Clinical trial results:
REDO study: RhEumatoid arthritis REtreatment with ultra-low dose Rituximab: Disease Outcome after Dose Optimization

Summary

EudraCT number	2016-002908-15
Trial protocol	NL
Global end of trial date	25 March 2019

Results information

Result version number	v1 (current)
This version publication date	07 July 2021
First version publication date	07 July 2021

Trial information

Trial identification

Sponsor protocol code	RR-152-REDO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch trial register: NL5936

Notes:

Sponsors

Sponsor organisation name	Sint Maartenskliniek
Sponsor organisation address	Hengstdal 3, Ubbergen, Netherlands, 6574 NA
Public contact	Lise Verhoef, Sint Maartenskliniek, L.Verhoef@maartenskliniek.nl
Scientific contact	Lise Verhoef, Sint Maartenskliniek, L.Verhoef@maartenskliniek.nl

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	15 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2019
Global end of trial reached?	Yes
Global end of trial date	25 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the difference in efficacy between two ultra-low doses (1 x 200 mg and 1 x 500 mg) and standard low dose (1 x 1000 mg) of rituximab retreatment on the change in DAS28-CRP, compared to a pre-specified non-inferiority margin of 0.6, at 3 and 6 months in patients with RA previously treated with RTX using a conventional dose

Protection of trial subjects:

Patients were monitored closely during follow-up. In case of disease flare, an extra dose of 1 x 1000 mg RTX could be given without unblinding since the registered dose of RTX is 2 x 1000 mg per 6 months and patients will never exceed this dose (maximum study dose is 1 x 1000 mg).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 142
Worldwide total number of subjects	142
EEA total number of subjects	142

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)	63

From 65 to 84 years	78
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 15 December 2016 until 20 September 2018

Pre-assignment

Screening details:

679 individuals with rheumatoid arthritis who were using rituximab were screened for inclusion in the study. 340 (50%) people did not meet criteria for inclusion, mainly because of an insufficient response after the last rituximab infusion. A further 196 (29%) individuals did not want to participate. 143 patients were randomised (1 excluded).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Blinding implementation details:

Patients and all people involved in treatment of patients and assessment of outcomes (researchers and care providers) were unaware of the random assignments during the study period. The physical appearance of the three interventions was identical (same volume and colour). Allocation was revealed to every patient (and relevant study staff) by the treating rheumatologist after the last study measurement (at 6 months).

Arms

Are arms mutually exclusive?	Yes
Arm title	1x1000mg rituximab (control)

Arm description:

Patients received 1x1000mg (standard low dose) rituximab at study start.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rixathon
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1 x 1000mg rituximab

Arm title	1x500mg rituximab

Arm description:

Patients received 1x500mg rituximab at study start

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rixathon
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1 x 500mg rituximab

Arm title	1x200mg rituximab

Arm description:

Patients received 1x200mg rituximab at study start.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	MabThera, Rixathon
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1 x 200mg rituximab

Number of subjects in period 1	1x1000mg rituximab (control)	1x500mg rituximab	1x200mg rituximab
Started	29	58	55
Completed	29	58	54
Not completed	0	0	1
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	1x1000mg rituximab (control)
Reporting group description:	
Patients received 1x1000mg (standard low dose) rituximab at study start.	
Reporting group title	1x500mg rituximab
Reporting group description:	
Patients received 1x500mg rituximab at study start	
Reporting group title	1x200mg rituximab
Reporting group description:	
Patients received 1x200mg rituximab at study start.	

Reporting group values	1x1000mg rituximab (control)	1x500mg rituximab	1x200mg rituximab
Number of subjects	29	58	55
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age at baseline			
Units: years			
arithmetic mean	63.8	64.0	64.2
standard deviation	± 9.0	± 10.9	± 12.2
Gender categorical			
Gender of participants			
Units: Subjects			
Female	18	37	40
Male	11	21	15

Reporting group values	Total		
Number of subjects	142		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Age at baseline			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Gender of participants			
Units: Subjects			
Female	95		
Male	47		

End points

End points reporting groups

Reporting group title	1x1000mg rituximab (control)
Reporting group description:	
Patients received 1x1000mg (standard low dose) rituximab at study start.	
Reporting group title	1x500mg rituximab
Reporting group description:	
Patients received 1x500mg rituximab at study start	
Reporting group title	1x200mg rituximab
Reporting group description:	
Patients received 1x200mg rituximab at study start.	
Subject analysis set title	1x1000mg (control) per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
For the per-protocol analysis, we included patients who had received study medication and completed followup of 6 months, or until treatment failure (with disease activity LOCF).	
Subject analysis set title	1x500mg per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
For the per-protocol analysis, we included patients who had received study medication and completed followup of 6 months, or until treatment failure (with disease activity LOCF).	
Subject analysis set title	1x200mg per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
For the per-protocol analysis, we included patients who had received study medication and completed followup of 6 months, or until treatment failure (with disease activity LOCF).	

Primary: Change in DAS28-CRP from baseline to 6 months

End point title	Change in DAS28-CRP from baseline to 6 months
End point description:	
End point type	Primary
End point timeframe:	
6 months follow-up	

End point values	1x1000mg (control) per-protocol set	1x500mg per-protocol set	1x200mg per-protocol set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	28	58	54	
Units: DAS28-CRP				
arithmetic mean (confidence interval 95%)	-0.35 (-0.67 to -0.04)	0.05 (-0.21 to 0.31)	-0.38 (-0.68 to -0.09)	

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary analysis was a per-protocol hierarchical testing procedure comparing ultra-low doses with a standard low dose (500 mg vs 1000 mg at 3 months, followed by 500 mg vs 1000 mg at 6 months, 200 mg vs 1000 mg at 3 months, and 200 mg vs 1000 mg at 6 months), using a non-inferiority margin of 0·60 on change from baseline in the 28-joint disease activity score based on C-reactive protein levels (DAS28-CRP).

Comparison groups	1x1000mg (control) per-protocol set v 1x500mg per-protocol set v 1x200mg per-protocol set
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.29
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.18

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

6 months follow-up

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5

Reporting groups

Reporting group title	Complete trial

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As this was a trial in which dose reduction of rituximab was investigated, very low risk of adverse events due to study interventions was present and we will not specifiy all non-serious adverse events that occurred durint the trial.

Serious adverse events	Complete trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 140 (9.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Acute type-B dissection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Inguinal hernia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Elective surgery foot			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract extraction			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spondylodiscitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pleural infection			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Complete trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 140 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported