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

Summary

EudraCT number	2012-003194-25
Trial protocol	LT HR
Global end of trial date	26 October 2017

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022
Summary attachment (see zip file)	Study Synopsis (MabionCD20-001RA_CSR synopsis_28032019_final.pdf)

Trial information

Trial identification

Sponsor protocol code	MabionCD20-001RA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02468791
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 Contact Point, Mabion S.A., 48 422077890, b.czubek@mabion.eu
Scientific contact	Clinical Trial Contact Point, Mabion S.A., 48 422077890, 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	26 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate biosimilarity between the Test Product: MabionCD20® and the Reference Product: MabThera® (rituximab) in patients with active rheumatoid arthritis (RA), based on the percentage of patients in each treatment group achieving the primary efficacy endpoint of a 20% improvement on the American College of Rheumatology score (ACR20) at Week 24.
To demonstrate bioequivalence in pharmacokinetic (PK) characteristics between MabionCD20® and MabThera® (rituximab).

Protection of trial subjects:

To decrease the incidence and severity of infusion-related reactions, patients received standard premedication with corticosteroid, analgesic/antipyretic and antihistamine prior to each MabionCD20®or MabThera®(rituximab) infusion.
An independent data and safety monitoring board (DSMB) regularly reviewed the study status and all efficacy and safety data. There were 6 DSMB meetings during the study - at each meeting, patients' safety as well as treatment efficacy was evaluated positively. DSMB members recommended continuing the study without any changes.

Background therapy:

All patients received background treatment with methotrexate at 10-25 mg/week for at least 12 weeks, with the last 4 weeks at a stable dose. Folic acid (5 - 15 mg/week) could be used to counter any undesired effects of methotrexate.

Evidence for comparator:

An equivalence study design was used to compare the efficacy and safety of MabionCD20 with the reference drug MabThera. This comparator was used to ensure that MabionCD20 is not less or more effective than original rituximab by a certain clinically relevant margin, when administered to patients with active moderate-to-severe rheumatoid arthritis.
MabThera is an EU-authorized brand of rituximab, manufactured by Hoffman-La Roche. It is approved by the EMA for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD), including one or more tumour necrosis factor (TNF) inhibitor therapies. MabThera has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Actual start date of recruitment	14 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bosnia and Herzegovina: 80
Country: Number of subjects enrolled	Poland: 274
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Georgia: 172

Country: Number of subjects enrolled	Ukraine: 139
Country: Number of subjects enrolled	Serbia: 40
Worldwide total number of subjects	709
EEA total number of subjects	278

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)	614
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was initiated in 7 countries (Croatia, Bosnia and Herzegovina, Georgia, Lithuania, Poland, Serbia and Ukraine) and conducted at 50 study centers in 6 countries, as no patients were enrolled in Croatia. The first patient was enrolled on 14th May 2013. A total od 993 patients were screened, of which 709 were enrolled.

Pre-assignment

Screening details:

Screening lasted up to 28 days, during which the patients were checked for eligibility criteria. Potential participants were required to undergo washout for all DMARDs, except methotrexate. Patients could re-enter the study for the second time if they were screening failures.

Period 1

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

Blinding implementation details:

Blinding of study medication was performed by external company and treatment identity was concealed during the entire double-blind study period. Sponsor, Investigators and patients were blinded to treatment allocation until Week 24, when the designated Sponsor staff was unblinded for the purpose of data analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	MabionCD20

Arm description:

Patients received two intravenous infusions of MabionCD20 on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Arm type	Experimental
Investigational medicinal product name	MabionCD20
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water.Two intravenous infusions of MabioCD20 at 1000mg/infusion were administered on Day 1 and Day 15.

Arm title	MabThera

Arm description:

Patients received two intravenous infusions of MabThera on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Arm type	Active comparator

Investigational medicinal product name	MabThera
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water. Two intravenous infusion 1000 mg/ infusion was administered on Day 1 and 15

Number of subjects in period 1	MabionCD20	MabThera
Started	358	351
Completed	345	338
Not completed	13	13
Consent withdrawn by subject	4	4
Physician decision	2	-
Adverse event, non-fatal	3	7
Other reasons	3	-
Lost to follow-up	-	1
Lack of efficacy	1	1

Period 2

Period 2 title	Open-label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Patients received MabionCD20 or MabThera in an open-label manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	MabionCD20 after Mabthera

Arm description:

Patients who in double-blind period were treated with MabThera could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at Week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Arm type	Experimental

Investigational medicinal product name	MabionCD20
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water.Two intravenous infusions of MabioCD20 at 1000mg/infusion were administered on Day 1 and Day 15.

Arm title	MabThera after MabionCD20

Arm description:

Patients who in double-blind study period were treated with MabionCD20 could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Arm type	Experimental
Investigational medicinal product name	MabThera
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water. Two intravenous infusion 1000 mg/ infusion was administered on Day 1 and 15

Arm title	MabionCD20 after MabionCD20

Arm description:

Patients who in double-blind study period were treated with MabionCD20 could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Arm type	Experimental
Investigational medicinal product name	MabionCD20
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water.Two intravenous infusions of MabioCD20 at 1000mg/infusion were administered on Day 1 and Day 15.

Arm title	MabThera after MabThera

Arm description:

Patients who in double-blind period were treated with MabThera could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or

MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Arm type	Active comparator
Investigational medicinal product name	MabThera
Investigational medicinal product code	ATC: L01XC02
Other name	Rituximab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The infusion solution was prepared by aseptically adding the necessary amount of concentrate into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection in water. Two intravenous infusion 1000 mg/ infusion was administered on Day 1 and 15

Arm title	MabionCD20 not re-treated

Arm description:

Patients who in double-blind study period were treated with MabionCD20 but did not receive re-treatment after Week 24.

Active substance: Rituximab

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	MabThera not re-treated

Arm description:

Patients who in double-blind study period were treated with MabThera but did not receive re-treatment after Week 24.

Active substance: Rituximab

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	MabionCD20 after Mabthera	MabThera after MabionCD20	MabionCD20 after MabionCD20
Started	92	116	87
Completed	90	116	84
Not completed	2	0	3
Consent withdrawn by subject	1	-	2
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Other reasons	-	-	-
Lost to follow-up	1	-	1

Number of subjects in period 2	MabThera after MabThera	MabionCD20 not re-treated	MabThera not re-treated
Started	113	142	133

Completed	109	125	114
Not completed	4	17	19
Consent withdrawn by subject	2	13	14
Physician decision	-	2	1
Adverse event, non-fatal	1	-	2
Other reasons	1	1	2
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	MabionCD20

Reporting group description:

Patients received two intravenous infusions of MabionCD20 on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Reporting group title	MabThera

Reporting group description:

Patients received two intravenous infusions of MabThera on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Reporting group values	MabionCD20	MabThera	Total
Number of subjects	358	351	709
Age categorical Units: Subjects			
Adults (18-64 years)	313	301	614
From 65-84 years	45	50	95
Age continuous Units: years			
median	54.0	54.0	
standard deviation	± 11.41	± 12.00	-
Gender categorical Units: Subjects			
Female	296	294	590
Male	62	57	119
Weight Units: kilogram(s)			
median	72.65	71.00	
standard deviation	± 14.57	± 14.87	-
Body surface area (BSA) Units: cubic metre			
median	1.8	1.78	
standard deviation	± 0.17	± 0.17	-

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

In the SAF population, patients were analyzed according to the treatment they actually received. Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

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

Subject analysis set description:

In the ITT set patients were analyzed according to the treatment group that they were randomized to.

Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

In analyses based on the per-protocl set, patients are analyzed according to the treatment that they actually received. Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

Reporting group values	SAF	ITT	PP
Number of subjects	628	629	590
Age categorical Units: Subjects			
Adults (18-64 years)	548	549	519
From 65-84 years	80	80	71
Age continuous Units: years			
median	54	54	54
standard deviation	± 11.78	± 11.77	± 11.72
Gender categorical Units: Subjects			
Female	522	522	491
Male	106	107	99
Weight Units: kilogram(s)			
median	71.8	71.8	72
standard deviation	± 15	± 15	± 15.1
Body surface area (BSA) Units: cubic metre			
median	1.79	1.79	1.79
standard deviation	± 0.17	± 0.17	± 0.17

End points

End points reporting groups

Reporting group title	MabionCD20

Reporting group description:

Patients received two intravenous infusions of MabionCD20 on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Reporting group title	MabThera

Reporting group description:

Patients received two intravenous infusions of MabThera on Day 1 and Day 15, at a dose of 1000 mg (standard regimen in rheumatoid arthritis).

Active substance: Rituximab

Reporting group title	MabionCD20 after Mabthera

Reporting group description:

Patients who in double-blind period were treated with MabThera could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at Week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Reporting group title	MabThera after MabionCD20

Reporting group description:

Patients who in double-blind study period were treated with MabionCD20 could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Reporting group title	MabionCD20 after MabionCD20

Reporting group description:

Patients who in double-blind study period were treated with MabionCD20 could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Reporting group title	MabThera after MabThera

Reporting group description:

Patients who in double-blind period were treated with MabThera could be treated again (re-treatment) when they had a clinical response followed by a clinical relapse and if assessments at week 24 indicated that the patient may benefit from re-treatment. An additional course of therapy with MabionCD20 or MabThera was then provided under open-label conditions as two infusions of 1000 mg each, separated by 2 weeks.

Active substance: Rituximab

Reporting group title	MabionCD20 not re-treated

Reporting group description:

Patients who in double-blind study period were treated with MabionCD20 but did not receive re-treatment after Week 24.

Active substance: Rituximab

Reporting group title	MabThera not re-treated

Reporting group description:

Patients who in double-blind study period were treated with MabThera but did not receive re-treatment after Week 24.

Active substance: Rituximab

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

In the SAF population, patients were analyzed according to the treatment they actually received. Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

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

Subject analysis set description:

In the ITT set patients were analyzed according to the treatment group that they were randomized to. Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

In analyses based on the per-protocl set, patients are analyzed according to the treatment that they actually received. Note: 80 patients randomized in Bosnia were excluded from the primary analysis due to concerns over GCP incompliance.

Primary: Percentage of patients in each treatment group achieving the primary efficacy endpoint of a ≥20% improvement on the American College of Rheumatology score (ACR20) at Week 24.

End point title	Percentage of patients in each treatment group achieving the primary efficacy endpoint of a ≥20% improvement on the American College of Rheumatology score (ACR20) at Week 24.

End point description:

Efficacy assessments of disease activity in RA were based on clinically validated response criteria of the American College of Rheumatology (ACR).
A patient achieved ACR20 criteria if the following criteria were satisfied:
• percent improvement from baseline was ≥ 20% in tender joint count;
• percent improvement from baseline was ≥ 20%in swollen joint count;
• percent improvement from baseline was ≥ 20% in 3 of the 5 remaining ACR core population measures including:
- patient’s assessment of pain,
- patient’s global assessment of disease activity,
- physician’s global assessment of disease activity,
- patient’s assessment of physical functions HAQ-DI,
- laboratory evaluation of acute phase reactant (erythrocyte sedimentation rate, ESR) .

End point type	Primary

End point timeframe:

Week 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)	79.2	84.9		

Statistical analyses

Statistical analysis title	Difference MabionCD20-MabThera

Statistical analysis description:

The two-sided 95% confidence interval (CI) for the between-group difference was calculated and checked for containment within the pre-specified equivalence interval of -13% to 13% (boundaries included).

Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Mean difference (final values)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	12

Notes:

[1] - The difference in percentages between the two treatment groups was computed and the exact 95% confidence limits. The hypothesis:
H_0: C-T>M or C-T<-M vs H_1: -M<=C-T<=M with C and T denoting the proportions of patients who achieve ACR20 at week 24 and were randomized to MabThera (C) or MabionCD20 (T) treatment, respectively, and equivalence margin M=13%.

Secondary: Percentage of patients achieving ACR20, ACR50 and ACR70 at Week 48

End point title	Percentage of patients achieving ACR20, ACR50 and ACR70 at Week 48

End point description:

Evaluation of long-term efficacy of the test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 48

End point values	MabionCD20 after Mabthera	MabThera after MabionCD20	MabionCD20 after MabionCD20	MabThera after MabThera
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	116	79	113
Units: Percentage				
number (not applicable)				
ACR20	93.8	94.0	86.1	87.6

ACR50	77.8	77.6	74.7	69.0
ACR70	51.9	52.6	45.6	42.5

End point values	MabionCD20 not re-treated	MabThera not re-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	104		
Units: Percentage				
number (not applicable)				
ACR20	73.5	66.3		
ACR50	44.9	33.7		
ACR70	19.4	14.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with good or moderate response on EULAR scale at Week 48

End point title	Percentage of patients with good or moderate response on EULAR scale at Week 48

End point description:

Evaluation of biosimiliarity between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 48

End point values	MabionCD20 after Mabthera	MabThera after MabionCD20	MabionCD20 after MabionCD20	MabThera after MabThera
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	116	75	109
Units: Percentage				
number (not applicable)				
Good	64.6	63.8	49.3	49.5
Moderate	35.4	32.8	50.7	47.7

End point values	MabionCD20 not re-treated	MabThera not re-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	89		
Units: Percentage				

number (not applicable)				
Good	22.7	15.7		
Moderate	58.8	65.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving ACR20 at weeks: 4, 8, 12, 16, 20

End point title	Percentage of patients achieving ACR20 at weeks: 4, 8, 12, 16, 20

End point description:

Comparison of efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16 and 20

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)				
Week 4	52.0	48.6		
Week 8	73.8	75.0		
Week 12	85.2	84.9		
Week 16	90.6	89.0		
Week 20	86.9	88.0		

Statistical analyses

Statistical analysis title	Difference MabionCD20-MabThera at Week 4
Comparison groups	MabThera v MabionCD20
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	4.8

Statistical analysis title	Difference MabionCD20-MabThera at Week 8
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	8.3

Statistical analysis title	Difference MabionCD20-MabThera at Week 12
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	5.6

Statistical analysis title	Difference MabionCD20-MabThera at Week 16
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	3.4

Statistical analysis title	Difference MabionCD20-MabThera at Week 20

Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6.6

Secondary: Percentage of patients achieving ACR50 at weeks: 4, 8, 12, 16, 20, 24

End point title	Percentage of patients achieving ACR50 at weeks: 4, 8, 12, 16, 20, 24

End point description:

Comparison of efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20 and 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)				
Week 4	13.4	9.7		
Week 8	29.9	25.7		
Week 12	46.6	47.6		
Week 16	64.8	65.1		
Week 20	66.8	67.8		
Week 24	46.0	48.6		

Statistical analyses

Statistical analysis title	Difference MabionCD20-MabThera at Week 4
Comparison groups	MabionCD20 v MabThera

Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	1.5

Statistical analysis title	Difference MabionCD20-MabThera at Week 8
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	3.2

Statistical analysis title	Difference MabionCD20-MabThera at Week 12
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	9.1

Statistical analysis title	Difference MabionCD20-MabThera at Week 16
Comparison groups	MabionCD20 v MabThera

Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	8.1

Statistical analysis title	Difference MabionCD20-MabThera at Week 20
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	8.6

Statistical analysis title	Difference MabionCD20-MabThera at Week 24
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	10.7

Secondary: Percentage of patients achieving ACR70 at Week 4, 8, 12, 16, 20, 24

End point title	Percentage of patients achieving ACR70 at Week 4, 8, 12, 16, 20, 24

End point description:

Comparison of efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:
Week 4, 8, 12, 16, 20 and 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)				
Week 4	3.4	3.8		
Week 8	8.4	8.2		
Week 12	19.5	18.2		
Week 16	32.6	33.6		
Week 20	29.2	32.5		
Week 24	11.1	12.3		

Statistical analyses

Statistical analysis title	Difference MabionCD20-MabThera at Week 4
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	3.7

Statistical analysis title	Difference MabionCD20-MabThera at Week 8
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	4.5

Statistical analysis title	Difference MabionCD20-MabThera at Week 12
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	5.1

Statistical analysis title	Difference MabionCD20-MabThera at Week 16
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	8.6

Statistical analysis title	Difference MabionCD20-MabThera at Week 20
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	10.9

Statistical analysis title	Difference MabionCD20-MabThera at Week 24

Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	6.6

Secondary: Percentage of patients with good response on European League Against Rheumatism (EULAR) scale at Week 4, 8, 12, 16, 20, 24

End point title	Percentage of patients with good response on European League Against Rheumatism (EULAR) scale at Week 4, 8, 12, 16, 20, 24

End point description:

Comparison of efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20 and 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)				
Week 4	3.4	3.4		
Week 8	10.7	7.9		
Week 12	22.1	18.2		
Week 16	51.0	47.6		
Week 20	45.3	48.6		
Week 24	6.7	6.5		

Statistical analyses

Statistical analysis title	Difference MabionCD20-MabThera at Week 4
Comparison groups	MabionCD20 v MabThera

Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	3.3

Statistical analysis title	Difference MabionCD20-MabThera at Week 8
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	1.9

Statistical analysis title	Difference MabionCD20-MabThera at Week 12
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	2.7

Statistical analysis title	Difference MabionCD20-MabThera at Week 16
Comparison groups	MabionCD20 v MabThera

Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	4.7

Statistical analysis title	Difference MabionCD20-MabThera at Week 20
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	11.4

Statistical analysis title	Difference MabionCD20-MabThera at Week 24
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4

Secondary: Percentage of patients with moderate response on the European League Against Rheumatism (EULAR) scale at Week 4, 8, 12, 16, 20, 24

End point title	Percentage of patients with moderate response on the European League Against Rheumatism (EULAR) scale at Week 4, 8, 12, 16, 20, 24

End point description:

Comparison of efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20 and 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: Percentage				
number (not applicable)				
Week 4	53.7	57.2		
Week 8	74.8	75.0		
Week 12	69.5	73.5		
Week 16	43.6	46.6		
Week 20	49.7	46.6		
Week 24	82.9	86.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach the minimum level of circulating CD19+ B-cells at Week 24 (Tmin B-cell) and duration of B cell depletion (T B-cell)

End point title	Time to reach the minimum level of circulating CD19+ B-cells at Week 24 (Tmin B-cell) and duration of B cell depletion (T B-cell)

End point description:

Comparison of pharmacodynamic properties of the test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Week 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	59		
Units: days				
geometric mean (full range (min-max))				
TminB-cell	12.513 (0.92 to 167.72)	9.423 (0.93 to 171.63)		
T B-cell	165.136 (125.09 to 170.99)	163.909 (124.45 to 172.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the circulating CD19+ B-cell level (AUC0-t B-cell)

End point title	Area under the circulating CD19+ B-cell level (AUC0-t B-cell)

End point description:

Comparison of pharmacodynamic properties between the test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

baseline to week 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	59		
Units: calls*days/mL				
least squares mean (full range (min-max))	192.4 (2.08 to 3490.34)	243.81 (29.68 to 3247.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Disease Activity Score (DAS28-ESR) at Week 48

End point title	Mean change from baseline in Disease Activity Score (DAS28-ESR) at Week 48

End point description:

Comparison of long-term efficacy between test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

From Baseline to Week 48

End point values	MabionCD20 after Mabthera	MabThera after MabionCD20	MabionCD20 after MabionCD20	MabThera after MabThera
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	116	75	109
Units: score on a scale				
least squares mean (full range (min-max))	-3.4 (-5.6 to -1.4)	-3.5 (-6 to -0.1)	-3.4 (-5.8 to -1.3)	-3.5 (-6.1 to -1)

End point values	MabionCD20 not re-treated	MabThera not re-treated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	89		
Units: score on a scale				
least squares mean (full range (min-max))	-2.4 (-6.5 to 0.6)	-2.3 (-6.6 to 0.4)		

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 the given category.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 48	

End point values	MabionCD20	MabThera	MabionCD20 after Mabthera	MabThera after MabionCD20
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	319[2]	309[3]	81	116[4]
Units: percent				
number (not applicable)				
All AEs	43.9	43.0	21.00	32.5
Treatment-emergent adverse events (TEAEs)	42.6	42.1	21.00	32.5
Severe TEAEs	1.3	1.9	2.5	0.9
Related TEAEs	28.2	28.5	12.3	22.2
Related severe TEAEs	0.6	1.3	2.5	0.0
Serious AEs (SAEs)	2.2	1.9	2.5	0.0
Treatment-emergent SAEs (TESAEs)	2.2	1.9	2.5	0.0
Related TESAEs	0.3	0.6	1.2	0.0

Notes:

[2] - 359 patients included in SAF population (classified according to the actually received treatment)

[3] - 349 patients included in SAF population (classified according to the actually received treatment)

[4] - 117 patients included in SAF population (classified according to the actually received treatment)

End point values	MabionCD20 after MabionCD20	MabThera after MabThera	MabionCD20 not re-treated	MabThera not re-treated
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	112	110	105[5]
Units: percent				
number (not applicable)				
All AEs	24.1	38.4	11.8	9.5
Treatment-emergent adverse events (TEAEs)	24.1	38.4	11.8	9.5
Severe TEAEs	1.3	0.9	0.0	0.0
Related TEAEs	16.5	25.9	2.7	2.9
Related severe TEAEs	1.3	0.0	0.0	0.0
Serious AEs (SAEs)	1.3	0.0	0.9	0.0
Treatment-emergent SAEs (TESAEs)	1.3	0.0	0.9	0.0
Related TESAEs	1.3	0.0	0.0	0.0

Notes:

[5] - 134 patients included in SAF population (classified according to the actually received treatment)

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity

End point title	Immunogenicity

End point description:

Anti-drug antibodies (ADAs) and neutralizing antibodies (nAbs) in serum samples were analyzed with the use of validated assays.
*Values for arms: MabionCD20 after Mabthera, MabThera after MabionCD20; MabionCD20 after MabionCD20;Mabthera after Mabthera were specifed for whole study period.

End point type	Secondary

End point timeframe:

Immunogenicity endpoints were analyzed from Day 1 to Week 48.

End point values	MabionCD20	MabThera	MabionCD20 after Mabthera	MabThera after MabionCD20
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316[6]	306[7]	81	115
Units: percent				
number (not applicable)				
Treatment-induced ADA	14.2	13.4	16.0	24.0
Treatment-boosted ADA	0.9	1	2.5	2.0
ADA positive response	15.2	14.4	18.5	26.00
Persistently positive ADA	12.7	12.7	9.9	5.2
Transiently positive ADA	1.6	0.7	6.2	15.7

Notes:

[6] - 355 patients included in the ADA evaluable set.

[7] - 346 patients included in the ADA evaluable set.

End point values	MabionCD20 after MabionCD20	MabThera after MabThera	MabionCD20 not re-treated	MabThera not re-treated
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	112	110	105[8]
Units: percent				
number (not applicable)				
Treatment-induced ADA	12.7	19.6	21.8	23.8
Treatment-boosted ADA	1.3	0.9	0.0	0.0
ADA positive response	13.9	20.5	21.8	23.8
Persistently positive ADA	6.3	8.9	15.5	21.9
Transiently positive ADA	6.3	10.7	6.4	1.9

Notes:

[8] - 134 patients included in the ADA evaluable set.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Disease Activity Score (DAS28-ESR) at weeks: 4, 8, 12, 16, 20, 24

End point title	Mean change from baseline in Disease Activity Score (DAS28-ESR) at weeks: 4, 8, 12, 16, 20, 24

End point description:

Mean change from baseline in Disease Activity Score (DAS28-ESR) from Baseline to weeks: 4, 8, 12, 16, 20 and 24.

End point type	Secondary

End point timeframe:

Week 4, 8, 12, 16, 20 and 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	292		
Units: score on the scale				
least squares mean (full range (min-max))				
Week 4	-1.49 (-5.6 to 0.3)	-1.47 (-5 to 1)		
Week 8	-2.15 (-6.4 to 0.3)	-2.08 (-5.3 to 0.6)		
Week 12	-2.69 (-6.9 to 0.00)	-2.64 (-6.6 to 0.2)		
Week 16	-3.23 (-7.3 to 0.8)	-3.14 (-6.2 to -0.2)		
Week 20	-3.13 (-7.2 to 0.5)	-3.14 (-6.3 to 0.4)		
Week 24	-2.47 (-7 to 0.4)	-2.52 (-6.9 to 0.6)		

Statistical analyses

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W4
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.125
upper limit	0.15

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W8
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.078
upper limit	0.223

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W12
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.208

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W16
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.252

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W20
Comparison groups	MabThera v MabionCD20
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.171
upper limit	0.148

Statistical analysis title	Difference in LS-Mean MabionCD20-MabThera at W24
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.184
upper limit	0.077

Secondary: Minimum level (Cmin B-cell) of circulating CD19+ B-cells

End point title	Minimum level (Cmin B-cell) of circulating CD19+ B-cells

End point description:

Comparison of pharmacodynamic properties of the test product (MabionCD20, rituximab) and reference product (MabThera, rituximab) in patients with active rheumatoid arthritis.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	59		
Units: cells/millilitre				
least squares mean (standard error)	-0.247 (± 0.109)	-1.087 (± 0.089)		

Statistical analyses

Statistical analysis title	LS-mean ratio
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	ratio of LS-means
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.37
upper limit	3.91

Secondary: Area under the plasma concentration-time curve from the first administration to final time point at Week 24 (AUC0-t)

End point title	Area under the plasma concentration-time curve from the first administration to final time point at Week 24 (AUC0-t)

End point description:

Demonstration of pharmacokinetic (PK) equivalence between MabionCD20 and MabThera based on the primary PK parameters.

End point type	Secondary

End point timeframe:

Day 1 to Week 24

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	58		
Units: (µg*h)/mL				
least squares mean (full range (min-max))	211893.08 (101574.95 to 395666.17)	207906.22 (95735.34 to 390675.61)		

Statistical analyses

Statistical analysis title	Ratio of LS-mean
Statistical analysis description:	
PK equivalence demonstrated if the 90% confidence interval of LS-means ratio is contained within the pre-specified 80%-125% equivalence margin.	
Comparison groups	MabionCD20 v MabThera
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	ratio of LS-means
Point estimate	1.0192
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9347
upper limit	1.1113

Secondary: Maximum measured plasma concentration after the second infusion of the treatment course (Cmax second) at week 24.

End point title	Maximum measured plasma concentration after the second infusion of the treatment course (Cmax second) at week 24.
End point description:	
Demonstration of pharmacokinetic (PK) equivalence between MabionCD20 and MabThera based on the primary PK endpoints.	
End point type	Secondary
End point timeframe:	
Day 1 to Week 24	

End point values	MabionCD20	MabThera		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	58		
Units: µg/mL				
least squares mean (full range (min-max))	414.44 (236.31 to 677.67)	417.76 (281.91 to 588.03)		

Statistical analyses

Statistical analysis title	Ratio LS-mean
Statistical analysis description:	
PK equivalence demonstrated if the 90% confidence interval of LS means ratio is contained within the pre-specified equivalence margin of 80%-125%.	
Comparison groups	MabThera v MabionCD20
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	ratio of LS-means
Point estimate	0.992
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9349
upper limit	1.0527

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization until the end of follow-up (up to 48 weeks after randomization)

Adverse event reporting additional description:

All adverse events spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures were recorded on the appropriate page of the eCRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	MabionCD20 (double-blind period)

Reporting group description:

Patients in MabionCD20 group received two 1000 mg intravenous infusions of MabionCD20 on Day 1 and Day 15.

Active substance: Rituximab

Reporting group title	MabThera (double-blind period)

Reporting group description:

Patients in MabThera group received two 1000 mg intravenous infusions of MabThera on Day 1 and Day 15.

Active substance: Rituximab

Reporting group title	MabionCD20 after MabThera (open-label period)

Reporting group description:

Patients in this group received MabThera in the double-blind period and MabionCD20 in the open-label.

Active substance: Rituximab

Reporting group title	MabThera after MabionCD20 (open-label period)

Reporting group description:

Patients in this group received MabionCD20 in the double-blind period and MabThera in the open-label.

Active substance: Rituximab

Reporting group title	MabionCD20 after MabionCD20 (open-label period)

Reporting group description:

Patients in this group received MabionCD20 in both double-blind and open-label periods.

Active substance: Rituximab

Reporting group title	MabThera after MabThera (open-label period)

Reporting group description:

Patients in this group received MabThera in both double-blind and open-label periods.

Active substance: Rituximab

Reporting group title	MabionCD20 not re-treated (open-label period)

Reporting group description:

Patients in this group received MabionCD20 in the double-blind period and no treatment in the open-label.

Reporting group title	MabThera not re-treated (open-label period)

Reporting group description:

Patients who in double-blind study period were treated with MabThera but didn't have sufficient clinical response and didn't receive second course of treatment.Active substance: Rituximab

Serious adverse events	MabionCD20 (double-blind period)	MabThera (double-blind period)	MabionCD20 after MabThera (open-label period)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 319 (2.19%)	6 / 309 (1.94%)	2 / 81 (2.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Cerebral ischaemia			

subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			
subjects affected / exposed	0 / 319 (0.00%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Aneamia			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 319 (0.00%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			

subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 319 (0.00%)	0 / 309 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 319 (0.00%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 319 (0.00%)	0 / 309 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MabThera after MabionCD20 (open-label period)	MabionCD20 after MabionCD20 (open-label period)	MabThera after MabThera (open-label period)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	0 / 112 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Neutrophil count decreased			

subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			

subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Aneamia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	MabionCD20 not re-treated (open-label period)	MabThera not re-treated (open-label period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee operation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aneamia			

subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	MabionCD20 (double-blind period)	MabThera (double-blind period)	MabionCD20 after MabThera (open-label period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 319 (18.50%)	54 / 309 (17.48%)	11 / 81 (13.58%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 319 (2.19%)	2 / 309 (0.65%)	1 / 81 (1.23%)
occurrences (all)	8	2	1
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	15 / 319 (4.70%)	11 / 309 (3.56%)	1 / 81 (1.23%)
occurrences (all)	15	12	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 319 (0.31%)	1 / 309 (0.32%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 319 (0.31%)	5 / 309 (1.62%)	1 / 81 (1.23%)
occurrences (all)	1	6	1
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	7 / 319 (2.19%)	4 / 309 (1.29%)	0 / 81 (0.00%)
occurrences (all)	8	7	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 319 (0.31%)	0 / 309 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 319 (0.00%) 0	0 / 309 (0.00%) 0	1 / 81 (1.23%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 319 (1.25%) 4	9 / 309 (2.91%) 9	3 / 81 (3.70%) 6
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	7 / 319 (2.19%) 7	7 / 309 (2.27%) 7	2 / 81 (2.47%) 2
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	4 / 319 (1.25%) 4	2 / 309 (0.65%) 3	1 / 81 (1.23%) 1
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	1 / 319 (0.31%) 2	3 / 309 (0.97%) 3	1 / 81 (1.23%) 1
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	6 / 319 (1.88%) 6	4 / 309 (1.29%) 4	0 / 81 (0.00%) 0
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	3 / 319 (0.94%) 3	1 / 309 (0.32%) 1	0 / 81 (0.00%) 0
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	0 / 319 (0.00%) 0	0 / 309 (0.00%) 0	1 / 81 (1.23%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 319 (0.00%) 0	3 / 309 (0.97%) 4	0 / 81 (0.00%) 0
Infections and infestations Influenza			

subjects affected / exposed	4 / 319 (1.25%)	9 / 309 (2.91%)	0 / 81 (0.00%)
occurrences (all)	4	9	0
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	6 / 319 (1.88%)	2 / 309 (0.65%)	0 / 81 (0.00%)
occurrences (all)	6	2	0

Non-serious adverse events	MabThera after MabionCD20 (open-label period)	MabionCD20 after MabionCD20 (open-label period)	MabThera after MabThera (open-label period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 117 (9.40%)	9 / 79 (11.39%)	14 / 112 (12.50%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 117 (0.85%)	3 / 79 (3.80%)	1 / 112 (0.89%)
occurrences (all)	1	3	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 117 (0.85%)	1 / 79 (1.27%)	3 / 112 (2.68%)
occurrences (all)	1	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 117 (0.85%)	0 / 79 (0.00%)	0 / 112 (0.00%)
occurrences (all)	1	0	0
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	3 / 117 (2.56%)	0 / 79 (0.00%)	2 / 112 (1.79%)
occurrences (all)	3	0	2
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 117 (0.00%)	1 / 79 (1.27%)	0 / 112 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	0 / 79 (0.00%) 0	0 / 112 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 117 (0.85%) 1	0 / 79 (0.00%) 0	2 / 112 (1.79%) 2
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	3 / 117 (2.56%) 3	0 / 79 (0.00%) 0	2 / 112 (1.79%) 2
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	1 / 79 (1.27%) 1	1 / 112 (0.89%) 1
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	1 / 79 (1.27%) 1	0 / 112 (0.00%) 0
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	0 / 79 (0.00%) 0	1 / 112 (0.89%) 1
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	0 / 79 (0.00%) 0	2 / 112 (1.79%) 3
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	0 / 79 (0.00%) 0	0 / 112 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0	0 / 79 (0.00%) 0	0 / 112 (0.00%) 0
Infections and infestations Influenza			

subjects affected / exposed	0 / 117 (0.00%)	3 / 79 (3.80%)	0 / 112 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	1 / 117 (0.85%)	1 / 79 (1.27%)	0 / 112 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	MabionCD20 not re-treated (open-label period)	MabThera not re-treated (open-label period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 110 (4.55%)	5 / 105 (4.76%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 110 (0.91%)	0 / 105 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences (all)	0	0	
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	1 / 110 (0.91%)	1 / 105 (0.95%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 110 (0.00%)	0 / 105 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 105 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	0 / 105 (0.00%) 0	
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	1 / 105 (0.95%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	1 / 105 (0.95%) 1	
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 105 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 105 (0.00%) 0	
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 105 (0.00%) 0	
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0	0 / 105 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	1 / 105 (0.95%) 1	
Infections and infestations Influenza			

subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1	1 / 105 (0.95%) 1	
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all)	 0 / 110 (0.00%) 0	 0 / 105 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2014	Version 2.0 of the protocol was quickly integrated into version 2.1 (03-Mar-2014 amendment).
03 March 2014	Conduct of the study was changed to reflect the following: - Additional and updated study contact information, changed study visit windows, additional information about non-clinical study results, an update to the newly approved indication of MabThera and an update of information on AEs in the new SmPC of MabThera - Inclusion criterion 4 and exclusion criterion 10 were changed to precise the naivety of patient population from patients who were naive of TNF antagonists or any other biological agents to patients who were naive of TNF antagonists or any other mAb therapies. Exclusion criterion 20 was changed to reflect that patients could re-enter the study for a second time after failing previous screening procedures in this trial. The screening period was prolonged to 28 days and situations in which screening procedures could be repeated were further specified. The indications for MabThera were updated to include granulomatosis with polyangiitis and macroscopic polyangiitis. The time window permitted for premedication was changed from 30 min into 30±10 min prior to study drug infusion - Further changes reflected a prolonged shelf-life of MabionCD20®, new information on the sensitivity of the investigational products to temperature changes, and the additional specification of storage temperature. - The description of actions to be taken if an infusion related reaction occurred were updated and time windows for PK sampling periods were added. - A new blood test for hepatitis B (anti-HBc antibody) was added to the screening procedures. Pregnancy testing at Week 24 was further specified; a urine test was to be performed only in the patients who were to receive a second course of therapy, which was changed into a serum test that was to be performed in all patients.
08 August 2015	Conduct of the study was changed to reflect the following: - Procedures to accommodate sampling for validation and optimization of analytical methods. - The second course of treatment was originally planned with MabionCD20®, but to compensate for production delays, the protocol was changed to allow open-label treatment with MabThera depending on the sponsor’s decision, as second course of treatment. - The shelf-life of MabionCD20 was changed to reflect results of stability tests. - The human anti-chimeric antibodies (HACA) against rituximab measurements were not performed at Mabion R&D Centre anymore but left unspecified. The contact information for SAE and pregnancy reporting was changed to the new safety contact.

29 September 2016	Conduct of the study was changed to reflect the following: - An update of the sponsor contact information and that the sponsor's approval of the protocol was transferred to another person. - Screening procedures could be repeated once, but were allowed to be repeatedtwice, in exceptional cases and after the sponsor's approval. - Depending on the sponsor's decision, less patients than the planned 863 patients(with a screening failure rate of 15%) could be enrolled into the study, in case the drop-out rate was less than expected. - During the second course of treatment, PK sampling before infusions were additionally clarified in the study procedures. - The procedure for the pregnancy test was changed to include the testing at Week 24 in all women participating in the study. - In special cases, labelling of the IMP was allowed with a single page label, dedicated for each individual country. - Study status was to be additionally reviewed by the DSMB. • The MM was assigned to receive the investigator's SAE report and SAE form (which was a single document: Notification of Serious Adverse Event / Pregnancy From). The MM was responsible for reviewing the SAE form for minimal required information and sending it to Mabion Pharmacovigilance Unit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported