CLINICAL STUDY REPORT

RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, COMPARATIVE BIOEQUIVALENCE TRIAL OF MABIONCD20 (MABION SA) COMPARED TO MABTHERA (RITUXIMAB BY HOFFMAN-LA ROCHE) IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

1 TITLE PAGE

Name of test drug/ investigational product(s):	MabionCD20® MabThera® (rituximab)
Indication studied	Diffuse Large B-cell Lymphoma
Study design:	Randomized, double-blind, parallel-group, active comparator study
Name and address of Sponsor:	Mabion S.A. Langiewicza str. 60, 95-050 Konstantynów Łódzki, Poland
Protocol identification	MabionCD20-002NHL (MADILYM)
EudraCT-Number	2013-005506-56
Development phase of study	Phase IIIb
Study initiation date:	29-Mar-2016 (screening of first patient)
Date of early study termination (if applicable):	Not applicable
Study completion date (last patient completed):	04 Jan-2018
Name and affiliation of Coordinating / Principal Investigator(s) or Sponsor's responsible medical officer:	Wiesław Jędrzejczak, MD, PhD, Prof. MTZ Clinical Research Sp. z o.o. Pawińskiego str. 5 02-106 Warsaw, Poland
Sponsor's contact person:	Slawomir Jaros. PhD, MBA tel: +48 509 877 045
GCP Statement	The trial was performed in compliance with Good Clinical Practice, including the archiving of essential documents.
Date and version of report:	28 March 2019, Version 2.0

2 SYNOPSIS

Name of Sponsor/Company: Mabion S.A.	Individual Study Table Referring to Study Report:	
Name of Finished Product: MabionCD20		
Name of Active Ingredient: Biosimilar to rituximab		
Study Title: Randomized, Parallel-group, Double-blind, Comparative Bioequivalence Trial of MabionCD20 (Mabion SA) Compared to MabThera (rituximab by Hoffman-La Roche) in Patients with Diffuse Large B-cell Lymphoma		
Sponsor's study number:	MabionCD20-002NHL (MADILYM) (MB02)	
EudraCT number:	2013-005506-56	
Sponsor:	Mabion S.A. (Langiewicza Str. 60, 95-050 Konstantynów Łódzki, Poland)	
Primary Investigator: Prof. Wiesław Jędrzejczak, MD, PhD		
Study centre(s): The trial was conducted in 17 study centres in 2 countries (Georgia and Ukraine). The trial was initiated in 7 countries (Croatia, Bosnia and Herzegovina, Georgia, Moldova, Poland, Serbia, and Ukraine). Patients were recruited from 21 study centres in 5 countries (Bosnia and Herzegovina, Georgia, Moldova, Poland, and Ukraine). In Poland, Bosnia and Herzegovina, and Moldova no patients were included due to screen failures and/or dropout after randomisation.		
Publication (reference): N/A		
Studied period (years): Total trial duration was 46 weeks. The first 26 weeks patients received treatment. After 26 week they were followed up until week 46 for the collection of additional pharmacokinetic (PK) and pharmacodynamic parameters (PD), safety, and immunogenicity data. Date of first enrolment: 29 March 2016 Date of first treatment administration: 25 April 2016 Date of last completed: 28 Aug 2017 (end of first trial period) Date of Last Patient Last Visit (end of follow-up period, week 46): 04 January 2018	**Phase of development:** Phase IIIb	
Objectives: Primary: To demonstrate the biosimilarity in terms of PK between MabionCD20 and the reference product MabThera in patients with CD20-positive Diffuse Large B-cell Lymphoma (DLBCL) Secondary: To demonstrate the biosimilarity between MabionCD20 and the reference product MabThera in patients with CD20-positive DLBCL based on a comparative analysis of the secondary PK, PD, efficacy, safety, and immunogenicity		
Methodology: Multicentre, randomized, parallel-group, double-blind phase IIIb comparative trial Patients were randomly assigned (ratio 5:2) to MabionCD20 (375 mg/m2, intravenous [IV]), or MabThera (375 mg/m^2, IV) given every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10) (all with a visit window of ± 2 days); and on Days 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22) (all with a visit window of ± 4 days) The aim of the unequal randomisation ratio was to expose relatively more patients to the investigational product MabionCD20. All patients concomitantly received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. PK blood samples were drawn at Day 1 (before and after the first infusion), Day 8 ± 1 (7 days after first infusion), Day 15 ± 1 (14 days after first infusion), Day 22 ± 2 (before and after completion of the second infusion), Day 43 ± 2 (before and after completion of the third infusion), Day 64 ± 2 (before and after completion of fourth infusion), Day 85 ± 4 (before and after completion of the fifth infusion), Day 106 ± 4 (before and after completion of sixth infusion), Day 127 ± 4 (before and after completion of the seventh infusion), Day 148 ± 4 (before and after completion of the eight infusion), Day 155 ± 4 (one week after last infusion), Day 176 ± 4 (one month after last infusion) and Day 316 ± 7 (six months after last infusion, PK evaluation during the follow-up period). Blood samples were taken within two hours before infusion of study medication and 30±15 minutes after completion of the infusion. Immunogenicity blood samples were drawn at Screening, Week 2 (Day 8), Week 10 (Day 64), Week 22 (Day 176), and Week 46 (Day 316		
Number of patients (planned and analysed): Screened = 191, planned = 140, randomized = 143, safety set = 140, intent-to-treat set = 136, intent-to-treat (week 13-26) = 125, per protocol set (week 1-4) = 129, per protocol set (week 13-26) = 103.		
Diagnosis and main criteria for inclusion: • Male or female subjects aged ≥ 18, with a histological confirmed CD20 positive DLBCL and a diagnosis of DLBCL according to the World Health Organization classification. • Eligible for treatment according to MabThera Summary of Product indications. • Life expectancy of at least 6 months. • Adequate haematological, renal, and liver functions, no signs of heart failure. • No prior immunotherapy for DLBCL within a period of 1.5 years prior to screening.		

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Test product, dose and mode of administration:
MabionCD20, 375 mg/m^{2,} IV

Duration of treatment:
22 weeks (8 cycles)

Reference therapy, dose and mode of administration:
MabThera, 375 mg/m^2, IV

Criteria for evaluation:

Pharmacokinetics

Primary PK endpoints:

$AUC_{(1-4)}$ Area under the serum concentration-time curve from time zero to final time point (AUC_{0-t}) measured after the first administration (Week 1) until the second administration at Week 4.

$AUC_{(13-26)}$ Area under the serum concentration-time curve from time zero to final time point (AUC_{0-t}) measured at steady state after the fifth administration (Week 13) until Week 26.

Secondary PK endpoints:

$AUC_{(1-26)}$ Area under the serum concentration-time curve from time zero to final time point (AUC_{0-t}) measured after the first administration (Week 1) until Week 26.

C_{trough} Serum concentration measured at the end of a dosing interval at steady state, taken directly before eighth infusion.

C_{max} Maximum serum drug concentration (C_{max}) at steady state after the 5_{th} and 8_{th} infusions.

K_{el} Elimination Rate Constant at steady state after the 5_{th} and 8_{th} infusions.

$T_{1/2}$ Elimination Half-Life at steady state after the 5_{th} and 8_{th} infusions.

CLss Clearance at steady state after the 5_{th} and 8_{th} infusions.

Efficacy

An efficacy assessment was made after 8 treatment cycles (at Week 26) based on tumour responses classified according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. Response was assessed based on clinical, radiologic and pathologic (bone marrow) criteria. Possible efficacy responses were: complete response, partial response, stable disease, and progressive disease.

A PD assessment was made based on the level of depletion of B-cell (CD19) in blood.

Safety

Safety assessments were based on the frequency and strength of reported adverse events (AEs) and significant changes in laboratory parameters.

Immunogenicity

Immunogenicity samples were tested for the presences of ADA. Samples confirming positive for anti-drug antibodies (ADA) were subsequently tested for the presence of neutralising antibodies.

Statistical methods:

Descriptive statistics were calculated for all PK endpoints.

Comparison between the MabionCD20 and MabThera groups was based on an analysis of variance model (with treatment and centre factors) of log-transformed primary PK endpoints. The difference in least squares means between Test and Reference product and the associated 90% confidence intervals (CIs) were estimated. Back-transformation was applied to produce the estimate of geometric mean ratio and its 90% CI.
Bioequivalence of the primary PK endpoint was to be determined if the resulting 90% CIs were within the pre-specified equivalence of interval 70% to 143%.

No formal statistics were performed on the efficacy and safety data.

A comparison of the number of patients reporting AE was made using the Clopper-Pearson method [7].

Summary – Conclusions:

PK results

In Table 1, the results of the analysis of the primary PK endpoints are displayed. ANOVA showed that the differences between treatments were not significant; the 90% CIs of ratios of the $AUC_{(1-4)}$ and the $AUC_{(13-26)}$ were contained in the equivalence interval of 70% to 143%. This means that the two treatments were bioequivalent. The ITT analysis of the primary PK endpoints confirmed the results of the PP analysis.

The secondary PK parameters AUC(1-26), Cmax, Ctrough, Kel, clearance at steady state after 5th and 8th infusion and t1/2 of were also similar between MabionCD20 and MabThera.

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Table 1. Summary of primary PK parameters (PP [W1-4 and W13-26] population)

	MabionCD20		MabThera		Results from ANOVA model	
	N	Estimated GEO LS mean	N	Estimated GEO LS mean	Estimated Geo LS mean ratio (%)	90%CI
$AUC_{(1-4)}$, (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

$AUC_{(1-4)}$ = area under the serum concentration-time curve from time zero to final time point (AUC_{0-t}) measured after the first administration (Week 1) until the second administration at Week 4, $AUC_{(13-26)}$ = area under the serum concentration-time curve from time zero to final time point (AUC_{0-t}) measured at steady state after the fifth administration (Week 13), LS = least square

PD results

Full B-cell depletion occurred rapidly, was sustained in both groups over the whole treatment period and started to recover at the end of the trial, 24 weeks after the last infusion.

Efficacy results

The total number of patients with a complete or partial response was comparable between the MabionCD20 and MabThera groups - 66 (89.2%) and 27 (93.1%), respectively. Differences in efficacy parameters between the MabionCD20 and MabThera group were considered not to be of clinical relevance. In the MabionCD20 group, 44.6% of patients had a complete response, and 44.6% had a partial response. In the MabThera group, 41.4% of patients had a complete response, and 51.7% had a partial response.

Safety results

Overall, the safety profile of MabionCD20 and MabThera was comparable up to 46 weeks.

In total, 627 AEs events were observed in 70.0% of patients who either received MabionCD20 or MabThera. Of these patients, 69.3% experienced one or more (≥1) treatment emergent AEs (TEAEs) and 17.1% experienced one or more treatment emergent SAEs (TESAEs). Fifty percent of the patients reported ≥1 related TEAE, 10.7% of the patients reported ≥1 related TESAE.

The incidence of treatment-emergent adverse events (TEAEs) was slightly higher in MabionCD20 group (71.0%) than in MabThera group (65.0%), although this difference was not statistically significant (based on CI intervals). Most of the events resolved or were resolving on follow-up with no significant difference between the two groups (85.0% in MabionCD20 and 82.5% in MabThera). Most common TEAEs occurred in the SOC categories of Blood and lymphatic system disorders (46.0% vs. 35.0%), Infections and infestations (24.0% vs. 15.0%) and Investigations (16.0% vs. 17.5%).

The proportion of patients experiencing ≥1 related TEAE or TESAE was slightly higher in the MabionCD20 than in the MabThera group (53.0% vs 42.5% and 13.0% vs 5.0%, respectively; unlikely related adverts event are classified as related). All related TEAEs were followed up and most of them resolved or were resolving (94.9%) with no marked differences between groups (94.3% vs 96.4% of the events, MabionCD20 and MabThera respectively). All related TESAEs were followed up, and outside of the fatal ones, most of the events resolved: 12 out of 16 events in in the MabionCD20 group and 2 out of 2 in the MabThera Group.

Around a third of the patients reported related TEAEs in the System Organ Class (SOC) Blood and Lymphatic System Disorders, mainly in the PT neutropenia (23.6%) and/or leukopenia (17.9%), and with no clinically relevant differences between the two groups at the PT level. The proportion of patients experiencing a TESAE was low and comparable across SOC categories. Differences in the frequency of related TEAEs and TESAEs between the two treatment groups did not exceed 5% for any of the SOCs with the exception of the SOC Investigations and Cardiac Disorders. In the MabionCD20 group, 12.0% of the patients reported a related TEAE in the SOC Investigations, in the Mabthera group the frequency was 17.5%. Six percent of the patients in MabionCD20 had a related cardiac TEAE compared to none in MabThera group. It must be noted that slightly higher percentage of patients had cardiac history at baseline 28.0% in MabionCD20 vs 22.5% in MabThera group and patients had background CHOP regimen which is associated with cardiac adverse effects.

Eight fatal cases with AEs leading to death were reported in the MabionCD20 group, none in the MabThera group which can partly be explained by the unequal randomization in the trial (5:2), small sample size, background therapy, and baseline condition of the patients. Six of the 8 cases were assessed as not related to treatment. For two fatal events (occurring at cycle no. 6 and 8; 4 and 103 days after the last dose of MabionCD20, respectively) the Investigator's assessment was that the current state of knowledge indicated that a relationship with MabionCD20 was unlikely, which is the most conservative causality assessment (thus conservatively categorised as related TEAE leading to death). One of the fatal cases occurred in the follow-up period of the trial. Involvement of CHOP therapy and progression of

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disease and/or comorbidities cannot be excluded in these 2 cases.

Statistical comparisons (based on CI intervals) confirmed the overall assessment of safety between the two treatment groups but given the small sample size and unequal allocation (5:2 i.e. N=100 in the MabionCD20 group and N=40 in the MabThera group) to treatment, the AE profile of both treatments in this trial should be interpreted with caution.

A post-hoc reassessment of related TEAEs, excluding events classified as unlikely related to study drug, revealed that the differences in the incidence of related TEAEs of between both groups became small (43.0% in MabionCD20 vs. 40.0% in MabThera group). The frequency of related serious TEAEs dropped as well, resulting in a drop in the incidence to 6% in the MabionCD20 group and 5% in the MabThera group. The 2 fatal cases previously assessed as unlikely related were categorised as not related.

Immunogenicity assessments

The treatment-induced ADA response was very low and comparable between the MabionCD20 and MabThera group, indicating very low potential of immunogenicity. All ADA tested patients had negative neutralising antibodies (NAb) test results at screening and subsequent visits, meaning that the functional activity of the both compounds was not reduced in this trial.

Conclusion

The results of this trial confirm that MabionCD20 and MabThera are bioequivalent for the primary PK parameters $AUC_{(1-4)}$ and $AUC_{(13-26)}$. The secondary PK parameters $AUC_{(1-26)}$, C_{max}, C_{trough}, k_{el}, clearance at steady state after 5th and 8th infusion and $t_{1/2}$ of were similar between MabionCD20 and MabThera.

The other secondary study endpoints, including the PD and efficacy response rates were comparable between the treatment groups and support the PK results.

MabionCD20 was generally well tolerated and the safety profile was acceptable. The overall safety profile of MabionCD20 was similar to MabThera. The minor imbalance and the higher incidence of related TEAEs, SAEs, and death in the MabionCD20 group compared to the MabThera group can be explained by the unequal randomization in the trial (5:2) and small sample size, background disease status, confounding by concomitant chemotherapy, and the fact that events assessed as unlikely related were considered as definitely related. A post-hoc reassessment of related TEAEs, excluding events classified as unlikely related to study drug, revealed that the differences in the incidence of related TEAEs between both groups became small.

The frequency of positive ADA response was very low and comparable between the treatment groups. No drug-induced NAb response occurred.

Overall, the PD, efficacy, safety, and immunogenicity data were similar across the two treatment groups and support the PK results and the results of the main trial in RA patients and the other preclinical data obtained in the whole trial programme and therefore the conclusion that MabionCD20 and MabThera are biosimilar.

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