CLINICAL STUDY PROTOCOL

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:	MABION SA ul. Langiewicza 60; 95- 050 Konstantynów Łódzki
Protocol Number:	MabionCD20- 002NHL
Protocol 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
Study Acronym:	MADILYM
EudraCT number:	2013-005506-56
Investigational Products:	MabionCD20 vs MabThera
Indication:	Diffuse Large B-cell Lymphoma
Phase:	IIIb
Design:	Randomized, Double-blind, Parallel-group, Active comparator study
Date:	21.09.2016
Version:	4
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PROTOCOL SYNOPSIS

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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
Study Phase	IIIb
Study Number	MabionCD20-002NHL
Overall Study Design	This will be a multicenter, randomized, parallel-group, double-blind phase IIIb comparative study of two monoclonal antibody medicinal products: MabionCD20 (Mabion SA) and MabThera (Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma eligible for treatment with rituximab according to MabThera Summary of Product Characteristic. Trial population will be diagnosed according to WHO classification of lymphomas Patient enrollment will be based on the diagnosis of DLBCL at each study center. Patients will be assigned to 1 of 2 treatment groups: MabionCD20 or MabThera, both with background chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP). The duration of the study is 12 months. The treatment and observation phase will last until week 26 with the follow-up phase until Week 46. The sponsor, investigators and patients will be blinded to treatment allocation until week 26 of last patient, at which time the sponsor will be unblinded for the purposes of data analysis.
Study Objectives	**Primary Objectives** Primary objectives of the study is to demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product: MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma, based on the percentage of patients achieving the primary pharmacokinetic endpoints: • Area under the plasma 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 1-4); • Area under the plasma 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 (AUC 13-26). **Secondary Objectives** To demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma based on: – Comparative analysis of the secondary pharmacokinetic parameters: • Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26

	(AUC 1-26); • Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion; • Maximum plasma drug concentration (Cmax) at steady state after the 5th and 8th infusions; • Elimination Rate Constant (Kel) at steady state after the 5th and 8th infusions; • Elimination Half-Life (T ½) at steady state after the 5th and 8th infusions; • Clearance at steady state after the 5th and 8th infusions; – Comparative analysis of the pharmacodynamic parameter: area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell); – The percentage of patients achieving the efficacy endpoints as following: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD). – Comparative safety and immunogenicity of MabionCD20 and MabThera based on the following safety endpoints: adverse events, clinical laboratory assessment, presence of Human Antichimeric Antibodies (HACA).
Number of Patients	With an expected mean ratio of 90 - 110% and Coefficient of Variation of 50%, at least 112 patients (80 patients in MabionCD20 group and 32 patients in MabThera group) are required to complete the study to achieve a power of 80% and to demonstrate equivalence within the 70%-143% interval. Assuming a 20% drop-out rate, total of 140 patients would be randomized (100 patients in MabionCD20 group and 40 patients in MabThera group). Assuming 20% screen failure rate 175 patients needs to be screened.
Diagnosis	Trial population consists of CD20 positive diffuse large B cell lymphoma (DLBCL) patients diagnosed according to WHO classification of lymphomas, patient eligible for rituximab treatment according to MabThera SmPC with life expectance at least 6 months. Diagnosis of CD20- positive DLBCL will be based on an adequate sample of tissue obtained from a biopsy of an abnormal lymph node or other tissue of involved organ or bone marrow biopsy if lymph node material is not available.
Criteria for Inclusion	Patients that met following inclusion criteria may be randomized to the study: 1. Gender: male or female; 2. Age ≥ 18 3. Patients with histological confirmed CD20 positive diffuse large B cell lymphoma (DLBCL) 4. Patients that had been diagnosed according to the WHO classification; 5. Performance status ≤ 2 on the ECOG/WHO scale, performance status of 3 will be accepted if impairment is caused by DLBCL complications and improvement is expected once therapy is initiated; 6. Patients eligible for rituximab treatment according to MabThera indications; 7. Life expectance at least 6 months; 8. No immunotherapy for DLBCL within 1,5 years prior to screening; 9. Written informed consent including information about benefits and potential risks of the trial; 10. Ability and willingness to comply with the requirements of the study protocol; 11. Willing to use acceptable forms of contraception for females and males patients with female sexual partners of childbearing potential; For females of reproductive potential use of a reliable means of contraception (e.g.,

	hormonal contraceptive, patch, intrauterine device, physical barrier) throughout study participation. Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following therapy; 12. Laboratory values within normal range unless abnormalities are related to lymphoma. The laboratory values should be obtained ≤ 28 days prior to MabionCD20/MabThera infusion. 13. Adequate hematological function: • hemoglobin ≥ 9 g/dl unless abnormalities are due to bone marrow involvement by lymphoma, • absolute neutrophil count (ANC) ≥ 1,500/µL unless abnormalities are due to bone marrow involvement by lymphoma, • platelet count ≥ 100,000 /µL, unless abnormalities are due to bone marrow involvement by lymphoma, 14. Adequate renal function: Creatinine ≤ 2.0 mg/dl or calculated creatinine clearance ≥ 40 unless abnormalities are related to lymphoma; 15. Adequate liver functions: • total bilirubin ≤ 2 mg/dl unless due to Gilbert's disease (patients with bilirubin between 2-3.0 mg/dl due to lymphoma may be entered); • Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3 the upper limit of normal unless abnormalities are related to lymphoma; 16. Alkaline phosphatase ≤ 5x upper limit of normal; 17. Left ventricular ejection fraction (LVEF) ≥50%; 18. A negative serum and urine pregnancy test prior to treatment.
Criteria for Exclusion	1. Life expectance less than 6 months; 2. Any chemotherapy, radiotherapy, immunotherapy, biologic, investigational or hormonal therapy for treatment of lymphoma within 28 days prior to treatment; 3. Rituximab, other anti-CD20 mAb drug treatment, treatment with any cell depleting therapies (e.g., anti-CD4, anti-CD5, anti-CD3, anti-CD19, anti CD11a, anti-CD22, BLys/BAFF) within 1,5 years before screening; 4. History of T-cell lymphoma, indolent lymphoma, central nervous system involvement by lymphoma Primary Central Nervous System (CNS) DLBCL; 5. History of other invasive malignancy within 5 years except for localized/in situ carcinomas such as non-melanoma skin cancer or cervical carcinoma in situ; 6. Primary or secondary immunodeficiency; 7. Evidence of significant uncontrolled concomitant disease such as, but not limited to, nervous system, renal, hepatic, endocrine, or gastrointestinal disorders within 5 years prior to screening which, in the Investigator's opinion, would preclude subject participation; 8. Active infections: known active bacterial, viral, fungal, mycobacterial, other infection (including tuberculosis, sepsis, opportunistic infections) but excluding fungal infections of nail beds; 9. Concurrent disease that would exclude giving of treatment as outlined in the protocol for example: patients with general status that doesn't permit the administration of eight courses of CHOP, patients with cardiac contraindication to doxorubicin therapy (e.g., abnormal contractility on echocardiography) or a neurologic contraindication to vincristine (e.g., peripheral neuropathy); 10. III or IV class of the New York Heart Association (NYHA) Classification;

	11. Existing serious vein disease; 12. History of currently treated relevant serious CNS and/or psychiatric disorders; 13. History of significant cytopenias or other serious bone marrow disorders within 5 years prior to screening; 14. Major surgery (excl. biopsies) within 30 days prior to MabionCD20/MabThera infusion; 15. Presence of HBs antigen or HBc antibody without HBs antibody, positive serology for HIV. In case of these results a PCR for HBV and/or HCV may be performed and patient can be enrolled if these results are negative; 16. Pregnancy or lactation (positive serum pregnancy test for women of child bearing age); 17. Recent vaccination (< 4 weeks prior treatment); 18. Participation in other clinical trial during the last two months prior to the start of the study; 19. Patients, who are unable to understand the written and verbal instructions, in particular the risks connected with the study; 20. Male patients (with female sexual partners of childbearing potential) and female patients of childbearing potential who refuse to use effective methods of contraception 21. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications. 22. Hypersensitivity to the active substance or to any other excipients of the medicine
Study Treatment	The general goal of the study is a comparison of two therapeutic monoclonal antibodies: MabionCD20 and reference product MabThera in patients with CD20 positive diffuse large B-cell lymphoma (DLBCL) eligible for the MabThera therapy according to MabThera labeled indications. Investigational Medicinal Products (IMPs): MabThera and MabionCD20 will be used in combination with CHOP chemotherapy. MabionCD20 and MabThera are concentrates for solutions for infusions and may be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. 375 mg/m^2 of MabThera or MabionCD20 will be given intravenously on Days 1, 22, 43, 64, 85, 106, 127 and 148 of the study. CHOP will be administered in the standard dosage regimen: • 50 mg of doxorubicin per square meter administrated IV on day 1 of each chemotherapy cycle • 1.4 mg of vincristine per square meter, up to a maximal dose of 2 mg, administrated IV on day 1 of each chemotherapy cycle • 750 mg of cyclophosphamide per square meter of body-surface area administrated IV on day 1 of each chemotherapy cycle 100 mg of prednisone administrated PO per day for five days, day 1-5 of each chemotherapy cycle
Criteria for evaluation	**Primary Study Endpoints** Primary study endpoints are following pharmacokinetic parameters: • Area under the plasma 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 1-4); • Area under the plasma 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 (AUC 13-26). **Secondary Study Endpoints** Secondary study endpoints are following parameters: **Pharmacokinetic Endpoints:** • Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26 (AUC 1-26); • Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion; • Maximum plasma drug concentration (Cmax) at steady state after the 5th and 8th infusions; • Elimination Rate Constant (Kel) at steady state after the 5th and 8th infusions; • Elimination Half-Life (T ½) at steady state after the 5th and 8th infusions; • Clearance at steady state after the 5th and 8th infusions; **Pharmacodynamic Endpoint:** Area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell); **Efficacy Endpoints:** Tumor responses will be classified according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. Following efficacy endpoints will be evaluated at Week 26: • Complete Response (CR) • Partial Response (PR) • Stable Disease (SD) • Progressive Disease (PD, nonresponders) **Safety Endpoints:** • Adverse events frequency and strength; • Clinically significant changes in clinical laboratory evaluations occurring during the protocol-specified reporting period; Safety endpoints will be evaluated at Week 26. **Immunogenicity Endpoints:** • Percentage of patients who developed detectable Human Antichimeric Antibodies (HACA) Immunogenicity endpoints will be evaluated at Week 26.

SCHEDULE OF EVENTS																
Visit Number	**V0[1]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7[13]**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**ET[2]**
Study Week	W-3	W1	W2	W3	W 4	W7	W10	W11	W13	W16	W19	W22	W23	W26	W46	
Study Day	-35to-8	D1	D8 ±1	D15 ±1	D22 ±2	D43 ±2	D64 ±2	D71 ±4	D85 ± 4	D106 ±4	D127 ±4	D148 ±4	D155 ±4	D176 ±4	D316 ±7	
ICF signed	X															
Inclusion/Exclusion Criteria Assessment	X	X														
Medical History	X															
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X		X	X	X
Weight/Height and BSA Calculation[3]		X			X	X	X		X	X	X	X				
Physical Examination, Vital Signs[4]	X	X	X		X	X	X	X	X	X	X	X		X	X	X
ECG[5]	X	XX	X		XX	XX	XX		XX	XX	XX	XX		X	X	X
Transthoracic echocardio-graphy (TTE)	X															
Tumor Biopsy[6]	X															
Bone Marrow Biopsy[6]	X													X		X
CT scan (neck, chest, abdomen, pelvis)[7]	X							X						X		X
Tumor and Disease Staging Assessment [8]	X	X						X						X		X
Efficacy Assessment		X												X		X

Visit Number	V0[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	ET[2]
Study Week	W-3	W1	W2	W3	W 4	W7	W10	W11	W13	W16	W19	W22	W23	W26	W46	
Study Day	-35 to-8	D1	D8±1	D15 ±1	D22 ±2	D43 ±2	D64 ±2	D71 ±4	D85 ± 4	D106 ±4	D127 ±4	D148 ±4	D155 ±4	D176 ±4	D316 ±7	
Randomization		X														
Premedication[9]		X			X	X	X		X	X	X	X				
IMP Infusion		**X**			**X**	**X**	**X**		**X**	**X**	**X**	**X**				
Chemotherapy		**X**			**X**	**X**	**X**		**X**	**X**	**X**	**X**				
Adverse Event Review		X	X		X	X	X	X	X	X	X	X		X	X	X
PK sampling[10]		X X	X	X	X X	X X	X X		X X	X X	X X	X X	X	X	X	X
PD sampling		X	X		X		X					X		X	X	X
HACA	X		X				X					X		X	X	X
HIV,HBV,HCV serology	X															
Chemistry, Hematology, IgG, IgM, IgA	X	X	X		X	X	X	X	X	X	X	X		X	X	X
Urinalysis[-11]	X													X	X	X
Anti-tetanus antibody	X													X		X
β2 microglobulin	X													X		X
Serum Pregnancy Test	X															
Urine Pregnancy Test[12]		X			X	X	X		X	X	X	X				

Sampling for validation and optimization of analytical methods	X[14]															

1. V0 is a screening visit, it may be performed 8-35 days before first visit (V1 on Day 1).
2. ET means Early Termination Visit - assessments should be performed for any patient terminating early from the study within 2 weeks of discontinuation. ET is performed only when patient discontinues the treatment before Week 26 (Visit 13).
3. BSA should be calculated according to the DuBois formula: BSA in m2 = (Weight (kg) $^{0.425}$ x Height (cm) $^{0.725}$) x 0.007184, BSA will be calculated with use of eCRF.
4. Physical examination and vital signs may be measured also between the treatment cycle if required during unscheduled visits.
5. 12-lead ECG should be obtained twice on visits when IMP is administered (prior to each IMP infusion and within 60 minutes after infusion completion).
6. Biopsy may be omitted at screening if results are available for the test performed within last 60 days before screening visit. This period may be extended to 90 days if basing on Investigator and Medical Monitor judgement the re-biopsy is highly invasive and previous results are expected to be up to date in screening.
7. CT scan of neck, chest, abdomen, pelvis should be performed if no results are available.
8. Clinical Tumor and disease staging assessment include: evaluation of all involved nodal and extranodal sites – measurements of diameters, tumor lesion assessment, assessment of spleen and liver enlargement, Ann Arbor staging, ECOG/WHO performance status, IPI assessment.
9. Premedication should be given 30-40 minutes prior to initiation of IMP infusion.
10. Blood samples for PK assessments should be collected twice during the day of IMP infusion: within two hours before infusion of study medication and 30±15 minutes after completion of infusion.
11. The Investigator may order additional blood/urine testing between treatment cycles if required during unscheduled visits.
12. Urine pregnancy tests will be performed before each treatment cycle.
13. Investigator has a right to perform Visit 7 prior to Day 71 but not earlier than after two cycles of treatment to check status of disease in case of any suspicion that patient does not benefit from the treatment or disease is in progress.
14. Additional blood samples will be collected on screening visit for validation and optimization of analytical methods.
15. 15. In case if infusion of IMP is postponed, unscheduled visit should be performed and all study procedures intended for the visit should be done.
16. 16. In case if the visit with IMP infusion is postponed, date of the next visit should be calculated starting from the postponed visit (not from V1).

1 INTRODUCTION AND STUDY RATIONALE

1.1 Disease Under Treatment

Lymphomas are neoplastic diseases divided into two main subgroups: Hodgkin's lymphomas and non-Hodgkin's lymphomas. The non-Hodgkin's lymphomas are a heterogeneous group, categorized according to the cell type, the clinical features and rate of progression of the disease. Most non-Hodgkin's lymphomas derive from the B lymphocytes, other types derive from T lymphocytes or undifferentiated cells. Diffuse Large B-cell Lymphoma (DLBCL) is the most frequent type of non-Hodgkin's lymphoma accounting for approximately 40 percent of new cases of lymphoma. DLBCL is present in every age group, however more than half of patients with diffuse large-B-cell lymphoma are over 60 years of age, and it is found more likely in men than in women [1].
DLBCL presents as a nodal or extranodal mass, sometimes with systemic symptoms, such as sweats, fatigue and fever. In about 40% of patients lymphomas appear in areas outside lymph nodes, including the digestive tract, skin, bone, thyroid and testes.

The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) administered every 21 days is the standard of care for younger and elderly patients with diffuse large-B-cell lymphoma, but it induces complete responses in only 40 to 50 percent of elderly patients, with three-year event-free and overall survival rates of 30 percent and 35 to 40 percent, respectively. Rituximab significantly improves treatment outcome in DLBCL. The addition of rituximab to CHOP chemotherapy to patients with diagnosed diffuse large-B-cell lymphoma, significantly increases the rate of complete response, decreases the rates of treatment failure and relapse, and improves event-free and overall survival as compared with standard CHOP alone [2,3,4].

1.2 Investigational Medicinal Products

The Investigational Medicinal Product (IMP) in this study is MabionCD20, developed as a therapeutic monoclonal antibody biosimilar to MabThera (rituximab, manufactured by Roche Registration Limited) granted a marketing authorization.

Physicochemical Properties

MabionCD20 (similarly to MabThera) is a highly purified amino acid chimeric recombinant mouse/human monoclonal antibody. It is produced in mammalian cell culture using Chinese Hamster Ovary (CHO) cells and purified by affinity chromatography and ion exchange including specific viral inactivation and removal steps. MabionCD20 the anti-CD20 monoclonal antibody is a glycosylated IgG1-κ immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences.

Pharmacodynamic Properties

MabionCD20 (similarly to MabThera) binds specifically to the CD20 antigen, which is located on pre-B and mature B-lymphocytes. CD20 - the transmembrane antigen is a non-glycosylated phosphoprotein and it is expressed on >95 % of all B-cells non-Hodgkin's lymphoma. CD20 antigen is not expressed on hematopoietic stem cells, pro-B lymphocytes and does not circulate in the plasma as a free antigen. The Fab domain of MabionCD20 binds to the CD20 antigen and the Fc domain can recruit

immune effector functions to mediate B-cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and apoptosis.

Clinical Formulation

Formulation and excipients of MabionCD20 are similar to those of MabThera. MabionCD20 is a clear, colorless, liquid concentrate for preparation of solution for infusion formulated for IV administration. MabionCD20 is a sterile product in 9.0 mg/ml sodium chloride, 0.7 mg/ml polysorbate 80, 7.35 mg/ml sodium citrateand water for injection. The pH is adjusted to 6.5. MabionCD20 is supplied as a concentration of 10 mg/ml in 10ml (100 mg of MabionCD20) and 50 ml (500 mg of MabionCD20) single-use vials. No preservative is used. The product packaging consists of type I borosilicate glass vial with 20-mm rubber and 20-mm aluminum flip-off cap with polypropylene disc. MabionCD20 is formulated for IV administration after dilution to a calculated concentration of 1 to 4 mg/ml into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection or 5% D-Glucose in water.

Additional information about investigational product: MabionCD20 are provided in the Investigational Brochure (IB). The Summary of Product Characteristics (SmPC) of MabThera is provided in the Protocol appendix.

1.3 Summary of Nonclinical Experience with MabionCD20

According to EMA guideline on similar medicinal products containing monoclonal antibodies – non clinical and clinical issues [EMA/CHMP/BMWP/403543/2010] in vitro assays are considered paramount in the nonclinical comparability exercise performed for monoclonal antibodies.

MabionCD20 is developed strictly according to relevant European standards and European Medicines Agency guidelines that regulate the non-clinical and clinical requirements for monoclonal antibody claiming to be similar to another one already authorized.

An extended set of comparative in vitro analyses have been conducted to demonstrate significant level of similarity of physicochemical and biological properties between MabionCD20 and MabThera.

During comparability tests similarity of following parameters has been investigated and proven for MabionCD20 and MabThera: molecular weight, amino acid structure, secondary structure, carbohydrate structure, glycan profiles, profiles of isoforms and aggregates, post –translational forms process-related impurities profiles.

Binding to target antigens and effector functions of MabionCD20 and MabThera such as complement-dependent cytotoxicity, antibody dependent cellular cytotoxicity, binding to C1q, stimulation of apoptosis and antiproliferative effects have been compared. Results of these analyses confirmed similar affinity to target receptors as well as similar activity of both antibodies.

In vivo comparative studies demonstrating similar efficacy and safety of MabionCD20 compared to MabThera have been performed in Severe Combined Immunodeficiency (SCID) mice and in Rhesus monkeys. The study in SCID mice evaluated changes in tumour development and survival time of SCID after MabionCD20 and MabThera administration. Tumour development was equally reduced in

SCID mice after MabionCD20 and MabThera administration compared to control mice receiving placebo. The volumes of tumours and survival time of mice revealed significant similarity in groups receiving MabionCD20 and MabThera.

According to EMA guidelines and EMA recommendations animal *in vivo* studies should be performed with use of the most sensitive, predictive for humans and relevant species, which allow to compare pharmacodynamic and safety of medicinal products. Because of specificity of monoclonal antibodies the most relevant species for study is non-human primate. Several pre-clinical studies in Rhesus monkeys were performed to compare pharmacokinetic, pharmacodynamic effects of two antibodies and to evaluate safety and toxicology profiles of MabionCD20 and MabThera.

The route, formulation, concentration of medication doses used in monkeys were as similar as possible to that used in human therapy.

MabionCD20 and MabThera pharmacokinetic profiles revealed high level of similarity. There were no significant differences between MabionCD20 and MabThera serum concentration measured at specified time points in monkeys.

B-cell depletion in peripheral blood was observed in monkeys after administration of MabionCD20 and MabThera as a pharmacodynamic marker. Similar level of B-lymphocytes decrease analyzed on the basis of CD79α was observed in blood samples in all monitored animals.

No signs of toxicity, no abnormalities in overall health, respiratory, circulatory and nervous system, no visual changes in skin, fur, eyes, mucous membranes, administration sites, body weight, food and water consumption were observed during the studies in monkeys.

No significant changes in clinical pathology values, immunoglobulin values, electrocardiography, body temperature, blood pressure, breathing frequency and gross pathology as well as histopathology examination were found in monkeys receiving single small doses and repeated toxic doses of MabionCD20 and MabThera.

Similarity of MabionCD20 and MabThera has been clearly demonstrated in numerous in vitro tests and non-clinical studies in animals. On the basis of preclinical development results it is assumed that MabionCD20 shall have equivalent pharmacokinetic /pharmacodynamic and safety profile to MabThera when administered to humans.

Following guidelines form the foundation of MabionCD20 non-clinical development:

- Guideline on Similar Biological Medicinal Products (CHMP/437/04)
- Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-Clinical and Clinical Issues (EMA/CHMP/BMWP/403543/2010)
- Guideline on Similar Biological Medicinal products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/ 42832/2005)
- ICH Topic S 6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)

Additional information related to comparability tests of MabionCD20 and MabThera are provided in the Investigational Brochure (IB).

1.4 Summary of Clinical Experience with MabionCD20

Clinical Development Plan of MabionCD20 includes two comparative bioequivalence studies in rheumatoid arthritis patient and DLBCL patients. The first multicenter, phase III study titled: "A Randomized, Double-blind, Parallel-group Comparative Bioequivalence Trial of MabionCD20 (Mabion SA) Compared to MabThera (rituximab, Roche) in Patients with Rheumatoid Arthritis" is currently running in central and eastern Europe to demonstrate comparative safety, efficacy, pharmacokinetic and pharmacodynamic profiles of MabionCD20 in comparison to MabThera. Study population includes patients with moderate to severe rheumatoid arthritis (RA), who fulfill the revised 1987 American Rheumatism Association criteria.

Until 26th of August 2013 ninety-nine (n=99) Caucasian male and female patients have been screened and fifty-six (n=56) patients have been randomized and received first infusion of IMP. Thirty-three (n=33) of them were already administered with two i.v. infusions of IMP. 50% of patients received MabionCD20, 50% of patients received MabThera.

Mean ± SD of age of all screened patients is 53 ± 13. The youngest and the oldest subjects are 27 and 76 years of age, respectively. Most of them (~85%) constitute female subjects that remains in line with the general epidemiologic global data reporting that over 75 percent of patients with Rheumatoid Arthritis are women.

Until 21th of June 2016 887 patients Caucasian male and female patients have been screened and 622 patients have been randomized and received first infusion of IMP.

An independent group of experts - Data and Safety Monitoring Board (DSMB) composed of 3 members: rheumatologist, pharmacologist and biostatistician monitor patients safety during the clinical trial in RA patients. First DSMB safety data review was performed according to protocol when first 20 patients completed first study drug infusion cycle. No AEs were reported, no study drug dose reduction was performed in evaluated group of patients. Additionally there were only 3 Panic Values in Laboratory results identified – all 3 related to Screening assessments before any IMP infusion.

Safety data for 56 randomized patients were additionally presented to DSMB. In this group 56 patients received first infusion, 33 patients of 56 randomized received second infusion of study drug, the total exposure in randomized group was 89 infusions. Six AEs were reported with following severity: 4 mild, 1 moderate, 1 severe and following seriousness: one classified as serious, 5 non-serious, no SUSARs.

One severe AE (cerebral ischemia) occurred during the study after first investigational medicinal product (IMP) infusion (the treatment assignment is not known). AE occurred during the gastrofiberoscopy with subsequent loss of consciousness and admission to hospital where CT exam was performed – this AE was classified (by trial investigator) as having no relation to the study drug. Patient received second infusion of IMP and no AE was observed.

Following mild AEs were reported : redness of the face and neck, mild leucopoenia, and itching of the head during infusion of study drug.

Five DSMB meetings have been performed so far. Data presented to DSMB during the latest DSMB meeting included blinded safety and efficacy data obtained from 512 patients included to the study till

15.06.2015 (cut off date). Patients were randomized in 6 countries: Poland, Bosnia, Serbia, Ukraine, Lithuania, Georgia. Only 16 SAE took place till the time of DSMB meeting.

After a review of study status as well as efficacy and safety data, DSMB recommended continuation of MabionCD20-001RA study.

1.5 Summary of Clinical Experience with Rituximab in NHL

1.5.1 MabThera Characteristic Summary

MabThera is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian CHO (Chinese Hamster Ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures [2].

MabThera is indicated for the treatment of Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis, granulomatosis with polyangiitis and macroscopic polyangiitis.

The Committee for Medicinal Products for Human Use (CHMP) decided, that MabThera's benefits are greater than its risks and recommended that it was given the marketing authorisation in 1998. MabThera with active substance rituximab is authorized as Mabthera 100 mg - concentrate for solution for infusion (intravenous use vial 10 ml - 10 mg/ml, 2 vials) and Mabthera 500 mg - concentrate for solution for infusion (intravenous use vial 50 ml - 10 mg/ml, 1 vial).

The recommended dosage of MabThera in DLBCL is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP [2].

Main contraindications for use:

- Hypersensitivity to the active substance or to any of the excipients of the medicine;
- Active, severe infections;
- Patients in a severely immunocompromised state.

The Summary of Product Characteristics (SmPC) of MabThera is provided in the Protocol appendix.

1.5.2 Pharmacokinetic Properties of Rituximab in NHL

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera as a single agent or in combination with CHOP therapy (applied MabThera doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V1) were 0.14 l/day, 0.59 l/day, and 2.7 l, respectively. The estimated median terminal elimination half-life of MabThera was 22 days (range, 6.1 to 52 days) [2].

Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in CL2 of MabThera in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher CL2.

However, a large component of inter-individual variability remained for CL2 after correction for CD19-positive cell counts and tumor lesion size. V1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of MabThera. This analysis suggests that dose adjustment of MabThera with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability [2].

MabThera, administered as an intravenous infusion at a dose of 375 mg/m^2 at weekly intervals for 4

doses to 203 patients with NHL naive to MabThera, yielded a mean Cmax following the fourth infusion of 486 µg/ml (range, 77.5 to 996.6 µg/ml). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment. Upon administration of MabThera at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean Cmax increased with each successive infusion, spanning from a mean of 243 µg/ml (range, 16 – 582 µg/ml) after the first infusion to 550 µg/ml (range, 171 – 1177 µg/ml) after the eighth infusion. The pharmacokinetic profile of MabThera when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with MabThera alone [2].

According to relevant literature, evaluation of serum levels and pharmacokinetic properties of rituximab in combination with CHOP in patients with DLBCL demonstrated increased levels of antibody after each subsequent cycle for the first 4 cycles. During cycle 5- 8 the rituximab serum levels reached a plateau and decreased constantly after the end of treatment with detectable levels even after 9 months. The median (range) of serum rituximab levels (µg/ml) in elderly DLBCL patients before each treatment cycle were: #1: 0 (0-0); #2: 39 (13-62); #3: 74 (47-109); #4: 95 (40-136); #5: 111 (55-157); #6: 114 (12-518); #7: 125 (72-207); #8: 116 (75-304). After therapy median (range) of serum rituximab levels were: 163 (67-248) at 1 week; 101 (44-163) at 1 month; 55 (1-123) at 2 months; 34 (1-577) at 3 months; 5 (0-103) at 6 months; 1 (0-128) at 9 months [5].

In the multicenter phase II trial in relapsed or refractory aggressive B-cell lymphoma patients (rituximab monotherapy) mean ± SD values of trough levels and AUCs of the responders and the non-responders were as following:

Table 3. Serum levels and pharmacokinetic properties of rituximab in combination with CHOP in patients with DLBCL.

PK parameter	Responders, mean± SD (*n* = 7)	Non-responders, mean ± SD (*n* = 5)
Trough (µg/ml)	59.7 ± 11.4	43.0 ± 6.4
Cmax (µg/ml)	502.9 ± 123.4	398.8 ± 52.2
t1/2 (h)	517.1 ± 165.9	314.5 ± 153.8
AUC (µgxh/ml)	608 585 ± 147 373	383 053 ± 176 903

There were significant differences between the two groups in the mean ±SD values of trough levels and AUCs of the responders and the non-responders. There were no significant differences between the two groups regarding maximum concentration (*C*max) or serum half-life of rituximab [6].

In the reported multicentre phase III clinical trial involving patients with recurrent low-grade lymphoma or follicular lymphoma treated with four infusions of 375 mg/m^2 of rituximab measurable concentrations of rituximab were detected in all patients after the first infusion and increased throughout the treatment course. The median serum level of rituximab after first infusion was 239 ug/ml (46 – 506 ug/ml). The median serum level of rituximab after the fourth and final infusion was between 400 and 500 ug/ml. At three months and six months post-treatment, the median rituximab serum levels were 20.3 ug/ml (range 0.0 to 96.8 ug/ml in 104 patients) and 1.3 ug/ml (range 0.0-28.7 ug/ml in 13 patients), respectively. The mean serum antibody concentration was inversely correlated with measurements of tumor bulk and with the number of circulating B cells at baseline. The levels of rituximab were statistically significantly higher for the responders [7,8].

The half-life of the rituximab increased from 76.3 hours (range, 31.5 to 152.6) after the first infusion to 205.8 hours (range, 83.9 to 407.0) after the fourth infusion. The clearance was slower after the fourth than after the first infusion (0.0092 *v* 0.0382 L/h), and the area under the curve was greater (86,125 *v* 16,320 pg x h/mL) [7,8].

Longer half-lives were found in patients being treated with murine anti-idiotype antibodies in situations where there were no circulating level of idiotype protein or no accessible lymphoma cells in the blood or bone marrow. The explanations for the long T1/2 may be a combination of factors including the absence of free circulating CD20 antigen, the minimal number of circulating CD20 positive B cells after the first infusion, and the homology between rituximab and a human antibody [7,8].

1.5.3 Efficacy of Rituximab Therapy in NHL

Table 4. Summary of the mean efficacy results of rituximab therapy

Study	Patients characteristic/ Number of cycles	CR/CRu Complete Response /unconfirmed CR	PR Partial Response	SD Stable Disease	PD Progressive Disease
Coiffier et al [3]	Elderly patients with DLBCL/eight cycles R+CHOP	52% / 23%	7%	2%	19%
Haberman et al [9]	Elderly patients with DLBCL/ 4-6 R+CHOP cycles	77%		13%	1%
Pfreundsch et al. [4]	Patients aged 18–60 years with DLBCL/ 6 cycles R+CHOP	86%			4%

The addition of rituximab to CHOP chemotherapy, given for eight cycles to patients with diagnosed diffuse large-B-cell lymphoma, significantly increases the rate of complete response, decreases the rates of treatment failure and relapse, and improves event-free and overall survival as compared with standard CHOP alone. Patients with different age with low risk disease, indicated by a score of 0 or 1 on the International Prognostic Index (P<0.001), as well as those with high-risk disease, indicated by a score of 2 or 3 on the International Prognostic Index (P<0.03) benefit of CHOP plus rituximab over CHOP alone [3, 10, 11, 12, 13].

In a randomized, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle. The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p = 0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68.2 % in the R-CHOP arm compared to 57.4 % in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32 %. The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI [2].

1.6 Safety Profile of MabThera in DLBCL

The overall safety profile of MabThera in DLBCL described in this section is based on data obtained from patients from clinical trials and from post-marketing surveillance (according to MabThera Summary of Product Characteristic - first published on 30/10/2009, last updated on 24/09/2013). Based on similarities between MabThera and MabionCD20 demonstrated during quality and preclinical studies as well as during ongoing first clinical trial in rheumatoid arthritis patients, it is expected that the safety profile of MabionCD20 in patients with DLBCL will be significantly similar to that of MabThera.

1.6.1 Special Warnings and Precautions for Use

1.6.1.1 Infusion reactions

Patients with a high tumour burden or with a high number (≥25 x 10^9/L) of circulating malignant cells, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

Severe cytokine release syndrome is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated sever cytokines release syndrome.

Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients). These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the MabThera infusion.

1.6.1.2 Progressive Multifocal Leukoencephalopathy

Use of MabThera may be associated with an increased risk of PML (Progressive Multifocal Leukoencephalopathy). Very rare cases of fatal PML have been reported following use of MabThera. Patients must be monitored 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. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with Neurologist should be considered as clinically indicated. If any doubt exists, further evaluation, including MRI scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician should be particularly alert to symptoms suggestive of PML, that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of MabThera must be permanently discontinued. Following reconstitution of the immune system in immunocompromised patients with PML, stabilization or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

1.6.1.3 Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

1.6.1.4 Haematological toxicities

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/L and/or platelet counts < 75 x 10^9/L as clinical experience in this population is limited. MabThera has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Regular full blood counts, including neutrophil and platelet counts, should be performed during MabThera therapy.

1.6.1.5 Infections

Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections). Physicians should exercise caution when considering the use of MabThera in patients with

a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.

Cases of hepatitis B reactivation have been reported in subjects receiving MabThera including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that MabThera treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should always be performed in patients at risk of infection with HBV before initiation of treatment with MabThera. Carriers of hepatitis B and patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during and for several months (up to seven) following MabThera therapy.

1.6.1.6 Immunizations

The safety of immunization with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera

1.6.1.7 Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported. In case of such an event, treatment should be permanently discontinued.

1.6.1.8 Fertility, Pregnancy and Lactation

Pregnancy

IgG immunoglobulins are known to cross the placental barrier. B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Contraception in males and females

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy.

Lactation

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

Fertility

There are no data currently available on the effects of MabThera on fertility.

1.6.2 Undesirable Effects

The overall safety profile of MabThera in DLBCL described in this section is based on data from patients from clinical trials and from post-marketing surveillance (according to MabThera Summary of Product Characteristic - first published on 30/10/2009, last updated on 24/09/2013). These patients were treated either with MabThera monotherapy or in combination with chemotherapy.

Based on similarities between MabThera and MabionCD20 demonstrated during quality and preclinical studies as well as during ongoing first clinical trial in rheumatoid arthritis patients, it is expected that the safety profile of MabionCD20 in patients with DLBCL will be significantly similar to that of MabThera.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera are infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55% of patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome)
- Infections
- Cardiovascular events
- Hepatitis B reactivation and PML

The frequencies of ADRs (adverse drug reactions) reported with MabThera alone or in combination with chemotherapy are summarized in the tables below. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (<1/10,000).

The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "unknown" (according to MabThera SmPC).

Table 5. ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, bronchitis	sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B		Serious Vidal infectin Pneumocystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, febrile neutropenia, thrombocytopenia	anaemia, pancytopenia, granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels	late neutropenia,
Immune system disorders	infusion related reactions, angioedema	Hypersensiti-vity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome, serum sickness	infusion-related acute reversible thrombocytopenia
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy facial nerve palsy,	cranial neuropathy, loss of other senses
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss
Cardiac disorders		myocardial infarction arrhythmia, atrial	left ventricular failure, supraventricular tachycardia,	severe cardiac events	heart failure	

		fibrillation, tachycardia, cardiac disorder	ventricular tachycardia, angina, myocardial ischaemia, bradycardia			
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease	respiratory failure,	Lung infiltration
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforati	
Skin and subcutaneous tissue disorders	pruritis, rash, alopecia	urticaria, sweating, night sweats, skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome toxic epidermal necrolysis (Lyell's Syndrome)	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure	
General disorders and administration site conditions	fever , chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure	infusion site pain			
Investigations	decreased IgG levels					

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Infusion-related reactions

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumor lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment.

Infections

MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients. Localized candida infections as well as Herpes zoster was reported at a higher incidence in the MabThera-containing arm of randomized studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a hematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in subjects receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic adverse reactions

In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7 % of the patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4%) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below $1x10^9$/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below $1x10^9$/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL first line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group. In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

Cardiovascular reactions

Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart

failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, 3% FC) and in the relapsed/refractory study (4% R-FC, 4% FC).

Respiratory system

Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic events

During the treatment period, four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the relapsed/refractory study (3% R-FC, 3% FC). Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal disorders

Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of non-Hodkgin lymphoma. In the majority of these cases, MabThera was administered with chemotherapy.

IgG levels

In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Skin and subcutaneous tissue disorders

Toxic Epidermal Necrolysis (Lyell Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported very rarely.

Patient subpopulations - MabThera monotherapy

Elderly patients (≥ 65 years)

The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

Bulky disease

There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment

The percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade ¾ ADRs).

1.7 Study Rationale

1.7.1 Regulatory Requirements For Assessing Biosimilarity

According to EMA guideline on similar biological medicinal products (EMA/CHMP/437/04) a company may develop a new biological medicinal product claimed to be "similar" to a reference medicinal product, which has been granted a marketing authorisation. Comparability studies are needed to generate evidences substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product already authorised. The pharmaceutical form, strength and route of administration of the similar biological medicinal product should be the same as that of the reference medicinal product. The standard generic approach is normally applied to chemically derived medicinal products. Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products. The " similar biological medicinal products" approach, based on a comparability exercise, will then have to be followed. It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established [14].

According to EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005) the biosimilarity exercise follows the main concept that clinical benefit has already been established by the reference medicinal product, and that the aim of a biosimilar development programme is to establish similarity to the reference product, not clinical benefit per se. The most sensitive disease model to detect differences should be used in a homogeneous patient population to reduce variability. Many biological products e.g. monoclonal antibodies, have several approved indications, and the principle emerges that the most sensitive one of them should be chosen to show therapeutic similarity. The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK)

and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for demonstrating clinical comparability [15].

According to EMA guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/ 2010) similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomised, parallel group, comparative clinical trial(s), preferably double-blinded and normally equivalence trials. In general the most sensitive patient population and clinical endpoint is preferred to be able to detect product-related differences, if present and, at the same time, to reduce patient and disease-related factors to a minimum in order to increase precision. A clinical trial in a homogeneous patient population with a clinical endpoint that measures activity as primary endpoint may be considered [16].

1.7.2 Rationale For Study Phase and Design

Clinical trial was carefully planned according to relevant EMA guidelines referring to the development of biosimilar medicinal products as well as EMA scientific advices and recommendations received from EMA experts during Scientific Advice procedures.

Clinical development plan of MabionCD20 includes two multicenter, randomized, comparative bioequivalence phase III studies in rheumatoid arthritis (RA) patient and DLBCL patients. Study in RA patients is the main study in over 730 patients with efficacy parameter as a primary endpoint and safety, immunogenicity, pharmacokinetic and pharmacodynamic parameters as secondary endpoints.

The aim of study in DLBCL patients is to provide the additional adequate and sufficient data required to determine the biosimilarity of two monoclonal antibodies. Pharmacokinetic parameters are the primary endpoints, pharmacodynamic, efficacy, safety and immunogenicity parameters will be additional supportive data from the oncology setting.

This will be a multicenter, randomized, parallel-group, double-blind, active-control, PK powered comparative study with use of two monoclonal antibody medicinal products in label indication of MabThera – in patients with CD20-positive diffuse large B cell lymphoma eligible for treatment with rituximab according to MabThera Summary of Product Characteristic.

Study phase and design have been approved by EMA/CHMP experts during Scientific Advice procedure in EMA.

1.7.3 Rationale For Treatment

According to numerous literature data rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective in the treatment of diffuse large-B-cell lymphoma. Rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have a good safety profile. Higher response rates and improved event-free and overall survival are found in patients treated with the combination of rituximab and CHOP. The longer survival in the CHOP-plus-rituximab groups is due to a lower rate of disease progression during therapy and fewer relapses among patients who have a complete response. Treatment with CHOP plus rituximab is well tolerated, and the incidences of severe or serious adverse events were no different from these in the CHOP group [3, 17].

Rituximab in combination with CHOP regimen has been chosen to be used in this study because it is effective and less toxic than, other, more recently developed chemotherapeutic regimens. According to MabThera SmPC it is strongly recommended to use MabThera in combination with CHOP chemotherapy in treatment of Diffuse Large B cell Lymphoma.

MabionCD20 and MabThera formulation, doses and treatment scheme in this study is the same as labeled recommendations for the use of MabThera in DLBCL patients.

The recommended dosage of MabionCD20/MabThera in DLBCL patients is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle (CHOP). Standard treatment scheme will be repeated every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity in accordance with MabThera SmPC.

1.7.4 Summary of the Known and Potential Risks and Benefits to Human Subjects

- Study Protocol follows current European Medicines Agency guidelines and recommendations on the clinical evaluation of monoclonal antibodies, that provide a regulatory path to evaluate the clinical comparability of two monoclonal antibodies source from the two different manufacturers.
- The study was designed based on relevant literature data and international guidelines on clinical assessments, laboratory criteria, and response evaluation criteria in lymphoma patients that provide consistent international standards for the diagnosis, treatment and assessment of Non Hodgkin's Lymphoma.
- Selected study endpoints are well-accepted, validated metrics, that are consistent with published guidelines and EMA/CHMP recommendations.
- Study protocol design was consulted during Scientific Advice procedure with European Medicines Agency experts. EMA/CHMP scientific recommendations and advices were implemented to the study protocol. Study phase and design have been approved by EMA/CHMP experts during Scientific Advice procedure in EMA.
- This study was designed to comply with all provisions of the Declaration of Helsinki and its current amendments.
- The clinical trial was carefully designed according to Good Clinical Practice (GCP) guidelines, an international ethical and scientific standards for designing, conducting, recording, and reporting the trials.
- Similar quality, safety and activity of MabionCD20 to MabThera have been demonstrated in numerous in vitro and pre-clinical tests. Current data obtained from ongoing comparative clinical trial in RA patients indicate that safety profile of MabionCD20 is not different from safety profile of MabThera.
- Inclusion/exclusion criteria for patients as well as study treatment regimen is in accordance with MabThera approved indication for use.
- The clinical trial will be started only after receiving approval from relevant Ethic Committees and Competent Authorities.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Primary objectives of the study is to demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product: MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma, based on the percentage of patients achieving the primary pharmacokinetic endpoints:

- **Area under the plasma 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 1-4);**
- **Area under the plasma 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 (AUC 13-26).**

2.2 Secondary Objectives

To demonstrate high level of biosimilarity between MabionCD20 (MABION SA) and the reference product MabThera (rituximab by Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma based on:

– Comparative analysis of the secondary pharmacokinetic parameters:

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26 (AUC 1-26);
- Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion;
- Maximum plasma drug concentration (Cmax) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Rate Constant (Kel) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Half-Life (T ½) at steady state after the 5^{th} and 8^{th} infusions;
- Clearance at steady state after the 5^{th} and 8^{th} infusions;

– Comparative analysis of the pharmacodynamic parameter: area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell);

– The percentage of patients achieving the efficacy endpoints as following: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD).

– Comparative safety and immunogenicity of MabionCD20 and MabThera based on the following safety endpoints: adverse events, clinical laboratory assessment, presence of Human Antichimeric Antibodies (HACA).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This will be a phase IIIb multicenter, randomized, parallel-group, double-blind phase IIIb comparative study of two monoclonal antibody medicinal products: MabionCD20 (Mabion SA) and MabThera (Hoffman-La Roche) in patients with CD20-positive diffuse large B-cell lymphoma eligible for treatment with rituximab according to MabThera Summary of Product Characteristic. Trial population will be diagnosed according to WHO classification of lymphomas (published in 2001 and updated in 2008 based on previously published "Revised European-American Lymphoma classification" - REAL, eligible for rituximab treatment according to MabThera SmPC with life expectance at least 6 months [18].

Patient enrollment will be based on the diagnosis of DLBCL at each study center. Diagnosis of CD20-positive DLBCL will be based on an adequate sample of tissue obtained from a biopsy of an abnormal lymph node or other tissue of involved organ or bone marrow biopsy if lymph node material is not available. The diagnosis of CD20-positive DLBCL and its subtype have to be assessed with use of WHO classification of lymphomas by hematopathologists with experience in diagnosing lymphomas using adequate method of analysis (morphology and immunophenotyping including CD20).

Study is designed to provide adequate supportive data required to determine the biosimilarity of two therapeutic monoclonal antibodies with pharmacokinetic parameters as a primary endpoints and pharmacodynamic, efficacy, safety, immunogenicity endpoints as a supportive data.

Patients will be assigned to 1 of 2 treatment groups: MabionCD20 or MabThera, both with background chemotherapy: cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP).

The randomization scheme for treatment allocation is 5:2 for MabionCD20 and MabThera respectively. The duration of the study is 12 months. The treatment and observation period will last 26 weeks starting from Day 1 – when first IMP infusion is administered until Week 26 – one month after last IMP infusion. The follow-up period will last until Week 48.

The sponsor, investigators and patients will be blinded to treatment allocation until Week 26 of last patient, at which time the sponsor will be unblinded for the purposes of data analysis.

After providing a signed informed consent form and confirmation of study eligibility, patients will be randomized to 1 of the 2 available treatments, either to the investigational product: MabionCD20 or the active control treatment: MabThera.

Table 6. Study treatment group assignment

Study group	Treatment	Route of administration	Number of patients randomized
1	MabionCD20	IV	100
2	MabThera	IV	40

Patients will receive MabionCD20 or MabThera intravenously on day 1 of each course of chemotherapy. Each patient will be given CHOP chemotherapy: cyclophosphamide IV, doxorubicin hydrochloride IV, vincristine sulfate IV on day 1, and prednisone PO on days 1-5. Standard treatment scheme will be repeated every 21 days for 8 courses in the absence of disease progression or unacceptable toxicity in accordance with MabThera SmPC.

Eligible patients will be randomly assigned to treatment with CHOP plus MabionCD20 or CHOP plus MabThera.

For the purpose of efficacy analysis patients will be stratified according to age-adjusted International Prognostic Index (IPI), which is based on disease stage, performance status, age, number of extranodal sites, serum lactate dehydrogenase level to predict treatment outcome. Either 0 or 1 point is assigned according to the present parameters. Scores can range from 0 to 5 for the IPI [19].

For the purpose of pharmacokinetic analysis patients will be stratified according to BSA, gender and presence or absence of bone marrow infiltration [20, 21].

After the fourth cycle of treatment the evaluation of treatment progress will be performed. If despite the four cycles of R-CHOP lymphoma is progressive, patient should be excluded from the study and should be offered alternative treatment.

Study endpoints will be evaluated in the PP (Per Protocol) population. Patient will be considered to have completed the study if the patient receives eight subsequent doses of study medication and completes protocol-specified procedures up to week 26. Patients receiving a portion of at least 1 infusion of MabionCD20 or MabThera will be included in the safety analysis.

If the treatment allocation of particular patients become unblinded (based on presence of serious adverse events) patients will be excluded from the PK, PD, efficacy analysis but will be included in the safety evaluation.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Primary study endpoints are following pharmacokinetic parameters:

- Area under the plasma 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 1-4);
- Area under the plasma 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 (AUC 13-26).

3.2.2 Secondary Study Endpoints

Secondary study endpoints are following parameters:

Pharmacokinetic Endpoints:

- Area under the plasma concentration-time curve from time zero to final time point (AUC 0-t) measured after the first administration (Week 1) until Week 26 (AUC 1-26);
- Trough plasma concentration (C through), concentration measured at the end of a dosing interval at steady state, taken directly before eight infusion;
- Maximum plasma drug concentration (Cmax) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Rate Constant (Kel) at steady state after the 5^{th} and 8^{th} infusions;
- Elimination Half-Life (T ½) at steady state after the 5^{th} and 8^{th} infusions;
- Clearance at steady state after the 5^{th} and 8^{th} infusions;

Pharmacodynamic Endpoint:

Area under the B-cell concentration-time curve from the first administration to final time point at Week 26 (AUC 1-26 B-cell);

Efficacy Endpoints:

Tumor responses will be classified according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas [22].

Following efficacy endpoints will be evaluated at Week 26:

Complete Response (CR) requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH]) definitely assignable to NHL).

2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes ≥1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to <1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, it must be histologically negative for lymphoma.

Partial Response (PR) requires the following:

1. ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by at least 50% in the SPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).

6. No new sites of disease.

Stable Disease (SD) is defined as less than a PR (as described above) but not progressive disease (see below).

Progressive Disease (PD, nonresponders) requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node.

2. Appearance of any new lesion during or at the end of therapy.

Safety Endpoints:

- Adverse events frequency and strength;
- Clinically significant changes in clinical laboratory evaluations occurring during the protocol-specified reporting period;

Safety endpoints will be evaluated at Week 26.

Immunogenicity Endpoints:

- Percentage of patients who developed detectable Human Antichimeric Antibodies (HACA)

Immunogenicity endpoints will be evaluated at Week 26.

3.3 Treatment in the Study

3.3.1 Primary Treatment Regimens

The general goal of the study is a comparison of two therapeutic monoclonal antibodies: MabionCD20 and reference product MabThera in patients with CD20 positive diffuse large B-cell lymphoma (DLBCL) eligible for the MabThera therapy according to MabThera labeled indications. According to MabThera SmPC (Summary of Product Characteristic) rituximab 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, prednisone) chemotherapy.

Test Product: MabionCD20 500mg/50ml vials and MabionCD20 100mg/10ml vials manufactured by Mabion SA.

Reference Product: MabThera® 500mg/50ml vials and MabThera® 100mg/10ml vials manufactured by Hoffman- La Roche Limited.

Investigational Medicinal Products (IMPs): MabThera and MabionCD20 will be used in combination with CHOP chemotherapy. The recommended dosage of IMPs is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after administration of premedication including prednisone as a component of CHOP chemotherapy. Infusion of other components of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

375 mg/m^2 of MabThera or MabionCD20 will be given intravenously on Days 1, 22, 43, 64, 85, 106, 127, 148 of the study.

BSA will be calculated during Visit 1 on the day of first IMP and chemotherapy administration as MabionCD20/MabThera and chemotherapy doses depend on BSA. BSA will be calculated according to the DuBois formula: BSA in m^2 = (Weight (kg) $^{0.425}$ x Height (cm) $^{0.725}$) x 0.007184, BSA will be calculated with use of eCRF.

Doses of chemotherapy during next cycles may be modified if significant changes in body weight occur (≥ 15%). Doses of MabionCD20/MabThera should not be changed during the study, no dosage adjustment should be performed in case of body weight changes.

3.3.2 Characteristic of Investigational Medicinal Products

3.3.2.1 Pharmaceutical Form

MabionCD20 is a genetically engineered, highly purified chimeric, recombinant mouse/human, therapeutic monoclonal antibody. MabionCD20 is a clear, colorless, liquid without the presence of solid particulate in the form of needles, threads, lint, concentrate for solution formulated for IV administration as a sterile product in 9.0 mg/mL sodium chloride, 0.7 mg/mL polysorbate 80, 7.35 mg/mL sodium citrate and water for injection. MabionCD20 is supplied as a concentration of 10 mg/ml in 10 ml and 50 ml single-use vials. No preservative is used. The product packaging consists of type I clear borosilicate glass vials with 20-mmaluminum flip-off cap with polypropylene disc. External cardboard box contains one10ml vial or one 50 ml vial.

MabThera is a genetically engineered, highly purified chimeric, recombinant mouse/human, therapeutic monoclonal antibody. MabThera is a clear, colourless, liquid concentrate formulated for IV administration as a sterile product in sodium chloride, polysorbate 80, sodium citrate, sodium hydroxide, hydrochloric acid and water for injection. MabThera is supplied as a concentration of 10 mg/ml in 10ml and 50 ml single-use vials. No preservative is used. The product packaging consists of type I clear borosilicate glass vials with 20-mmaluminum flip-off cap with polypropylene disc.. External cardboard box contains two 10ml vials or one 50 ml vial.

3.3.2.2 Packaging and Labeling

As this is a double-blinded study, sponsor, the investigators, study team, patients will not have knowledge which specific study medication (MabionCD20 or MabThera) is administered to particular patient.

MabionCD20 and MabThera are repacked and relabeled by the third company for the purpose of blinding. MabionCD20 and MabThera are provided in clear glass vials identical in appearance. Appearance of MabionCD20 and MabThera packaging materials makes them indistinguishable.

Each vial is labeled with an individual booklet label (extended content label with several pages, each page is dedicated to one language) In exceptional cases use of single- page labels (dedicated for individual countries) is acceptable. The labels contain information defined by relevant regulations and country specific law in the languages of involved countries. The first page of booklet label is in English.

The external packaging material is white cardboard box, protective against light and breakage of the vials. Each box contains one 50ml vial or one 10ml vial. Each box is labeled with an individual booklet label, similar to the vial label. Each label contains information about the batch number, expiry date, vial number on the first page.

There is a special space on the label left to be filled in with the patient's screening number and Investigator's name.

All infusions of IMPs will be prepared according to the predefined randomization schedule. Study database will indicate the treatment arm that should be given to the particular patient.

3.3.2.3 Storage and Stability

MabionCD20 and MabThera should be stored in the refrigerator at the temperature: 2°C – 8°C. The glass vials with the product should be always kept in the outer carton to protect from light. Shelf life of MabThera is 30 months. Shelf life of MabionCD20 is given on the basis of stability tests. Product cannot be used beyond the expiration date.

The Investigational Medicinal Products as proteins molecules are very sensitive to temperature changes. MabionCD20 as well as MabThera require the storage in controlled temperature conditions throughout the course of the study. Range of the temperature during the storage of the IMPs cannot exceed 2-8℃. Any deviations from that range have to be reported, documented and kept in the study files.

Products affected with temperature deviations over 25°C and under 0°C may be dangerous for patients, because protein molecules start to degrade. Every effort should be made to prevent the medicinal products against freezing. Investigator is responsible for the assurance of the proper temperature conditions of IMPs.

Before the first patient visit the Sponsor will provide each site with the temperature data logger. Delegated site representative should check the storage temperature on a daily basis, measure and register the temperature of IMPs storage, check the presence of temperature deviations on a daily basis, print the data saved by the device.

If the temperature deviation occurs the IMPs cannot be used until receiving the confirmation, that products can be used despite the temperature deviation, because of lack of deviation influence on the quality of IMPs. During the period of temperature deviation assessment, the IMPs should be put in quarantine. The quarantined IMPs should remain in the refrigerator in the controlled temperature, however should be separated from IMPs with different status and visibly marked as "QURANTINE from … *(insert date of temperature deviation).* DO NOT USE!".

Detailed procedures related to study supplies, storage, product accountability and infusion of IMPs will be delivered in separate guidelines.

3.3.3 Posology and Methods of Administration

3.3.3.1 Preparation and Stability of Infusion Solution

MabionCD20 and MabThera are concentrates for solutions for infusions and may be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. The prepared solutions should be administered in concentration of 1 to 4 mg/ml as an intravenous infusion through a dedicated line with use of volumetric infusion pump, that enable to control and adjust rate of infusion. MabionCD20/MabThera cannot be administered as an intravenous push or bolus. MabionCD20/MabThera solution infusion cannot be mixed with other drugs.

Dilution of the concentrate for solution for infusion should take place in controlled and validated aseptic conditions (preferably in laminar flow hood with high efficiency particulate air filter (HEPA) or isolator) and should be made by trained study nurse or pharmacist. The site is responsible for ensuring the proper aseptic conditions, equipment and materials required to maintain the controlled and validated aseptic conditions.

The site is responsible for ensuring all materials required for preparation of infusion solution (syringes, needles, gloves, antiseptic surface cleaners).

MabionCD20 and MabThera are single use vials and do not contain any preservatives thus are intended for single administration only. Once opened vials cannot be stored for subsequent use.

Only polyvinyl chloride or polyethylene infusion bags and infusion sets may be used. No incompatibilities between MabThera or MabionCD20 and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

To prepare aseptically infusion solution necessary amount of concentrate should be added into infusion bag (500ml) containing sterile, pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. Products should be administered in concentration of 1 to 4 mg/ml. For mixing the solution, the bag should be gently inverted several times in order to avoid foaming.

Care should be taken to ensure the sterility of prepared solutions, visual inspection will be needed to check the presence of particulate matter and discoloration prior to administration.

The prepared infusion solution should be used as soon as possible (preferably within 4 hours after preparation, the infusion should be started). Longer storage time significantly increases the risk of dangerous bacterial contamination of prepared solution.

If the solution is prepared properly in validated and controlled aseptic conditions (in isolator or laminar flow hood), infusion solutions are biologically and chemically stable at the temperature 2–8°C for 24 hours and subsequently at room temperature (15–25°C) for additional 12 hours; storage temperature (2–8°C) should be monitored and documented.

During storage and administration, the infusion bag has to be protected from direct sun light.

3.3.3.2 MabionCD20/MabThera Infusion

MabionCD20 and MabThera infusions should be administered only under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. MabionCD20 and MabThera infusion should be performed before chemotherapy administration.

Pre Infusion Assessment

Before each IMP (MabionCD20 or MabThera) infusion following procedures should be performed: physical examination, vital signs measurements, ECG, blood sampling , urine pregnancy tests, weight and high measurements, BSA (Body Surface Area) calculation.

BSA will be calculated for the first time during Visit 1 on the day of first IMP infusion as MabionCD20/MabThera doses depend on BSA. Doses of MabionCD20/MabThera should not be changed during the study, no dosage adjustment should be performed in case of body weight changes.

Before each infusion patients should be informed about potential infusion related reactions and instructed to alert medical personnel immediately if they feel any side effects. Symptoms suggesting an acute infusion reaction are: pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough and bronchospasm, with or without associated hypo- or hypertension.

Before infusion, availability of following medicines should be checked: epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, paracetamol.

Premedication (anti-pyretic, antihistaminic and prednisone as a component of CHOP chemotherapy should be given about 30-40 minutes before IMP infusion).

First infusion

The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. In total, infusion may last 5 - 8 hours, depending on patient's reactions.

Subsequent infusions

Subsequent doses can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

During each infusion temperature, pulse, blood pressure should be recorded 30 minutes after the infusion start and every 60 minutes throughout the course of the infusion.

If the infusion duration has exceeded 12 hours, the infusion should be stopped because of limited stability of infusion solution at room temperature.

Infusion Related Reactions

Patients should be closely monitored for the onset of cytokine release syndrome. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms. Patients, who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia will have the infusion interrupted immediately.

If mild to moderate reactions occur (low grade fever; hypotension <30mmHg from baseline) administration of anti-pyretic, an antihistamine should be considered if required and the infusion rate should be reduced at a 50% (e.g. from 200 mg/h to 100 mg/h) until symptoms are completely resolved.

If moderate to severe reactions occur (e.g. fever >38.5ºC; chills; mucosal swelling; shortness of breath; hypotension by >30mmHg from baseline) the infusion should be stopped immediately and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids should be considered if required. The infusion cannot be restarted until complete resolution of all serious symptoms.

At this time, the infusion should be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for the second time, the decision to stop the treatment should be considered on a case by case basis.

It is the responsibility of Investigator to ensure that rescue medication as epinephrine (adrenaline), antihistamines, glucocorticoids, oxygen, bronchodilators, intravenous saline are available at the site during MabionCD20/MabThera infusion.

Schedule of events during day of IMP infusion

Assessment of inclusion/exclusion criteria

(physical examination, vital signs, ECG, urine pregnancy test, BSA, AE assessment)

Blood sampling (hematology, chemistry, PK/PD)

(within two hours before infusion, however before premedication is given)

Administration of premedication (30-40 minutes before IMP infusion)

Infusion of IMP

Blood sampling for PK (serum IMP concentration analysis)

(within 30±15 minutes after completion of IMP infusion)

ECG and AE assessment

(within 60 after infusion)

Administration of premedication prior to CHOP

(30-40 minutes before CHOP infusion)

Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine)

(started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized)

Post-infusion Procedures

When the infusion is completed, it is recommended to add some amount of saline to infusion bag to infuse any residual MabionCD20/MabThera dose remaining in the tubing.

Additional blood samples should be collected 30±15 minutes after completion of infusion for serum concentration analysis. Additional adverse events assessment and 12-lead ECG should be performed within 60 minutes after IMP infusion completion before administration of chemotherapy.

Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

3.3.4 Prior and Concomitant Treatment

3.3.4.1 Premedication

MabThera and MabionCD20 may be associated with infusion related reactions (IRR) related to release of cytokines and/or other chemical mediators. Premedication with anti-pyretic and antihistamine significantly reduces the incidence and severity of these events and should be administered prior to MabThera and MabionCD20 administration.

Premedication prior to IMP infusion should be given 30-40 minutes before IMP administration and should consists of:

- anti-pyretic (paracetamol 1 g) given orally,
- antihistamine (diphenhydramine 50 mg or equivalent antihistamine e.g. loratadine) given orally,
- prednisone (as a component of CHOP chemotherapy) 100 mg given orally.

Since hypotension may occur during infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabionCD20/MabThera infusion.

Premedication prior to CHOP administration should be given 30-40 minutes before CHOP infusion and should consists of: ondansetron 8 or 16 mg PO or equivalent.

3.3.4.2 Concomitant Medication

Patients will be treated every three weeks (21 days) for eight cycles of CHOP.

CHOP will be administered in the standard dosage regimen:

- 50 mg of doxorubicin per square meter administrated IV on day 1 of each chemotherapy cycle
- 1.4 mg of vincristine per square meter, up to a maximal dose of 2 mg, administrated IV on day 1 of each chemotherapy cycle
- 750 mg of cyclophosphamide per square meter of body-surface area administrated IV on day 1 of each chemotherapy cycle
- 100 mg of prednisone administrated PO per day for five days, day 1-5 of each chemotherapy cycle.

Table 7. CHOP chemotherapy posology

Day	Drug	Dose	Route	Comments
1	Doxorubicin	50 mg/m^2	IV infusion	slow IV infusion over at least 3 to 5 minutes in sodium chloride 0.9%
1	Vincristine	1.4mg /m^2 (max 2mg)	IV infusion	diluted in about 25-50ml 0.9% sodium chloride and infused over 5-10 minutes
1	Cyclophosphamide	750 mg/m^2	IV infusion	slow IV infusion over at least 30 minutes in 250ml sodium chloride 0.9%
1	Prednisolone	100mg	Oral	given orally 30-40 minutes before MabionCD20/MabThera administration
2-5	Prednisolone	100mg	Oral	taken in the mornings, swallowed with food to prevent indigestion

If patient experience serious adverse events during or after MabionCD20/MabThera administration, CHOP chemotherapy may be postponed for the Day 2.

Patients should receive full supportive care at the clinical site, including transfusions of blood and blood products, antibiotics, anti-emetics, and hematopoietic growth factors (e.g. G-CSF) or other supportive treatment when required according to standard medical practice (f. eg mesna in case of high doses of cyclophosphamide). Concomitant medications for other medical conditions are permitted as clinically indicated.

All medications that are administered during the study, dose modifications should be recorded in the patient's CRF and in the source documents.

3.3.4.3 Dose Modifications of Concomitant Medication

BSA will be calculated for the first time during Visit 1 on the day of first IMP and chemotherapy administration as MabionCD20/ MabThera and chemotherapy doses depend on BSA. BSA will be calculated according to the DuBois formula with use of eCRF. Doses of chemotherapy during next cycles may be modified if significant changes in body weight occur (≥ 15%). Doses of MabionCD20/MabThera should not be changed during the study, no dosage adjustment should be performed in case of body weight changes.

For patients ≥ 65 years old cyclophosphamide and doxorubicin doses should be administered at decreased dose (at 75%). If patient tolerate infusion well, doses may be escalated up to full 100% dose for the next course of treatment. For patients ≥ 65 years old, vincristine dose may be decreased for 1.5 mg.

Other dose modifications of cyclophosphamide, doxorubicin and vincristine depends on the patients conditions, the final decision regarding dose modifications should be made by Investigator.

Neutropenia

Before each CHOP administration Investigator should assess the risk of neutropenic fever occurence resulted from chemotherapy infusion. If the anticipated risk of neutropenic fever in patient is greater than 20%, Investigator should consider necessity of G-CSF (e.g. filgrastim) support after chemotherapy administration and reduction of chemotherapy dose.

Table 8. Dose modifications in case of neutropenia

Neutropenia	Dose modifications
neutrophil count is lower than 1500/µl	the cycle may be delayed for one week (up to two weeks) until parameters improve
grade 4 (severe) neutropenia or febrile neutropenia following any cycle of chemotherapy	consideration should be taken to decrease the doses of cyclophosphamide and doxorubicin by 75% or 50%
grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	consideration should be taken to stop the treatment with CHOP

Thrombocytopenia

Table 9. Dose modifications in case of thrombocytopenia

Thrombocytopenia	Dose modifications
platelet count lower than 75,000/µl	the cycle may be delayed for one week (up to two weeks) until parameters improve
grade 3 or 4 thrombocytopenia following any cycle of chemotherapy	consideration should be taken to decrease the doses of cyclophosphamide and doxorubicin by 75% or 50%
grade 3 or 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	treatment with CHOP should be stopped

Renal impairment

Table 10. Cyclophosphamide dose modifications in case of renal impairment

Creatinine Clearance [ml/min]	Cyclophosphamide Dose
>20	100%
10 - 20	75%
<10	50%

Hepatic impairment

Table 11. Dose modifications in case of hepatic impairment

ALT/AST	Bilirubin (µmol/l)	Doxorubicin Dose
2 – 3 x ULN	-	75%
> 3 x ULN or	20 – 50	50%
	50 - 85	25%
> 3 x ULN and	> 50	-
	> 85	Omit

Heart impairment

Doxorubicin should be discontinued if evidence of congestive heart failure is observed. In case the risk of cardiac complications associated with cumulative doses of doxorubicin exceeding 450 mg/m^2 is high, Transthoracic echocardio-graphy (TTE) should be considered prior to each doxorubicin administration.

Neurotoxicity

Dose of vincristine should be reduced by 50% in case of moderate/severe motor/sensor toxicity (grade 2-3) for all subsequent courses of therapy until the end of the treatment period.

In case of organ toxicity grade 3-4 administration of vincristine should be delayed until the parameters improve to grade 2. Consideration should be taken to decrease the dose of vincristine to max 1mg. In case of repeating organ toxicity treatment with vincristine should be discontinued. If the number of leucocytes decreases <3000 µl the Investigator should stop the treatment and antibiotics have to be administered to the patient.

Decision on modifications of CHOP doses should made by Investigator based on risk-benefit balance of treatment.

3.3.4.4 Storage of Concomitant Medication

The Investigator is obliged to ensure the proper conditions of concomitant medication storage at the site according to labeled recommendations of the manufacturer.

Concomitant medication should be stored in a dedicated place where the proper temperature conditions recommended by the manufacturer are kept. Concomitant medication delivered by Sponsor should be marked/labeled with number of the study: MabionCD20-002NHL and should be used only in MabionCD20-002NHL study.

Delegated site personnel is responsible for checking the storage temperature of concomitant medication and verifying the expiry dates of concomitant medication. It is strictly forbidden to use any medicines beyond the expiry date in the study. Investigator is obliged to inform patients about storage conditions of concomitant medicines that are dispensed to patients and will be taken by the patients outside the clinical site.

3.3.4.5 Rescue Treatment

MabThera and MabionCD20 may be associated with infusion related reactions (IRR), which may be related to release of cytokines and/or other chemical mediators. Premedication significantly reduced the incidence and severity of these events and should be administered prior to each MabionCD20/ MabThera treatment.

IRR are usually reversible with a reduction in rate, or interruption, of MabThera/MabionCD20 infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, paracetamol should be available for immediate use in the event of an allergic reaction during administration of MabThera and MabionCD20.

3.3.4.6 Medications Not Permitted Before and During the Trial

Following medicines/treatment is not permitted during the clinical trial:

- investigational or unlicensed/unapproved products
- immunotherapy / radio-immunotherapy (other than protocol-specified)
- chemotherapy (other than protocol-specified)
- radiotherapy

If any of described above therapy is administered, patient should be withdrawn from the study.

3.3.5 Interactions with IMPs

There are limited data on possible drug interactions of MabionCD20 and MabThera with other medicinal products. No specific drug interaction studies have been performed.

Since hypotension may occur during MabionCD20/MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabionCD20/MabThera infusion.

3.3.6 Overdose of IMPs

According to MabThera SmPC doses of rituximab higher than 1000 mg have not been tested in controlled clinical trials in patients. The highest dose tested was 5g in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.

In the postmarketing assessment of MabThera five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

3.4 Selection of Study Population

3.4.1 Diagnosis of DLBCL

Trial population consists of CD20 positive diffuse large B cell lymphoma (DLBCL) patients diagnosed according to WHO classification of lymphomas (published in 2001 and updated in 2008 based on previously published "Revised European-American Lymphoma classification" - REAL, eligible for rituximab treatment according to MabThera SmPC with life expectance at least 6 months [18].

Patient enrollment will be based on the diagnosis of DLBCL at each study center. Diagnosis of CD20-positive DLBCL will be based on an adequate sample of tissue obtained from a biopsy of an abnormal lymph node or other tissue of involved organ or bone marrow biopsy if lymph node material is not available.

The diagnosis of CD20-positive DLBCL and its subtype have to be assessed with use of WHO classification of lymphomas by hematopathologists with experience in diagnosing lymphomas using adequate method of analysis (morphology and immunophenotyping including CD20). Tumor biopsy should document the level of CD20 expression and identity histological transformation, if present.

Based on the diagnosis of a local/site pathologist Investigator will be able to enroll patient in the study.

Histological review requires morphology and immune- histochemistry. Histopathological report should be available and archived the site.

3.4.2 Number of Patients

With an expected mean ratio of 90 - 110% and Coefficient of Variation of 50%, at least 112 patients (80 patients in MabionCD20 group and 32 patients in MabThera group) are required to complete the study to achieve a power of 80% and to demonstrate equivalence within the 70%-143% interval. Assuming a 20% drop-out rate, total of 140 patients would be randomized (100 patients in MabionCD20 group and 40 patients in MabThera group).

Assuming 25% screen failure rate 175 patients needs to be screened.

3.4.3 Inclusion Criteria

Patients that met following inclusion criteria may be randomized to the study:

1. Gender: male or female;
2. Age ≥ 18
3. Patients with histological confirmed CD20 positive diffuse large B cell lymphoma (DLBCL)

4. Patients that had been diagnosed according to the WHO classification;
5. Performance status ≤ 2 on the ECOG/WHO scale, performance status of 3 will be accepted if impairment is caused by DLBCL complications and improvement is expected once therapy is initiated;
6. Patients eligible for rituximab treatment according to MabThera indications;
7. Life expectance at least 6 months;
8. No immunotherapy for DLBCL within 1,5 years prior to screening;
9. Written informed consent including information about benefits and potential risks of the trial;
10. Ability and willingness to comply with the requirements of the study protocol;
11. Willing to use acceptable forms of contraception for females and males patients with female sexual partners of childbearing potential; For females of reproductive potential use of a reliable means of contraception (e.g., hormonal contraceptive, patch, intrauterine device, physical barrier) throughout study participation. Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following therapy;
12. Laboratory values within normal range unless abnormalities are related to lymphoma. The laboratory values should be obtained ≤ 35 days prior to MabionCD20/MabThera infusion.
13. Adequate hematological function:
    - hemoglobin ≥ 9 g/dl unless abnormalities are due to bone marrow involvement by lymphoma,
    - absolute neutrophil count (ANC) ≥ 1,500/μL unless abnormalities are due to bone marrow involvement by lymphoma,
    - platelet count ≥ 100,000/μL, unless abnormalities are due to bone marrow involvement by lymphoma,
14. Adequate renal function: Creatinine ≤ 2.0 mg/dl or calculated creatinine clearance ≥ 40 unless abnormalities are related to lymphoma;
15. Adequate liver functions:
    - total bilirubin ≤ 2 mg/dl unless due to Gilbert's disease (patients with bilirubin between 2-3.0 mg/dl due to lymphoma may be entered);
    - Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3 the upper limit of normal unless abnormalities are related to lymphoma;
16. Alkaline phosphatase ≤ 5x upper limit of normal;
17. Left ventricular ejection fraction (LVEF) ≥50%;
18. A negative serum and urine pregnancy test prior to treatment.

3.4.4 Exclusion Criteria

Patients that met at least one of the following exclusion criterion cannot be randomized to the study:

1. Life expectance less than 6 months;
2. Any chemotherapy, radiotherapy, immunotherapy, biologic, investigational or hormonal therapy for treatment of lymphoma within 28 days prior to treatment;
3. Rituximab, other anti-CD20 mAb drug treatment, treatment with any cell depleting therapies (e.g., anti-CD4, anti-CD5, anti-CD3, anti-CD19, anti CD11a, anti-CD22, BLys/BAFF) within 1,5 years prior to screening;
4. History of T-cell lymphoma, indolent lymphoma, central nervous system involvement by lymphoma Primary Central Nervous System (CNS) DLBCL;
5. History of other invasive malignancy within 5 years except for localized/in situ carcinomas such as non-melanoma skin cancer or cervical carcinoma in situ;
6. Primary or secondary immunodeficiency;
7. Evidence of significant uncontrolled concomitant disease such as, but not limited to, nervous system, renal, hepatic, endocrine, or gastrointestinal disorders within 5 years prior to screening which, in the Investigator's opinion, would preclude subject participation;
8. Active infections: known active bacterial, viral, fungal, mycobacterial, other infection (including tuberculosis, sepsis, opportunistic infections) but excluding fungal infections of nail beds;
9. Concurrent disease that would exclude giving of treatment as outlined in the protocol for example: patients with general status that doesn't permit the administration of eight courses of CHOP, patients with cardiac contraindication to doxorubicin therapy (e.g., abnormal contractility on echocardiography) or a neurologic contraindication to vincristine (e.g., peripheral neuropathy);
10. III or IV class of the New York Heart Association (NYHA) Classification;
11. Existing serious vein disease;
12. History of currently treated relevant serious CNS and/or psychiatric disorders;
13. History of significant cytopenias or other serious bone marrow disorders within 5 years prior to screening;
14. Major surgery (excl. biopsies) within 30 days prior to MabionCD20/MabThera infusion;
15. Presence of HBs antigen or HBc antibody without HBs antibody, . In case of these results a PCR for HBV and/or HCV may be performed and patient can be enrolled if these results are negative, positive serology for HIV;
16. Pregnancy or lactation (positive serum pregnancy test for women of child bearing age);
17. Recent vaccination (< 4 weeks prior treatment);
18. Participation in other clinical trial during the last two months prior to the start of the study;

19. Patients, who are unable to understand the written and verbal instructions, in particular the risks connected with the study;
20. Male patients (with female sexual partners of childbearing potential) and female patients of childbearing potential who refuse to use effective methods of contraception
21. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.
22. Hypersensitivity to the active substance or to any other excipients of the medicine

3.4.5 Removal of Patients from Treatment or Assessment

Patients are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. A patient will be considered to have completed the study if the patient receives eight infusions of study medication and completes protocol-specified procedures up to week 26. Every effort will be made to complete Week 26 and Week 46 follow-up assessments for any patients.

The Investigator may withdraw a patient from the study if the patient:

- Violates the requirements of the protocol;
- Experiences a serious or intolerable AE, that in the Investigator's opinion would preclude subject participation;
- Experiences progressive disease;
- Develops, during the course of the study, conditions listed in the exclusion criteria, that in the Investigator's opinion, would preclude subject participation;
- Becomes pregnant;
- Requests to be withdrawn from the study;
- Enters into another clinical study with the treatment that in the Investigator’s opinion excludes subject participation

The Investigator will also withdraw the patient from the study upon the request of the Sponsor - Mabion SA or if Mabion SA terminates the study.

Upon occurrence of a serious or intolerable adverse event or other reasons that contribute to withdrawing the patient from the study the Investigator will notify Mabion SA before discontinuing the patient.

A patient may withdraw consent to participate in the study at any time and for any reason. The reason(s) for a patient’s withdrawal from the study are to be recorded on the case report form (CRF).

3.4.6 Monitoring of Patient Compliance

Investigational medicinal products: MabionCD20, MabThera and other medications will be administered under a physician's supervision. Any deviations from the planned treatments will be recorded in the patient's CRF.

All medications that are administered during the study will be recorded in the patient's CRF and in the source documents. Concomitant medications for other medical conditions are permitted as clinically indicated. All concomitant medications taken during the study will be recorded in the patient CRF.

Lot numbers of all medications purchased and dispensed for the study will be captured in the patient CRF.

3.5 Study Assessments

3.5.1 Pharmacokinetic Assessment

Blood samples will be taken before and after each MabionCD20/MabThera infusion. Blood samples for PK assessments should be collected within two hours before infusion of study medication and 30±15 minutes after completion of infusion. Additional samples will be taken after last infusion at the following time points: after 1 week, 1 month, 6 months after last infusion.

Blood samples for PK evaluation will be collected on the following days:

- Day 1, Visit 1 (before and after completion of first infusion)
- Day 8 ± 1, Visit 2 (7 days after first infusion)
- Day 15 ± 1, Visit 3 (14 days after first infusion)
- Day 22± 2, Visit 4 (before and after completion of second infusion)
- Day 43 ± 2, Visit 5 (before and after completion of third infusion)
- Day 64 ± 2, Visit 6 (before and after completion of fourth infusion)
- Day 85 ± 4, Visit 8 (before and after completion of fifth infusion)
- Day 106 ± 4, Visit 9 (before and after completion of sixth infusion)
- Day 127 ± 4, Visit 10 (before and after completion of seventh infusion)
- Day 148 ± 4, Visit 11 (before and after completion of eight infusion)
- D 155 ± 4, Visit 12 (one week after last infusion)
- D 176 ± 4, Visit 13 (one month after last infusion)
- D 316 ± 7, Visit 14 (six months after last infusion, PK evaluation during follow-up)

Determination of serum concentration and pharmacokinetic parameters of MabThera and MabionCD20 will be performed using a direct-antigen enzyme-linked immunosorbent assay (ELISA) in Research and Development Centre of Mabion SA.

Blood samples should be centrifuged to obtain serum for analysis. Serum samples will be kept frozen at the site at the temperature below -15°C until shipment to Mabion for analysis.

3.5.2 Pharmacodynamic Assessment

MabThera and MabionCD20 bind specifically to the transmembrane antigen: CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The Fab domain of MabionCD20 and MabThera binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Because circulating antibodies bind to CD20+ B cells, the B-cell surface antigen CD19 is used as a marker for CD20 because both have a similar expression profile on B cells. Levels of circulating CD19+ B cells will be measured by flow cytometry.

B cell depletion as levels of CD19+ B cells as well as the level of CD3+, CD4+, and CD8+ T cells and NK cells (CD16/CD56 positive) will be measured on the following days:

- Day 1, Visit 1 (within two hours before first infusion of study medication)
- Day 8 ± 1, Visit 2 (7 days after first infusion)
- Day 22 ± 2, Visit 4 (within two hours before second infusion)
- Day 64 ± 2, Visit 6 (within two hours before fourth infusion)
- Day 148 ± 4, Visit 11 (within two hours before eight infusion)
- D 176 ± 4, Visit 13 (one month after last administration)
- D 316 ± 7, Visit 14 (six months after last administration, PD evaluation during follow-up)

Fresh blood samples are required to measure subpopulation of lymphocytes.

3.5.3 Efficacy Assessment

Efficacy assessment will be made based on tumor responses classified according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. Response will be assessed on the basis of clinical, radiologic and pathologic (bone marrow) criteria. Possible efficacy responses are following: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD).

Following parameters should be checked to evaluate efficacy endpoints at Screening Visit – V0 (confirmed at V1) and at Visit 13 (Week 26) - one month after last treatment cycle:

- CT scans; CT scan of neck, chest, abdomen, pelvis are the standard evaluation of tumors;
- Bone marrow biopsy; biopsy may be omitted at screening if results are available for the test performed within last 60 days before screening visit; This period may be extended to 90 days if basing on Investigator and Medical Monitor judgement the re-biopsy is highly invasive and previous results are expected to be up to date in screening
- Evaluation of all involved lymph nodes greatest transverse and diameters;
- Evaluation of all extranodal sites of disease;

- Assessment of spleen and liver enlargement based on CT scan and physical examination;
- Size of other organs affected with lymphoma based on CT scan and physical examination.

Other methods of patient's staging are allowed to be performed in justified cases when:

• CT does not allow for accurate efficacy assessment of the used therapy;

• CT does not allow to detect abnormalities which may exclude patient from the study due to non-fulfillment of inclusion criteria;

Table 12. Standard response criteria for lymphoma

Response category	Physical examination	Spleen, liver	Lymph nodes	Lymph nodes mass	Bone marrow
CR	normal	normal	normal	normal	normal
PR	normal	normal	normal	normal	Positive
	normal	normal	≥50% decrease	≥50% decrease	Irrelevant
	normal	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
PD	appearance of any new lesion	normal/ enlargement	≥50% increase	≥50% increase	normal/ reappearance

Tumor staging will be performed at Screening Visit – V0, (confirmed at V1) at Visit 7 after four treatment cycles and at Visit 13 (Week 26) - one month after last treatment cycle:

Tumor staging will consist of: IPI, ECOG performance status, Ann Arbor staging.

IPI - International Prognostic Index

IPI is commonly used to predict the prognosis of patients with aggressive lymphoma. IPI is based on disease stage (Ann Arbor) , ECOG performance status, age, number of extranodal sites, serum lactate dehydrogenase level to predict treatment outcome.

Table 13. International Prognostic Index for NHL

	0 points	1 point
Age (years)	≤60	>60
Stage (Ann Arbor)	1 or 2	3 or 4
Number of extranodal sites	≤1	>1
ECOG Performance Status	0 or 1	≥2
LDH	Normal	Elevated

Either 0 or 1 point is assigned according to the present parameters. Scores can range from 0 to 5 for the IPI [19].

The sum of the points correlates with the following risk groups:

- Low risk (0-1 points)
- Low-intermediate risk (2 points)
- High-intermediate risk (3 points)
- High risk (4-5 points)

Ann Arbor staging

Ann Arbor staging is the system used to evaluate the extent of a cancer's spread [23].

Stage I

Either of the following means the disease is stage I:

- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I)
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE)

Stage II

- The lymphoma is in 2 or more groups of lymph nodes on the same side (above and below) the diaphragm (the thin band of muscle that separates the chest and abdomen)
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm

Stage III

Either of the following means the disease is stage III:

- The lymphoma is found in lymph node areas on both sides (above and below) the diaphragm
- The cancer may also have spread into an area or organ next to lymph nodes (IIIE), into the spleen (IIIS) or both (IIISE)

Stage IV

Either of the following means the disease is stage IV:

- The lymphoma has spread outside the lymph system into an organ that is not right next to an involved node
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord or the pleura (thin lining of the lungs)

Other modifiers may also be used to describe the lymphoma stage:

Bulky disease

The term is used to describe tumors in the chest that are at least one-third as wide as the chest, or tumors in other areas that are at least 10 cm across. It is usually designated by adding the letter X to the stage. Bulky disease may require more intensive treatment.

A vs. B

Each stage may be designated A or B. The letter B is added (stage IIIB, for example) if a person has any of the B symptoms listed below:

- Loss of more than 10% of body weight over the previous 6 months (without dieting)
- Unexplained fever of at least 101,5 ºF
- Drenching night sweats

If no B symptoms are present the letter A is added to the stage.

ECOG/WHO performance status

ECOG/WHO scales and criteria are used to assess disease is progressing and how the disease affects the daily living abilities of the patient [24].

Table 14. ECOG/WHO performance criteria for lymphoma

Definition	Grade
Fully active, able to carry on all pre-disease performance without restriction.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.	**1**
Ambulatory and capable of all self-care but unable to carry out any work activities. Out of bed more than 50% of waking hours.	**2**
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	**4**
Dead	**5**

3.5.4 Laboratory Safety Tests

Laboratory tests to be performed on screening visit:

- **Hematology:** red blood cells (RBC), hematocrit, hemoglobin, platelet count, white blood cells (WBC) with deferential
- **Clinical chemistry:** glucose, sodium, potassium, calcium, phosphor, AST, ALT, total bilirubin, serum creatinine, alkaline phosphatase, gammaglutamylotranspeptidase, total protein, albumin,

blood urea nitrogen, LDH (lactate dehydrogenase), and other relevant parameters if required in the Investigator's opinion

- **Immunoglobulin concentration** in blood: IgG, IgA, and IgM levels
- **Serology panel** includes tests for HIV, hepatitis B (surface antigen HBsAg and anti-HBcAg) and hepatitis C antibody
- **Urinalysis:** pH, glucose, total protein, erythrocytes, white blood cells (WBC), microscopic examination
- **Pregnancy test** (serum pregnancy tests at screening, urine pregnancy tests before each treatment cycle)
- **β2 microglobulin**
- **Anti-tetanus antibody**

Laboratory tests performed on other visits:

- **Hematology:** red blood cells (RBC), hematocrit, hemoglobin, platelet count, white blood cells (WBC) with deferential
- **Clinical chemistry**: AST, ALT, total bilirubin, serum creatinine, alkaline phosphatase, blood urea nitrogen
- **Immunoglobulin concentration in blood:** IgG, IgA, and IgM levels **(on particular visits)**
- **Pregnancy test:** urine pregnancy test **(on particular visits)**
- **PK analysis (on particular visits)**
- **PD analysis (on particular visits)**
- **HACA, anti-tetanus antibody, β2 microglobulin and urinalysis (on some visits)**

Blood samples for clinical chemistry and hematology should be obtained after overnight fasting (at least 6 hours before blood sampling.

Laboratory safety tests as: haematology, clinical chemistry, immunoglobulin levels will be performed at screening, before each treatment cycle, 1 month and 6 months after last infusion.

Urinalysis will be performed at screening 1 month and 6 months after last infusion.

Assessment of β2 microglobulin and anti-tetanus antibody will be performed at screening and 1 month after last infusion.

Antibody status (HIV, HBV, HCV) will be performed only at screening.

The Investigator may invite patient to unscheduled visits between treatment cycles in order to check blood parameters after CHOP therapy. Routinely one unscheduled visit can be performed between each two treatment cycles. In reasonable cases when patient requires intensive care and monitoring of blood parameters additional visits can be scheduled.

Laboratory tests performed on unscheduled visits:

- **Hematology:** red blood cells (RBC), hematocrit, hemoglobin, platelet count, white blood cells (WBC) with deferential

• **Clinical chemistry**: AST, ALT, total bilirubin, serum creatinine, alkaline phosphatase, blood urea nitrogen

3.5.5 Immunogenicity assessment

The presence of HACA (Human Antichimeric Antibody) in serum will be measured to check the immunogenicity of MabionCD20 in comparison to MabThera. Immunogenicity assessment will be performed:

- At screening
- D 8 ± 1, Visit 2
- D 64 ± 2, Visit 6 (before 4 administration)
- D 148 ± 4, Visit 11 (before 8 administration)
- D 176 ± 4, Visit 13 (one month after last administration)
- D 316 ± 7, Visit 14 (six months after last administration, evaluation during follow-up)

4 STUDY PROCEDURES

SCREENING

4.1 Visit 0 Screening Visit

Visit 0 (Day -35 to Day – 8 prior Visit 1)

After patient agreed to participate in the study and signed Informed Consent Form, eligibility assessment should be performed within days prior to the first treatment cycle.

During Screening Visit following procedures have to be performed to verify if patient meets protocol specific inclusion and exclusion criteria:

1. Patient Information Letter and Informed Consent Form should be presented to patient, documents must be reviewed and ICF has to be signed by patient or patient's representative prior to any other protocol procedure;
2. Medical history should be assessed with regards to present and past diseases and therapies especially conditions specified in Protocol inclusion/exclusion criteria;
3. Concomitant medication review;
4. Assessment of inclusion/exclusion criteria;
5. Physical examination;
6. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
7. Tumor and disease staging assessment;
8. 12-lead ECG and echocardiography;
9. Tumor biopsy (biopsy may be omitted at screening if results are available for the test performed within last 60 days before screening visit;);
10. Bone marrow biopsy (biopsy may be omitted at screening if results are available for the test performed within last 60 days before screening visit);
11. CT scan (CT scan of neck, chest, abdomen, pelvis should be performed)
12. Blood samples should be collected for:
    - Clinical Chemistry, including serum pregnancy test,
    - Hematology,
    - Serology (HIV, HBV, HCV),
    - Immunoglobulin titers (IgG, IgA, and IgM),
    - HACA (Human Antichimeric Antibody),
    - Anit-tetanus antibody,
    - β2 microglobulin;

13. Urine samples should be collected for urinalysis;
14. Additional blood samples will be collected for validation and optimization of analitycal methods.

Tumor biopsy, bone marrow biopsy, CT scan should be perform at screening after verification of other parameters of eligibility.

ACTIVE TREATMENT PERIOD

4.2 Visit 1

Visit 1 (Day 1, Week 1)

During Visit 1 following procedures have to be performed:

1. Patient Information Letter and ICF – confirmation that patient understands all clinical trial procedures and ICF is signed;
2. Inclusion/exclusion criteria assessment – confirmation that all tests results are available and patient meets all specified criteria to be enrolled in the study;
3. Concomitant medication review;
4. Physical examination;
5. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
6. Tumor and disease staging assessment;
7. Weight, high measurements and BSA (Body Surface Area) calculation;
8. 12-lead ECG should be performed before the premedication and the IMP infusion;
9. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
   - PD analysis,
10. Efficacy assessment
11. Urine pregnancy test should be performed (before IMP infusion);
12. Adverse events assessment should be performed before premedication and IMP infusion;
13. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
14. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;

15. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
16. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
17. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
18. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.3 Visit 2

Visit 2 (Day 8± 1, Week 2)

During Visit 2 following procedures have to be performed to check the tolerance for first IMP and chemotherapy infusion:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. 12-lead ECG;
5. Adverse events assessment;
6. Blood samples should be collected for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - HACA analysis
   - PK analysis,
   - PD analysis,

4.4 Visit 3

Visit 3 (Day 15 ± 1, Week 3)

During Visit 3 following procedures have to be performed:

1. Blood samples should be collected for PK analysis.

4.5 Visit 4

Visit 4 (Day 22 ± 2, Week 4)

During Visit 4 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
   - PD analysis,
7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.6 Visit 5

Visit 5 (Day 43 ± 2, Week 7)

During Visit 5 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;

5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.7 Visit 6

Visit 6 (Day 64 ± 2, Week 10)

During Visit 6 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,

- Immunoglobulin titers (IgG, IgA, and IgM),
- PK analysis,
- PD analysis,
- HACA analysis

7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.8 Visit 7

Visit 7 (Day 78 ± 4, Week 12)

During Visit 7 the response of patient should be evaluated based on following procedures:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. CT scan of involved organs;
5. Tumor and disease staging assessment;
6. Efficacy assessment;
7. Blood samples should be collected for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
8. Adverse events assessment

4.9 Visit 8

Visit 8 (Day 85 ± 4, Week 13)

During Visit 8 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.10 Visit 9

Visit 9 (Day 106 ± 4, Week 16)

During Visit 9 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;

3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.11 Visit 10

Visit 10 (Day 127 ± 4, Week 19)

During Visit 10 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:

- Clinical chemistry,
- Hematology,
- Immunoglobulin titers (IgG, IgA, and IgM),
- PK analysis,

7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.12 Visit 11

Visit 11 (Day 148 ± 4, Week 22)

During Visit 11 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. Weight, high measurements and BSA (Body Surface Area) calculation;
5. 12-lead ECG should be performed before the premedication and the IMP infusion;
6. Blood samples should be collected before IMP infusion (within two hours before infusion, and before premedication is given) for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - PK analysis,
   - PD analysis,

- HACA analysis

7. Urine pregnancy test should be performed (before IMP infusion);
8. Adverse events assessment should be performed before premedication and IMP infusion;
9. Premedication (including prednisone as a component of CHOP chemotherapy) should be given 30-40 minutes before IMP infusion;
10. INVESTIGATIONAL MEDICINAL PRODUCT INFUSION;
11. Additional blood samples should be collected 30±15 minutes after completion of infusion for PK analysis;
12. Additional 12-lead ECG should be performed within 60 minutes after IMP infusion completion;
13. Additional adverse events assessment should be performed within 60 minutes after IMP infusion completion;
14. Infusion of chemotherapy (cyclophosphamide, doxorubicin, vincristine) should be started at the earliest 60 minutes following completion of IMP infusion, and when other study visit procedures are finalized.

4.13 Visit 12

Visit 12 (Day 155 ± 4, Week 23)

During Visit 12 following procedures have to be performed:

1. Blood samples should be collected for PK analysis.

4.14 Visit 13

Visit 13 (Day 176 ± 4, Week 26)

During Visit 13 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. 12-lead ECG;
5. CT scan;
6. Bone marrow biopsy;
7. Tumor and disease staging assessment;
8. Efficacy assessment;
9. Adverse events assessment;
10. Blood samples should be collected for:

- Clinical chemistry,
- Hematology,
- Immunoglobulin titers (IgG, IgA, and IgM),
- HACA analysis,
- PK analysis,
- PD analysis,
- β2 microglobulin,
- Anti-tetanus antibody,

11. Urine samples should be collected for urinalysis;

4.15 Visit 14

Visit 14 (Day 316 ± 7, Week 46)

During Visit 14 following procedures have to be performed:

1. Concomitant medication review;
2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. 12-lead ECG;
5. Adverse events assessment;
6. Blood samples should be collected for:
   - Clinical chemistry,
   - Hematology,
   - Immunoglobulin titers (IgG, IgA, and IgM),
   - HACA analysis,
   - PK analysis,
   - PD analysis,
7. Urine samples should be collected for urinalysis;

4.16 Early Termination Visit

Early Termination assessment should be performed for any patient terminating early from the study within 2 weeks of discontinuation.

During Early Termination Visit following procedures have to be performed:

1. Concomitant medication review;

2. Physical examination;
3. Vital signs measurements: blood pressure, heart rate, temperature and respiratory rate;
4. 12-lead ECG;
5. Bone marrow biopsy (if not done within last 28 days);
6. CT scan (if not done within last 28 days);
7. Tumor and disease staging assessment;
8. Efficacy assessment;
9. Adverse events assessment;
10. Blood samples should be collected for:
    - Clinical chemistry,
    - Hematology,
    - Immunoglobulin titers (IgG, IgA, and IgM),
    - HACA analysis,
    - PK analysis,
    - PD analysis,
    - β2 microglobulin,
    - Anti-tetanus antibody,
11. Urine samples should be collected for urinalysis;
12. Tumor biopsy is recommended if early termination is caused by progression disease – for the purpose of assess CD20 expression level and to identify any histological transformation.

4.17 Unscheduled Visit and Telephone Contacts

Routinely one unscheduled visit can be performed between each two treatment cycles. In reasonable cases when patient requires intensive care and monitoring of blood parameters additional visits can be scheduled.

The date, reason and procedures performed during the unscheduled visit should be recorded in e-CRF and source documentation.

Any investigator's telephone contacts with patients should be also recorded in source documentation if during telephone contact investigator receives important information including but not limited to: patient health condition, adverse events occurrence, patient withdrawal.

5 ADVERSE EVENTS

5.1 Definitions

Described definitions are consistent with European Medicines Agency Guideline on Good Pharmacovigilance Practices.

Adverse Event (AE); synonym: Adverse Experience

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction; synonyms: Adverse Drug Reaction (ADR), Suspected Adverse (drug) Reaction, Adverse Effect, Undesirable Effect

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

Serious Adverse Reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Unexpected Adverse Reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics. This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product.

5.2 Adverse Events Reporting

Investigators are obliged to register in e-CRF all adverse events (AEs) occurring in patients from the moment of signing Informed Consent Form (ICF) by the first patient up to and including 30 days after last study assessment. Investigators are responsible for seriousness assessment of adverse events according to EMA Guideline on Good Pharmacovigilance Practices definitions described in the Study Protocol.

Investigator should report all SAEs (Serious Adverse Events) to Mabion Pharmacovigilance Department with use of the special Serious Adverse Event/Pregnancy Report Form preferably via e-mail (or fax if sending via email is not possible) within 24 hours after Investigator becomes aware of the SAE. All safety information, reports, additional correspondence between Investigators, CRO and Mabion shall be in English.

The Serious Adverse Event/Pregnancy Report Form should be filled according to the best Investigator's knowledge at the time of report. All of the additional documents, e.g. laboratory data, that are related to SAE, shall be send to Mabion Pharmacovigilance Department in a blinded form (i.e. patient's name shall be replaced with patient's number).

If a patient becomes pregnant during the clinical trial, the treatment must be permanently discontinued and the Investigator must report that fact to Mabion Pharmacovigilance Department with use of the SAE/Pregnancy Report Form within 24 hours after Investigator becomes aware of the fact. The pregnancy must be followed-up, until the outcome is known.

Investigator is responsible for following-up each SAE, until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

The Investigator is responsible for notifying relevant ethic committees as required locally.

Mabion Pharmacovigilance Department is responsible for data collection, quality control of SAE/Pregnancy Reports, communication with sites involved in the study, coordination of the safety reporting process, the medical review of all SAEs, generation of queries, the causality and expectedness assessment of SAEs.

Investigators are obliged to store all hardcopies of SAE/Pregnancy Reports as well as all related documentation in the study files during the clinical trial. At the end of the study documents will be send to Mabion for archiving.

SAE Reporting Contact:

pharmacovigilance@mabion.eu

(+48) 0 530 803 170

5.3 Unblinding in the Study

Unblinding is the process by which the allocation code of treatment is broken. Unblinded persons become aware of the intervention dedicated for a particular patient participating in a trial. Every effort should be undertaken to ensure that no unnecessary unblinding occurs during the trial.

The Sponsor, Investigators and patients are blinded to treatment allocation until Week 26 of last patient participating in the trial, at which time the CRO, statisticians and Sponsor will be unblinded for the purposes of data analysis to determine the comparative analysis of the study data.

Each clinical site will be supplied with Investigational Medicinal Products: MabionCD20 and MabThera. Appearance of MabionCD20 and MabThera packaging materials makes them indistinguishable. Each vial and external cardboard box is labeled with an individual label containing the information about vial number. Individual vial number determines the content of the vial (MabionCD20 or MabThera).

MabionCD20 and MabThera are biosimilar medicinal products with proven high level of similarity in activity and safety. In case of any serious safety concerns the procedure of adverse symptoms treatment will be the same for patients receiving MabionCD20 as for patients receiving MabThera. There are no potential reasons for unblinding the patient treatment allocation by the Investigator at the site.

If there is a reasonable, justified necessity of unblinding the treatment allocation of particular patient at the site, Investigator should contact Mabion Pharmacovigilance Department (pharmacovigilance@mabion.eu) and send completed Unblinding Request. Mabion Pharmacovigilance Department will have the power to unblind particular patient assignment and inform Investigator which Investigational Medicinal Product has been administered to patient.

6 ETHICAL CONSIDERATION

This clinical trial was carefully designed and will be conducted according to the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP), ethical principles of the Declaration of Helsinki, relevant European Medicines Agency guidelines, regulatory requirements, an international ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials.

Study protocol design has been consulted during Scientific Advice procedures with European Medicines Agency experts. EMA/CHMP scientific recommendations and advices were implemented to the study protocol.

This study is design to comply with all provisions of the Declaration of Helsinki and its current amendments.

The trial will be conducted in compliance with the study protocol, GCP, the applicable SOPs and regulatory requirements.

Prior to activation, the clinical study must be approved by relevant Ethic Committee and Institutional Review Board.

The study protocol and any amendment that is not an administrative nature will be approved by relevant Ethic Committee and Institutional Review Board.

All blood samples collected from patients during the study can be used only for purpose of clinical trial (including validation and optimization of analitycal methods).

Patient Informed Consent

Written Informed Consent of patients is required before enrollment into the study, before any study-specific procedure. Investigators are responsible for obtaining written Informed Consent from each patient.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

The Investigator has the right to withdraw a patient for any reason if in investigator's opinion it is in the best patient's interest. Reason for withdrawal should be always documented in CRF.

7 INVESTIGATOR'S RESPONSIBILTY

Main investigator's responsibilities are following:

- To conduct the trial in according to the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP), ethical principles of the Declaration of Helsinki, relevant European Medicines Agency guidelines, regulatory requirements;
- To conduct the trial in compliance with the protocol provided by Sponsor, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies);

- To ensure the accuracy, completeness and timeliness of the data reported in the patient's eCRF;
- To report to the Sponsor immediately and document in e-CRF and source documentation any deviation from the protocol;
- To report to Mabion Pharmacovigilance Unit within 24 hours any clinical serious adverse event;
- To protect the personal data of the patients received in connection with performing the study procedures;
- To review, learn and comply with all relevant study documents, guidelines and procedures as: MabionCD20 Investigator's Brochure, Informed Consent Form and Patient Information Letter, other study specific procedures: Investigator's Study Guide, Infusion Guideline, Laboratory Manual and others.

8 DATA HANDLING AND RECORD KEEPING

Each study site will be provided with training and access to electronic case report form (eCRF). It is the Investigator's responsibility to ensure the accuracy, completeness and timeliness of the data reported in the eCRF for each patient participating in the study.

The investigator, or responsible site representative, should complete the eCRF as soon as possible after information is collected, preferably on the day of patient's visit and no longer that 5 calendar days. Any queries or missing data should be explained as soon as possible.

Source documentation should also indicate the patient's participation in the trial and should document the dates and details of study procedures and patient condition. Clinical data should be transcribed from the source documents to the eCRF by responsible site personnel.

Only investigators and authorized by investigators site personnel is allowed to enter eCRF. Investigators must sign electronically each subject's eCRF after completion of data entry, signifying that the data entered in the eCRF is complete and accurate.

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or longer if required by applicable regulatory requirement(s).

9 STUDY MONITORING

Contract Research Organization subcontracted by Sponsor will monitor the quality of the study and compliance with GCP, study protocol and study procedures based on regular monitoring visits. Monitors will visit the site before first patient is randomized and every 4-8 weeks throughout the course of the study. The investigators have to allow the monitor to verify any or all the study materials needed for source data verification. Monitoring will be done by personal visits by dedicated site monitor who will review the study documentation (e-CRF, source data, study forms and logs) and verify the storage conditions of IMPs and other products delivered by Sponsor.

The site monitor will be responsible for training of the site personnel involved in the study, constant contact with investigator via phone, fax or email when required by the investigator and assisting in conducting the clinical trial on a daily basis.

10 QUALITY CONTROL AND QUALITY ASSURANCE

All materials used in this study are subjected to quality control. Regulatory authorities, the IEC/IRB, Sponsor or Sponsor's designee may perform audit/inspection at the clinical site and may request an access to all source documents, CRFs, and other study documentation and materials. Investigator is obliged to grant the direct access to study documents and materials during the audit/inspection as well as dedicate sufficient time to participate in the audit/inspection.

The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11 LIABILITY AND INSURANCE

All patients participating in the study will be insured by the sponsor according to local regulations in each country.

12 CONFIDENTIALITY AND USE OF INFORMATION

All information obtained in the study must be treated as confidential to ensure the patient's privacy. The Investigators are responsible for ensuring the patient's anonymity. All CRFs, clinical logs and records, study reports, and communications will identify the patient by initials (if in accordance with local regulations) and/or the assigned patient number.

The investigators have to keep a separate confidential log with patient's names and addresses corresponding to each patient number. These data should be treated as strictly confidential.

All information regarding Investigational Medicinal Products, study protocol, study procedures and specific guidelines are confidential information.

13 INVESTIGATOR'S AGREEMENT

I have thoroughly read the Protocol number MabionCD20-002NHL, titled: 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. I understand the requirements and conditions of the study protocol and I agree to perform the clinical study according to the study protocol and study specific guidelines. I understand that any violation of the protocol may lead to early termination of the study at my site.

I agree to conduct the study in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements. I agree to report to Mabion Pharmacovigilance Unit within 24 hours any clinical serious adverse event.

I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator's Name	
Principal Investigator's Signature	
Date	
Name and Address of the Investigational Site	

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