mabion S.A.
The time points for blood sampling for PK analysis were:
Within 60 min before the first and second infusion and 30 min after completion of the first and second infusion (Day 1 or 15), 24 h (Day 2 or 16) and 48 h (Day 3 or 17) after first and second infusion, and on Day 28 (Week 4), Day 56 (Week 8), Day 84 (Week 12), Day 112 (Week 16), Day 140 (Week 20) and Day 168 (Week 24) after the first infusion.
Pharmacodynamic and pharmacokinetic parameters were derived using non-compartmental analysis with Phoenix WinNonlin Version 8.0 according to the SAP for PK and PD analysis.

Safety:

Incidence of adverse events, concomitant medication use, laboratory values, physical examinations, vital signs, chest x-ray, and ECG abnormalities were assessed at regular intervals for up to 24 Weeks (double-blind period) and up to 48 Weeks (open-label period). Medical histories, current medical conditions and adverse events were coded using the MedDRA version 16.0.

Statistical methods:

Clinical equivalence:

The percentage of treated patients who achieved ACR20 at Week 24 (primary objective) was calculated with the exact 95% confidence interval (CI, according to Clopper-Pearson) for each treatment, MabionCD20® and MabThera® (rituximab). The difference in percentages between both treatments and the exact 95% confidence limits were computed (according to Zhang and Chan). Clinical equivalence of treatments was demonstrated if the two-sided 95% CI for the between-group difference was within -13 to +13%. The primary analysis was performed with the PP population and sensitivity analyses with the ITT population.
For secondary efficacy endpoints: percent of patients achieving ACR20, ACR50, ACR70, and percent of patients with moderate or good response on the EULAR scale at Weeks 4, 8, 12, 16, 20, 24 (except for ACR20 as it was the primary objective), were reported with their exact 95% CI for the between-group difference. The change in DAS28-ESR at Weeks 4, 8, 12, 16, 20, 24 was analyzed using an ANCOVA model with treatment and pooled center as factors and baseline value as covariate. Least square (LS) means differences with 95% CI between both treatments were derived at each time point.

Pharmacodynamic biosimilarity:

The main analysis for pharmacodynamic biosimilarity was performed on $AUC_{0\text{-}t}$ B-cell and C_{min} B-cell on the PD-PP population. The between-group mean differences and 95%CI were calculated using an ANOVA with treatment and pooled center as factors. The data were log-transformed to account for the skewed distribution and the ratios of means were used to compare both treatment groups. Point estimates (geometric means and ratio of geometric means) were calculated from back-transforming the LS-means of the natural log-transformed values of PD parameters. 95%CIs for the ratio of the geometric means of both treatments were estimated.

Pharmacokinetic bioequivalence:

The main analysis for pharmacokinetic bioequivalence was performed on C_{max}-second and $AUC_{(0\text{-}t)}$ on the PP population, using an ANOVA model with treatment and pooled center as fixed effects. Point estimates (geometric means and ratio of geometric means) were calculated from back-transforming the LS-Means of the natural log-transformed values of PK parameters. PK parameters were natural log-transformed prior to analysis and 90%CIs for the ratio of the geometric means of both treatments were produced. Due to the formal interim analysis that was performed when 106 patients with evaluable PK profiles completed their Week-4 assessments, to control for the planned alpha level of 5%, an adjusted alpha of 4.7% was used for PK analyses when calculating the confidence intervals.
Bioequivalence between both treatments was confirmed when both two-sided 90% CIs for the geometric means of PK endpoints were completely contained within the acceptance criteria interval 0.80 to 1.25. Sensitivity analyses for the primary PK endpoints using the PK-ITT population were also performed on log-transformed geometric means of the AUCs and C_{max}–second. Between-group mean differences of the log-transformed data and their 90% CI were calculated using an ANOVA with treatment and pooled center as factors. Back-transformation was applied to produce the estimate of between-group geometric mean ratio and its 90% CI. Bioequivalence was demonstrated if the resulting CI's for geometric means of $AUC_{(0\text{-}t)}$ and C_{max}-second were within 0.8 to 1.25.

Safety:

Safety evaluations based on incidence, severity, and type of adverse events, and clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results are analyzed and presented descriptively.
Mean changes from baseline in each of the ACR core population components, other PK endpoints and PD endpoints are presented descriptively.

Open-label treatment:

For the analysis of data collected between Week 24 and Week 48, patients were divided in 2 groups: patients eligible for a second course of study drug receiving one portion of an infusion of the second course of study medication and patients who did not receive a portion of the second course of study medication. Further, patients were analyzed according to the actual treatment that they had received during the first and the second course of treatment. If a patient had received MabionCD20 and MabThera during the same course, the patient was assigned to the same patient group who had received MabionCD20 only. Since the treatment group of the second course of treatment did not depend on the randomized treatment group from the double-blind study phase, patients who received a second course of treatment were summarized within the following groups: MabionCD20 after MabThera, MabThera after MabionCD20, MabionCD20 constantly, and MabThera constantly.

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Subgroups:

Subgroup analyses were performed for the primary efficacy endpoint (ACR20 at Week 24) for the ITT population. The subgroups were gender, baseline sero-positivity (for RF or anti-ACPA), duration of RA and baseline DAS28-ESR.

SUMMARY

- The double-blind period of the study was conducted between 14-May-2013 and 15-May-2017, the open-label period of the study lasted until 26-Oct-2017. A total of 898 patients were screened and 709 subjects were randomized into the study. The 80 patients (11.3% out of 709 enrolled) in Bosnia and Herzegovina were excluded from the efficacy, safety and immunogenicity data presented in this report. In the remaining 629 patients that were randomized, 318 patients were randomized into the MabionCD20 and 311 into the MabThera treatment group.
- 628 patients received study medication: 319 received MabionCD20 at least once and 309 received only MabThera during the first course of treatment and comprised the SAF. Four patients randomized to MabionCD20 received only MabThera and five patients randomized to MabThera received MabionCD20 at least once during the double-blind study period. Of the SAF, 273 patients (43.5%) were enrolled in Poland, 172 patients (27.4%) in Georgia, 139 patients (22.1%) in Ukraine, 40 patients (6.4%) in Serbia and 4 patients (0.6%) in Lithuania. In Croatia the study was initiated, but no patients were recruited.
- A total of 604 patients entered the open-label period, 215 of these patients did not receive a second course of treatment whereas 389 patients received at least one infusion of MabionCD20 or MabThera at Week 24. Of the 389 patients, 81 patients received MabionCD20 after having received MabThera, 117 patients received MabThera after having received MabionCD20, 79 patients received MabionCD20 in both study periods and 112 patients received MabThera in both study periods. Of the 215 patients who did not receive any further treatment with MabionCD20 or MabThera during the open-label period, 110 patients had received MabionCD20 and 105 patients had received MabThera during the double-blind study period.
- Patients enrolled in the study were all Caucasian, most of them being women (83.1% of 628 patients in SAF). Most patients were younger than 65 years (87.3% of 628 patients in SAF), their age ranged from 20 to 76 years, with a median age of 54.0 years (52.2 ± 11.78, mean ± SD).
- The proportion of patients with major and minor protocol deviations was balanced between both treatments. A total of 39 patients (21 patients randomized to MabionCD20 and 18 patients to MabThera) had at least one major protocol deviation or the ACR20 at Week24 was not available and were therefore excluded from the per protocol analysis. As a result, the per-protocol set comprised 590 patients; since 4 patients randomized to MabionCD20 only received MabThera and 3 patients randomized MabThera only received MabionCD20, 298 patients were analyzed in the MabionCD20 group and 292 patients in the MabThera group.
- Nearly all patients (604 patients, 96.2%) in the SAF completed the double-blind period of the study with 24 weeks of treatment. Overall, 24 patients (3.8%) terminated the study early (before 24 weeks), of whom 13 patients were treated with MabionCD20 and 11 with MabThera. Nearly all patients who received a second course of treatment (380 patients, 97.7%) completed the open-label period of the study. Overall, 9 patients (2.3%) terminated the study prematurely (between 24 and 48 weeks), of whom 2 patients were treated with MabionCD20 after having received MabThera in the double-blind study period, 3 patients treated with MabionCD20 in both study periods and 4 patients who were treated with MabThera during the whole study period. Not only the number of patients, who terminated, but also the time points and the reasons for early termination were balanced between both groups. Of the 24 patients who terminated the study early before 24 weeks, 2 patients terminated the study on Day 1, 5 patients terminated between Day 2 and prior to receiving a second infusion, and 17 patients terminated the study after the second infusion. Nine patients discontinued before the second infusion (with 4 patients in the MabionCD20 and 5 patients in the MabThera group). One AE led to discontinuation of the first infusion on Day 1, ("bronchospasm" and "urticaria" in the MabThera group). The infusion was stopped because of the event and the patient did not receive any further study medication. The patient discontinued the study due to 'Withdrawal by subject' and recovered completely from this event. One further patient in the MabThera group discontinued the study on Day 1 due to the adverse event "cough and rhinorrhea" after having completed the first infusion. The other 7 patients who discontinued before receiving the second infusion discontinued the study due to adverse event (2 patients in each treatment group), withdrawal by subject (1 patient in each treatment group) and technical problem (1 patient in the MabionCD20 group).
- Demographics and other baseline characteristics of the treated patient population were balanced between both treatment groups in all analyses. The two treatment groups were similar with respect to all baseline efficacy variables in SAF, ITT and PP populations. Also, medical history and current medical conditions were balanced with respect to SOCs and incidences of PTs.
- Between treatment groups, prior and concomitant medication was balanced with respect to the occurrence of therapeutic main group (ATC level 2) and chemical, therapeutic and pharmacological subgroup (ATC level 4) and recorded use in patients. In 47 patients (7.5%) and balanced between both treatment groups, the use of rescue medication was recorded during the double-blind study period. In the open-label study period, 18 patients (4.4%) overall and mostly in the patient group who received MabThera constantly in both study periods (10 patients, 8.9%) received rescue medication.

EFFICACY RESULTS

Primary endpoint:

This multicenter, randomized, double-blind, parallel-group, active-control study of MabionCD20 versus MabThera met its primary objective in the PP analysis set. The percentage of patients achieving ACR20 response at Week 24 was 79.2% for MabionCD20 and 84.9% for MabThera. The 95% confidence interval for the difference of 5.7% between both treatments of [-0.5%; 12.0%] was contained in the equivalence interval of -13% to 13%.

The efficacy analysis of the ACR20 response at Week 24 with updated ITT population with various imputation methods or no imputation

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showed consistent and comparable results. In all analyses based on the ITT, the two-sided 95% CI for the difference was contained in the equivalence interval of -13% to 13% (boundaries included). Therapeutic equivalence between MabionCD20 and MabThera was confirmed in all ITT analyses, showing consistent equivalence of both treatments. All analyses yielded very similar results.

Secondary efficacy endpoints, PK and PD analyses

- The secondary endpoints, the percentages of patients in the PP set achieving ACR20, ACR50, ACR70, changes in DAS28-ESR, and the percentages of patients with a moderate or good response on the EULAR scale at Weeks 4, 8, 12, 16, 20 and 24, were comparable between the treatment groups.
- Both treatments had similar effects on circulating B-cells. The PD effect of both treatments had its onset at Day 3 with complete depletion and slight repletion of B-cells after Week 16, corresponding to low serum levels of rituximab. At Week 16, C_{min} B-cell was above 0 in 4 patients of the MabionCD20 group and in 7 patients of the MabThera group. The two-sided 95%CI of the estimated mean ratio was [51.8; 120.1] for AUC_{0-t} B-cell and [136.9; 391.5] for C_{min} B-cell with both treatments.
- Bioequivalence in pharmacokinetic endpoints between both treatments was confirmed and consistent between PK PP and PK ITT populations. The two-sided 90% CIs were completely contained within the acceptance criteria interval 80% to 125% for both primary PK endpoints (AUC_{0-t} and C_{max}-second) and all secondary PK endpoints in both PK PP and PK ITT populations.
- In the open-label study period, patients who received a second course of treatment clearly showed better efficacy results at Week 48 compared to patients who did not receive a second course of treatment. This could be seen for the ACR20, ACR50, ACR70, DAS28-ESR, and with good EULAR response. These results are in line with the selection criteria to provide a second course of treatment to patients. No relevant differences between the two treatments were noted at Week 48 irrespective of a possible switch of treatment during the second course at Week 24.
- The results in the analysis that included patients from Bosnia were very similar to the presented analysis excluding patients from Bosnia. All analyses with respect to efficacy variables would lead to the same interpretation as shown in this section. Of note, no Bosnian patient was included in the pharmacokinetic or pharmacodynamic sampling.

SAFETY RESULTS:

- Overall, 98.7% of patients in the MabionCD20 group and 98.4% of patients in the MabThera group received the complete set of 2 infusions as per the protocol (i.e. infusion at Day 1 and Day 15) during the 24-weeks double-blind study period. Four patients in the MabionCD20 group (1.3%) and 5 patients in the MabThera group (1.6%) received only 1 infusion. Of the 389 patients, who received a second course of treatment at Week 24, 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 1 infusion only at Week 24.
- During the double-blind study period, the overall incidence of TEAEs was comparable between the two rituximab preparations: 42.6% in the MabionCD20 group and 42.1% in the MabThera group. During the open-label study period, the overall rates of all TEAEs that started after the first infusion of study drug of the second course of treatment were 21.0% in the MabionCD20 after MabThera group, 32.5% in the MabThera after MabionCD20 group, 24.1% in the group receiving MabionCD20 constantly, and 38.4% in the group receiving MabThera constantly. The overall rates of all TEAEs during the course of the open-label study period in those 215 patients who received no second course of treatment were 11.8% in the MabionCD20 group and 9.5% in the MabThera group.
- During the double-blind study period, most TEAEs were of mild or moderate intensity; only few were severe (1.3% in the MabionCD20 and 1.9% in the MabThera group). Also, during the open-label study period, most TEAEs were mild or moderate in those 389 patients who received a second course of treatment. In those 215 patients who did not receive second course of treatment during the open-label study period, all TEAEs were of mild or moderate intensity.
- During the double-blind study period, study drug-related TEAEs occurred in 28.2% of patients in the MabionCD20 group and 28.5% in the MabThera group. The infusion related reactions (IRRs) and leukopenia were the most frequently reported events in both treatment groups. During the open-label study period and in those patients, who received a second course of treatment, study drug-related TEAEs occurred in 22.2% of patients switching to MabThera after MabionCD20, 25.9% of patients receiving MabThera constantly,12.3% of patients receiving MabionCD20 after MabThera and 16.5% receiving MabionCD20 constantly. Study drug-related TEAEs were relatively infrequent in those patients who received no second course of treatment; they occurred in 2.7% of patients in the MabionCD20 group and in 2.9% of patients in the MabThera group. The reported drug-related TEAEs are in line with the known safety profile of rituximab.
- No patient died during the double-blind and open-label period of study. During the double-blind study period, serious TEAEs were infrequent and their incidence was comparable between the treatment arms, occurring in 2.2% of patients in the MabionCD20 and 1.9% of patients in the MabThera group. During the open-label study period and in the patients with no second course of treatment, there was 1 serious TEAE reported in 1 patient (0.9%) in the MabionCD20 and no serious TEAE in the MabThera group. Patients who received a second course of treatment reported 2 serious TEAEs (2.5%) in the MabionCD20 after MabThera group and 1 serious TEAE (1.3%) in the MabionCD20 constant group.
- Consistent with the adverse event analyses, the results of safety laboratory data and vital signs did not indicate any relevant differences between the two treatment groups during the double-blind study period, but also between the treatments groups during the open-label study period. This also holds true for the autoantibodies RF and ACPA, the inflammation markers CRP and ESR, and the immunoglobulins IgA, IgG, and IgM. Responsiveness to rituximab treatment was evident during the study from the decreased rheumatoid factors (RF and ACPA) and inflammation markers (CRP and ESR).
- During the double-blind period, the ADA incidence (treatment induced or boosted) was comparable between the MabionCD20 (15.2%)

Name of Sponsor/Company: Mabion S.A.	Individual Study Table Referring to Study Report:	(For National Authority Use only)
Name of Finished Product: MabionCD20®		
Name of Active Ingredient: Recombinant mouse/human glycosylated IgG1-k immunoglobulin against CD20		

and the MabThera group (14.4%). The treatment induced NAb positivity was very low with 2 patients (0.6%) in the MabionCD20 group and no NAb positive patients in the MabThera group. During the open label period, in patients not retreated at Week 24, there were 21.8% (24 out of 110) patients who were ADA positive in the MabionCD20 group compared to 23.8% (25/105) in the MabThera group. In patients who did not receive a second course of treatment, 1 patient in each treatment group was reported to have confirmed NAb positivity up to Week 48.

- Overall, the immunogenicity profile of MabionCD20 and MabThera was comparable. There was no clinically significant impact of the ADA on the PK, efficacy or safety profile.
- Overall, the MabionCD20 was well tolerated and safety profile was acceptable. The AE pattern and the intensity of the TEAEs reported in the MabionCD20 group were comparable to MabThera, and were in line with the established safety profile of rituximab, and do not point to any new signals or an undue safety risk of rituximab in the treatment of patients with RA.
- Safety and tolerability of a single course of treatment (2 infusions spaced 2 weeks apart) of MabionCD20 and MabThera was comparable. Also, a second course of treatment with MabionCD20 or MabThera during the open-label study period at Week 24 and an observation period up to 48 weeks showed both treatments to be safe and well tolerated.
- Similar results were observed in the analysis performed by including patients from Bosnia. All analyses with respect to safety endpoints and variables would lead to the same interpretation as shown above.

CONCLUSION:

- The clinical equivalence and PK bioequivalence of MabionCD20 and MabThera was evaluated in patients with moderate to severe active RA according to 1987-ARA criteria, despite treatment with at least 10 mg of MTX per week. The therapeutic equivalence of MabionCD20 and MabThera in patients with RA was confirmed based on the results in the PP set, with the 95% confidence interval [-0.5%; 12.0%] for the difference of 5.7% in ACR20 response rate between both treatments was contained in the equivalence interval of -13% to 13% (boundaries included). Results from sensitivity analysis in the ITT population also corroborated the primary analysis result. The results of the secondary efficacy endpoints were comparable between MabionCD20 and MabThera. The secondary endpoints included analyses on the percentage of patients in the PP and ITT set achieving ACR20, ACR50, ACR70, changes in DAS28-ESR, and the percentage of patients with moderate or good response on the EULAR scale at Weeks 4, 8, 12, 16, 20 and 24.
- Bioequivalence based on pharmacokinetic endpoints was confirmed as the 90% CIs for the primary PK endpoints (AUC0-t and Cmax-second) were completely contained within the interval 80% to 125%. Similar pharmacokinetic profile of both treatment groups was also observed in the descriptive evaluation of primary and secondary PK endpoints and in the mean serum concentrations with respective SDs for each time point.
- Pharmacodynamic biosimilarity based on pharmacodynamic endpoints (Cmin B-cell, AUC0-t B-cell, Tmin B-cell and T B-cell) showed that both treatments had similar effects on circulating B-cells, although biosimilarity could not be confirmed statistically.
- Inclusion of patients who were naive of TNF-alpha inhibitor or other biological antibody treatment presented the most “sensitive” testing environment for rituximab comparability testing and provides data that may support the broadening of the labeled indication for rituximab in patients who are naive of TNF-inhibitors.
- MabionCD20 was well tolerated and safety profile was acceptable. The AE pattern and the intensity of the TEAEs reported in the MabionCD20 group were comparable to MabThera. Also, a second course of treatment with MabionCD20 or MabThera at Week 24 showed the safety profile to be comparable between the treatments up to Week 48. In addition, the safety profile was also comparable between MabionCD20 and MabThera up to 48 weeks in patients who did not receive a second course of treatment at Week 24.
- The immunogenicity profile of MabionCD20 and MabThera was comparable. There was no clinically significant impact of the ADA on the PK, efficacy or safety profile.
- The safety and immunogenicity profile of MabionCD20 is in line with the established safety profile of rituximab and does not point to any new signals or an undue safety risk of rituximab in the treatment of patients with RA.
- In summary, the results demonstrated that MabionCD20 and MabThera are clinically equivalent with comparable PK, efficacy, safety and immunogenicity profile. Thus MabionCD20 and MabThera can be considered biosimilar.

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