Clinical trial results:
Randomized, Parallel-group, Double-blind, Comparative Bioequivalence Trial of MabionCD20 (Mabion S.A) Compared to MabThera (rituximab by Hoffman-La Roche) in Patients with Diffuse Large B-cell Lymphoma.

Summary

EudraCT number	2013-005506-56
Trial protocol	PL HR
Global end of trial date	04 January 2018

Results information

Result version number	v1 (current)
This version publication date	30 April 2022
First version publication date	30 April 2022
Summary attachment (see zip file)	MabionCD20-002NHL synopsis (MabionCD20-002NHL_CSR synopsis_28032019_final (1).pdf)

Trial information

Trial identification

Sponsor protocol code	MabionCD20-002NHL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02617485
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mabion S.A
Sponsor organisation address	Langiewicza 60, Konstantynow Lodzki, Poland, 95-050
Public contact	Clinical Trial Coordination Unit, Mabion SA, +48 422908210, b.czubek@mabion.eu
Scientific contact	Clinical Trial Coordination Unit, Mabion SA, +48 422908210, a.tuszyner@mabion.eu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective 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.

Protection of trial subjects:

Patients received premedication consisting of corticosteroid (prednisone, a component of CHOP), anti-pyretic (acetaminophen) and anti-histamine (diphenhydramine or equivalent) 30-40 minutes prior to each study drug administration in order to lower the incidence of infusion-related reactions related to the release of cytokines and/or other mediators.

This clinical trial was conducted in accordance with all local legal and regulatory requirements, as well as the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use(ICH) Independent Ethics Committee guideline E6: Good Clinical Practice (GCP).

Background therapy:

All patients concomitantly received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. CHOP was administered every three weeks (21 days) for a total of eight cycles.
CHOP was administered on the first day of each of the 8 chemotherapy cycles, in a standard body surface adjusted dosage regimen of 50 mg/m2 of doxorubicin (IV), 1.4 mg/m2 of vincristine, up to a maximal dose of 2 mg(IV), 750 mg/m2 of cyclophosphamide (IV), and 100 mg of prednisone (oral, for a period of five days).

Evidence for comparator:

MabThera is an EU-approved brand of rituximab, manufactured by Hoffman-La Roche. It is officially indicated for the treatment of DLBCL in adults.

Actual start date of recruitment	29 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Georgia: 21
Country: Number of subjects enrolled	Ukraine: 119
Worldwide total number of subjects	140
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	107
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was initiated in 7 countries (Croatia, Bosnia and Herzegovina, Georgia, Moldova, Poland, Serbia, and Ukraine), but finally only 5 countries with 21 study sites recruited patients (Bosnia and Herzegovina, Georgia, Moldova, Poland, and Ukraine).

Pre-assignment

Screening details:

Screening lasted 28 days (from Day -35 to -8 before randomization), during which the eligibility status of patients was verified.

Period 1

Period 1 title	Treatment and observation period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Blinding of study medication packages was performed at the external company, according to the GMP regulation and Sponsor’s applicable standard operating procedures (SOPs). The blinding information was kept under restricted access. Personnel responsible for re-packaging signed a confidentiality statement.

Arms

Are arms mutually exclusive?	Yes
Arm title	MabionCD20

Arm description:

Patients assigned to this arm received 375 mg/m2 of MabionCD20 intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).

Arm type	Experimental
Investigational medicinal product name	MabionCD20
Investigational medicinal product code	L01FA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

MabionCD20 is a concentrate for solution for infusion and could be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. The prepared solutions were administered in concentration of 1 to 4 mg/ml as an IV infusion through a dedicated line with use of volumetric infusion pump that enabled to control and adjust the rate of infusion.
The MabionCD20 dose was adjusted for body weight (body surface area [BSA]) and was based on the standard dose of 375 mg/m2.The maximum allowed dose in the trial was 900 mg.
The dosage was 375 mg/m2, administered on Day 1 of each chemotherapy cycle for 8 cycles after administration of premedication.Standard treatment scheme was repeated every 21 days for 8 courses (Trial Days 1, 22, 43, 64, 85, 106, 127, and 148)

Arm title	MabThera

Arm description:

Patients assigned to this arm received 375 mg/m2 of MabThera intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).

Arm type	Active comparator

Investigational medicinal product name	MabThera
Investigational medicinal product code	L01FA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

(Trial Days 1, 22, 43, 64, 85, 106, 127, and 148)
MabThera is a concentrate for solution for infusion and could be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. The prepared solutions were administered in concentration of 1 to 4 mg/ml as an IV infusion through a dedicated line with use of volumetric infusion pump that enabled to control and adjust the rate of infusion.
The MabThera dose was adjusted for body weight (body surface area [BSA]) and was based on the standard dose of 375 mg/m2.The maximum allowed dose in the trial was 900 mg.The dosage was 375 mg/m2, administered on Day 1 of each chemotherapy cycle for 8 cycles after administration of premedication.Standard treatment scheme was repeated every 21 days for 8 courses (Trial Days 1, 22, 43, 64, 85, 106, 127, and 148) .

Number of subjects in period 1	MabionCD20	MabThera
Started	100	40
Completed	85	35
Not completed	15	5
Adverse event, serious fatal	7	-
Consent withdrawn by subject	4	1
Physician decision	-	1
Adverse event, non-fatal	2	1
Lack of efficacy	1	2
Patient needed radiotherapy	1	-

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The Sponsor, Investigators and patients were blinded to treatment allocation until the last patient completed the visit at Week 26. After database lock at Week 26, the Sponsor was unblinded for the purpose of data analysis and CSR creation.

Arms

Are arms mutually exclusive?	Yes

Arm title	MabionCD20

Arm description:

Patient randomly assigned to MabionCD20 were followed up until Week 46.

Arm type	Experimental
Investigational medicinal product name	MabionCD20
Investigational medicinal product code	L01FA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

MabionCD20 is a concentrate for solution for infusion and could be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. The prepared solutions were administered in concentration of 1 to 4 mg/ml asan IV infusion through a dedicated line with use of volumetric infusion pump that enabled to control and adjust the rate of infusion.
The MabionCD20 dose was adjusted for body weight (body surface area [BSA]) and was based on the standard dose of 375 mg/m2.The maximum allowed dose in the trial was 900 mg.
The dosage was 375 mg/m2, administered on Day 1 of each chemotherapy cycle for 8 cycles after administration of premedication.Standard treatment scheme was repeated every 21 days for 8 courses (Trial Days 1, 22, 43, 64, 85, 106, 127, and 148) .

Arm title	MabThera

Arm description:

Patient randomly assigned to MabThera were followed up until Week 46.

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	L01FA01
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

MabThera is a concentrate for solution for infusion and could be administered only after dilution in pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection in water. The prepared solutions were administered in concentration of 1 to 4 mg/ml as an IV infusion through a dedicated line with use of volumetric infusion pump that enabled to control and adjust the rate of infusion.
The MabThera dose was adjusted for body weight (body surface area [BSA]) and was based on the standard dose of 375 mg/m2.The maximum allowed dose in the trial was 900 mg.
The dosage was 375 mg/m2, administered on Day 1 of each chemotherapy cycle for 8 cycles after administration of premedication.Standard treatment scheme was repeated every 21 days for 8 courses (Trial Days 1, 22, 43, 64, 85, 106, 127, and 148) .

Number of subjects in period 2	MabionCD20	MabThera
Started	85	35
Completed	70	29
Not completed	15	6
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Patient needed BM transplantation	1	-
Need for CNS prophylaxis	1	-
disease progression	2	1
Patient needed radiotherapy	9	5

Baseline characteristics

Reporting groups	
Reporting group title	MabionCD20
Reporting group description:	
Patients assigned to this arm received 375 mg/m2 of MabionCD20 intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).	
Reporting group title	MabThera
Reporting group description:	
Patients assigned to this arm received 375 mg/m2 of MabThera intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).	

Reporting group values	MabionCD20	MabThera	Total
Number of subjects	100	40	140
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	78	29	107
From 65-84 years	22	11	33
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	51.5	54.3	
standard deviation	± 16.2	± 13.5	-
Gender categorical			
Units: Subjects			
Female	54	20	74
Male	46	20	66
Body Weight			
Units: kilogram(s)			
arithmetic mean	76.2	73.6	
standard deviation	± 17.4	± 17.0	-
BSA			
Units: cubic metre			
arithmetic mean	1.9	1.8	
standard deviation	± 0.2	± 0.2	-

Subject analysis sets	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population – all patients randomized into the study and receiving at least one infusion of MabionCD20 or MabThera.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent to treat population (ITT) – a subset of safety population based on patients who had at least one complete post baseline assessment of the area under the serum concentration-time curve from time zero to final time point (AUC(0-t)), measured after the first administration (Week 1) until the second administration at Week 4(AUC(1-4)).

Subject analysis set title	PP W1-W4
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol (W1-W4) population –subset of ITT population based on patients without major protocol deviations to Week 4 (visit 4) and having a PK assessment on this visit. Completion of the study was not necessary for inclusion into this population.

Subject analysis set title	PP W13-26
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol (W13-W26) population –subset of ITT population based on patients without major protocol deviations and having a PK assessment from Week 13 to Week 26

Subject analysis set title	ITT W13-W26
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of safety population based on patients who had at least one complete post baseline assessment of the area under the serum concentration-time curve from time zero to final time point (AUC(0-t)) measured after Week 13 until Week 26.

Reporting group values	SAF	ITT	PP W1-W4
Number of subjects	140	136	129
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	107	104	99
From 65-84 years	33	32	30
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.3	52.4	52.3
standard deviation	± 15.5	± 15.5	± 15.5
Gender categorical Units: Subjects			
Female	74	71	68
Male	66	65	61
Body Weight Units: kilogram(s)			
arithmetic mean	75.5	75.8	76.1
standard deviation	± 17.2	± 17.3	± 17.6

BSA			
Units: cubic metre			
arithmetic mean	1.8	1.9	1.9
standard deviation	± 0.2	± 0.2	± 0.2

Reporting group values	PP W13-26	ITT W13-W26	
Number of subjects	103	125	
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	83		
From 65-84 years	20		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	51.5		
standard deviation	± 14.3	±	
Gender categorical			
Units: Subjects			
Female	54		
Male	49		
Body Weight			
Units: kilogram(s)			
arithmetic mean	76.1		
standard deviation	± 17.6	±	
BSA			
Units: cubic metre			
arithmetic mean	1.9		
standard deviation	± 0.2	±	

End points

End points reporting groups

Reporting group title	MabionCD20
Reporting group description:	
Patients assigned to this arm received 375 mg/m2 of MabionCD20 intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).	
Reporting group title	MabThera
Reporting group description:	
Patients assigned to this arm received 375 mg/m2 of MabThera intravenously every 3 weeks for 8 cycles on Days 1, 22 (Week 4), 43 (Week 7), 64 (Week 10), 85 (Week 13), 106 (Week 16), 127 (Week 19), and 148 (Week 22).	
Reporting group title	MabionCD20
Reporting group description:	
Patient randomly assigned to MabionCD20 were followed up until Week 46.	
Reporting group title	MabThera
Reporting group description:	
Patient randomly assigned to MabThera were followed up until Week 46.	
Subject analysis set title	SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population – all patients randomized into the study and receiving at least one infusion of MabionCD20 or MabThera.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent to treat population (ITT) – a subset of safety population based on patients who had at least one complete post baseline assessment of the area under the serum concentration-time curve from time zero to final time point (AUC(0-t)), measured after the first administration (Week 1) until the second administration at Week 4(AUC(1-4)).	
Subject analysis set title	PP W1-W4
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol (W1-W4) population –subset of ITT population based on patients without major protocol deviations to Week 4 (visit 4) and having a PK assessment on this visit. Completion of the study was not necessary for inclusion into this population.	
Subject analysis set title	PP W13-26
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol (W13-W26) population –subset of ITT population based on patients without major protocol deviations and having a PK assessment from Week 13 to Week 26	
Subject analysis set title	ITT W13-W26
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
A subset of safety population based on patients who had at least one complete post baseline assessment of the area under the serum concentration-time curve from time zero to final time point (AUC(0-t)) measured after Week 13 until Week 26.	

Primary: Area under the serum concentration-time curve from time zero to final time point measured after the first administration (Week 1) until Week 4 (AUC(W1-W4))

End point title	Area under the serum concentration-time curve from time zero to final time point measured after the first administration (Week 1) until Week 4 (AUC(W1-W4))

End point description:

Area under the serum concentration-time curve from time zero to final time point measured after the first administration (Week 1) until the Week 4 (AUC(1-4)).

End point type	Primary

End point timeframe:

From Baseline to Week 4.

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	35		
Units: µg*day/ml				
arithmetic mean (standard deviation)	1559.516 (± 358.092)	1509.795 (± 382.559)		

Statistical analyses

Statistical analysis title	Estimated Geo LS Mean ratio

Statistical analysis description:

Geometric least-squares mean ratio between MabionCD20 and MabThera arm for AUC(W1-W4) parameter, estimated with the use of ANOVA model.

Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Ratio of Geo LS-means
Point estimate	1.0406
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9565
upper limit	1.1321

Notes:

[1] - Equivalence met if the 90% CI of the Geo LS Means ratio is contained with the pre-specified equivalence margin of 70% - 143%.

Primary: Area under the serum concentration-time curve from time zero to final time point measured after the first administration (Week 13) until Week 26 (AUC(W13-W26))

End point title	Area under the serum concentration-time curve from time zero to final time point measured after the first administration (Week 13) until Week 26 (AUC(W13-W26))

End point description:

Area under the serum concentration-time curve from time zero to final time point (AUC(0-t)) measured after the first administration (Week 13) until the second administration at Week 26 (AUC(13-26))

End point type	Primary

End point timeframe:

Week 13 to Week 26.

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: µg*day				
arithmetic mean (standard deviation)	16498.932 (± 3492.394)	15647.444 (± 3629.83)		

Statistical analyses

Statistical analysis title	Estimated Geo LS Mean ratio

Statistical analysis description:

Geometric least-squares mean ratio between MabionCD20 and MabThera arms for AUC(W13-W26) endpoint, estimated with the use of ANOVA model.

Comparison groups	MabThera v MabionCD20
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Ratio of Geo LS-means
Point estimate	1.0611
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9822
upper limit	1.1464

Notes:

[2] - Equivalence met if the 90% CI of the Geo LS Means ratio is contained with the pre-specified equivalence margin of 70% - 143%.

Secondary: Ctrough (before 8th infusion)

End point title	Ctrough (before 8th infusion)

End point description:

Trough serum concentration measured at the end of a dosing interval at steady state, taken directly before eighth infusion.

End point type	Secondary

End point timeframe:

Week 22

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: µg/ml				
arithmetic mean (standard deviation)	102.246 (± 43.897)	90.61 (± 41.994)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax (post 5th and 8th infusion)

End point title	Cmax (post 5th and 8th infusion)

End point description:

Maximum serum drug concentration (Cmax) at steady state after the 5th and 8th infusions.

End point type	Secondary

End point timeframe:

Week 13 (5th infusion) and Week 22 (8th infusion)

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: µg/ml				
arithmetic mean (standard deviation)				
5th infusion	273.356 (± 65.452)	266.439 (± 66.086)		
8th infusion	296.784 (± 58.295)	296.462 (± 69.641)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kel (post 5th and 8th infusion)

End point title	Kel (post 5th and 8th infusion)

End point description:

Elimination Rate Constant at steady state after the 5th and 8th infusions.

End point type	Secondary

End point timeframe:

Week 13 (5th infusion) and Week 22 (8th infusion)

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: 1/day				
arithmetic mean (standard deviation)				
5th infusion	0.05663 (± 0.01794)	0.05418 (± 0.01884)		
8th infusion	0.04335 (± 0.01528)	0.04379 (± 0.0123)		

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 (post 5th and 8th infusion)

End point title	T1/2 (post 5th and 8th infusion)

End point description:

Elimination Half-Life at steady state after the 5th and 8th infusions.

End point type	Secondary

End point timeframe:

Week 13 to Week 16 and Week 22 to Week 26

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: day				
arithmetic mean (standard deviation)				
5th infusion	14.801 (± 12.218)	15.217 (± 7.889)		
8th infusion	18.301 (± 7.92)	16.997 (± 4.515)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLss (post 5th and 8th infusion)

End point title	CLss (post 5th and 8th infusion)

End point description:

Clearance at steady state after the 5th and 8th infusion.

End point type	Secondary

End point timeframe:

Week 13 to Week 16 and Week 22 to Week 26

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	29		
Units: mL/day				
arithmetic mean (standard deviation)				
5th infusion	198.701 (± 53.427)	206.905 (± 78.213)		
8th infusion	179.168 (± 58.509)	191.272 (± 89.016)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(W1-W26) B-cell

End point title	AUC(W1-W26) B-cell

End point description:

Area under the serum concentration-time curve of CD19+ B cell counts, measured from the first administration to the final time point at Week 26 (AUC(1-26) B-cell)

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	38		
Units: cells*days/mL				
arithmetic mean (standard deviation)	3395.824 (± 22364.503)	10476.248 (± 56943.014)		

Statistical analyses

Statistical analysis title	Estimated LS Mean ratio

Statistical analysis description:

LS Mean ratio between MabionCD20 and MabThera arms for AUC(W1-W26) B cell endpoint, calculated with the use of ANOVA model.

Comparison groups	MabionCD20 v MabThera

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Ratio of LS-means
Point estimate	0.3447
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1501
upper limit	0.7914

Notes:

[3] - Equivalence met if 95% CI included in the 70%-143% margin.

Secondary: AUC(W1-W26)

End point title	AUC(W1-W26)

End point description:

Area under the serum concentration-time curve measured after the first administration (Week 1) until Week 26 (AUC(1-26))

End point type	Secondary

End point timeframe:

Week 1 until Week 26

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	28		
Units: µg*day/ml				
arithmetic mean (standard deviation)	28413.693 (± 5194.987)	26955.355 (± 5849.227)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy Assessment at Week 26

End point title	Efficacy Assessment at Week 26

End point description:

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

End point type	Secondary

End point timeframe:

Week 26

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96[4]	38[5]		
Units: percent				
number (not applicable)				
Complete	35.4	36.8		
Partial	43.8	47.4		
Stable disease	10.4	10.5		
Progressive disease	10.4	5.3		

Notes:

[4] - 4 patients had missing data.

[5] - 2 patients had missing data.

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Percentage of patients with at least one AE in a given category. Data from the entire follow-up are included (Period 1 and Period 2).

End point type	Secondary

End point timeframe:

From Baseline to Week 46.

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	40		
Units: percent				
number (not applicable)				
All AEs	71.0	67.5		
Treatment-emergent AEs (TEAEs)	71.0	65.0		
Treatment-emergent SAEs (TESAEs)	19.0	12.5		
Severe TEAEs	40.0	22.5		
Related TEAEs	53.0	42.5		
Related severe TEAEs	29.0	22.5		
Related TESAEs	13.0	5.0		
TEAEs leading to death	8.0	0.0		
Related TEAEs leading to death	2.0	0.0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunogenicity

End point title	Immunogenicity

End point description:

Percentage of patients with positive ADA or NAb results in a given category. Data pertain to the entire follow-up period (from Baseline to Week 46).

End point type	Other pre-specified

End point timeframe:

From Baseline to Week 46.

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	40		
Units: percent				
number (not applicable)				
Treatment-induced ADA	6	1		
Persistent ADA	4	1		
Transient ADA	2	0		
Treatment-boosted ADA	0	0		
NAb positive	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline to Week 46.	
Adverse event reporting additional description:	
AEs were collected at each trial visit and followed up 30 days after patients completed the trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	MabionCD20
Reporting group description:	
Patient who received MabionC20 in treatment and observation period and then were followed up up to Week 46.	
Reporting group title	MabThera
Reporting group description:	
Patient who received MabThera in treatment and observation period and then were followed up up to Week 46.	

Serious adverse events	MabionCD20	MabThera	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 100 (19.00%)	5 / 40 (12.50%)	
number of deaths (all causes)	8	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	3 / 100 (3.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Disease progression			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic necrosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	MabionCD20	MabThera	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 100 (67.00%)	28 / 40 (70.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 100 (2.00%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	1	2	
Chest pain			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	5 / 100 (5.00%)	1 / 40 (2.50%)	
occurrences (all)	8	1	
Hyperthermia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	5 / 100 (5.00%)	0 / 40 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	4 / 100 (4.00%)	1 / 40 (2.50%)	
occurrences (all)	6	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 100 (3.00%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	3	2	
Blood bilirubin increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Monocyte count increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Neutrophil count decreased			
subjects affected / exposed	8 / 100 (8.00%)	4 / 40 (10.00%)	
occurrences (all)	54	16	
Platelet count decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	6	
Transaminases increased			
subjects affected / exposed	3 / 100 (3.00%)	2 / 40 (5.00%)	
occurrences (all)	3	5	
White blood cell count decreased			
subjects affected / exposed	9 / 100 (9.00%)	4 / 40 (10.00%)	
occurrences (all)	57	18	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 100 (3.00%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Sinus tachycardia			

subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	1	2	
Supraventricular tachycardia			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 100 (4.00%)	0 / 40 (0.00%)	
occurrences (all)	5	0	
Neurotoxicity			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 100 (14.00%)	5 / 40 (12.50%)	
occurrences (all)	33	10	
Febrile neutropenia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Leukopenia			
subjects affected / exposed	22 / 100 (22.00%)	10 / 40 (25.00%)	
occurrences (all)	59	17	
Neutropenia			
subjects affected / exposed	29 / 100 (29.00%)	10 / 40 (25.00%)	
occurrences (all)	76	23	
Thrombocytopenia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 100 (3.00%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Gastritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pancreatitis chronic			

subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	3 / 100 (3.00%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Vomiting			
subjects affected / exposed	2 / 100 (2.00%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	15 / 100 (15.00%)	5 / 40 (12.50%)	
occurrences (all)	15	5	
Dermal cyst			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	

Gingivitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	5 / 100 (5.00%)	0 / 40 (0.00%)	
occurrences (all)	5	0	
Respiratory tract infection			
subjects affected / exposed	7 / 100 (7.00%)	1 / 40 (2.50%)	
occurrences (all)	8	1	
Respiratory tract infection viral			
subjects affected / exposed	1 / 100 (1.00%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	2 / 100 (2.00%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 100 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2014	The conduct of the study was changed to reflect the following major changes: - An update of the paragraph with Secondary Study Endpoints by removal of section about Complete Response unconfirmed because this did not represent separate secondary study endpoint. - An update of the Dose Modifications of Concomitant Medication section to clarify the Study Procedures related to consideration of necessity of G-CSF support after chemotherapy administration and reduction of chemotherapy dose depending on the patient's condition. - A change of Inclusion Criterion 8 to indicate that the patients with prior immunotherapy for DLBCL (>1,5 years prior to screening) can be included into the study. - An update of Inclusion Criterion 13 for safety reasons:the parameters of adequate haematological function were changed. - An update of Inclusion Criterion 18 for safety reasons the need of both serum and urine pregnancy tests was added. An update of Exclusion Criteria 3, 8 and 14 to clarify the conditions of exclusion to provide treatment options to more patients. - The addition of new Exclusion Criterion 24 for safety reasons: excluding patients with hypersensitivity to the active substance or to any other excipients of the medicine. - An update of the criteria of withdrawal a patient from the study for safety reasons: adding that the patient can be removed from the study by the Investigator when he/she enters into another clinical study with the treatment that in the Investigator's opinion excludes patient's participation. - A clarification of study procedures for to safety reasons: Related to Efficacy Assessment and adding new Laboratory Safety Tests due to safety reasons. - An update of the screening, visit 7, visit 13 and Early Terminated Visit procedures to simplify and accelerate the procedures of tumour assessment
11 August 2015	The conduct of the study was changed to reflect the following major changes: - A clarification of Inclusion Criterion 3 for safety reasons and to make the protocol consistent by removal the time of biopsy performance. - An update of the content of the box in Pharmaceutical Form and Packaging and Labelling sections from two 10 ml vials to one 10 ml vial. - An update of the section Storage and Stability to clarify the shelf life of MabionCD20. - The addition of a new additional blood samples collection to Screening Visit procedures for purpose of validation and optimization of analytical methods. - Clarifying the purpose of blood samples collection in Ethical Consideration section.
21 September 2016	The conduct of the study was changed to reflect the following major changes: - An update of the Inclusion Criterion 12 by extending the screening window to make the protocol consistent. - An update ofthe HACA/ADA samples schedule in accordance with EMA recommendations by adding additional blood sampling to the Visit 2, Visit 6 and Visit 11 procedures. - An update of the period when the bone marrow biopsy can be performed before the Screening visit. The period was changed to 60 days and could be extended to 90 days when the re-biopsy is highly invasive,and the previous results are expected to be up to date in screening, basing on Investigator's and Medical Monitor's decision. - The change of the Screening Window from 28 to 35 days for safety reasons:to provide treatment to every patient included into the trial but did not receive the trial treatment within 28 days from Screening Visit. - The addition of the Efficacy Assessment to the Visit 1 procedures for safety reasons.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported