CLINICAL TRIAL PROTOCOL

Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis:

Protocol of the RITUXERA Trial

Version number: v2.0 **– Date:** **13-11-2023**

EU CT Number: 2023-506638-59-01

Internal ref. number: **S67309**

Sponsor

University Hospitals Leuven (UZ Leuven)

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Coordinating Investigator

Prof. Dr. Patrick Verschueren

PARTICIPATING SITES

Participating Sites

1. University Hospitals Leuven (UZ Leuven)
2. Cliniques Universitaires Saint-Luc Bruxelles
3. Heilig Hart Leuven
4. ZNA Jan Palfijn
5. OLV Aalst
6. ReumaClinic Genk
7. Reumacentrum Genk

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ACA	Active control arm
ACPA	Anti-citrullinated protein antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
asap	as soon as possible
ASES	Arthritis Self-Efficacy Scale
AUC	Area Under the Curve
bDMARD	Biological Disease-Modifying Antirheumatic Drug
CA	Competent Authority
CD	Cluster of Differentiation
CI	Coordinating/Chief Investigator
C.I.	Confidence Interval
CM	Concomitant Medication
CRA	Clinical Research Associate
CRP	C-reactive protein
csDMARD	Conventional synthetic Disease-Modifying Antirheumatic Drug
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
CTIS	Clinical Trial Information System
CTR	EU Clinical Trial Regulation 536/2014
DAS28	Disease Activity Score in 28 joints
DMARD	Disease-Modifying Antirheumatic Drug
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EA	Experimental arm
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
EoT	End of Trial
EQ-5D	EuroQol 5 Dimensions
ESR	Erythrocyte Sedimentation Rate
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	EU General Data Protection Regulation 2016/679
HAQ	Health Assessment Questionnaire

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JAK	Janus Kinase
JCI	Joint Commission International
LDA	Low Disease Activity
LPLV	Last Patient Last Visit
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MP	Monitoring Plan
MTX	Methotrexate
NaCl	Sodiumchloride
NYHA	New York Heart Association
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PI	Principal Investigator (Participating Site)
PM	Project Manager
PRO	Patient Reported Outcome
Q	Quartile
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
RF	Rheumatoid Factor
RTX	Rituximab
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDAI	Simple Disease Activity Index
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNF	Tumour Necrosis Factor
TSC	Trial Steering Committee
tsDMARD	Targeted synthetic Disease-Modifying Antirheumatic Drug
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment questionnaire

FUNDING AND SUPPORT

Funder	Type of Financial or Non-Financial Support
Fonds voor Wetenschappelijk Reumaonderzoek/ Fonds pour la Recherche Scientifique en Rhumatologie	Research grant for financial support.
Celltrion Healthcare (pharmaceutical company)	Provides support to the hospital pharmacies of University Hospitals Leuven and Cliniques Universitaires Saint-Luc Bruxelles for the provision of rituximab administered outside of the Belgian reimbursement criteria in the experimental arm (see point 2.4).
UZ Leuven	Application for Research Grant "Fonds academische studies".

Reasonable travel expenses incurred by Trial participants and directly related to participation in the Trial, will be reimbursed by the Sponsor, as follows:

All patients in the experimental arm who need to travel to University Hospitals Leuven Campus Gasthuisberg to receive an administration of rituximab outside the Belgian reimbursement criteria (see point 2.4) will receive a Sodexo voucher per administration of rituximab at University Hospitals Leuven Campus Gasthuisberg, with the exception of participants from Heilig Hart Leuven. The monetary value of vouchers will be calculated based upon the traveling distance between the participating site and University Hospitals Leuven Campus Gasthuisberg.

A travel reimbursement payment log will be kept by the Investigator Site staff and made available for monitoring and verification purposes

ROLES AND RESPONSIBILITIES

The Principle Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting…) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Council on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

Coordinating Investigator (CI)	Prof. Dr. Patrick Verschueren
Principal Investigators (PI)	One PI is chosen by every participating site.
Project manager (back-up)	Johan Joly (Dr. Elias De Meyst)
Trial data manager (back-up)	Dr. Elias De Meyst (Johan Joly)
Trial steering committee (TSC)	Composed of the coordinating investigator, the project manager, the trial data manager, two experts and a patient research partner.

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis: the RITUXERA trial
Protocol Short Title Acronym	RITUXERA
Trial Phase (I, II, III, IV)	IV
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Prof. Dr. Patrick Verschueren
Contact Address CI	Onderzoekscentrum voor Skeletale Biologie en Engineering ON1 Herestraat 49 bus 7003 3000 Leuven Belgium
Contact Email CI	[redacted]
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EU CT number	2023-506638-59-01
Other public database nbr	Clinicaltrials.gov: NCT06003283
Principal Investigators and Participating Sites	One PI is chosen by every participating site. Participating sites: 1. University Hospitals Leuven (UZ Leuven) (site of the CI) 2. Cliniques Universitaires Saint-Luc Bruxelles 3. Heilig Hart Leuven 4. ZNA Jan Palfijn 5. OLV Aalst 6. ReumaClinic Genk 7. Reumacentrum Genk
Medical condition or disease under investigation	Rheumatoid arthritis (RA)
Trial rationale	Investigation of the optimal treatment/tapering strategy with the biological disease-modifying antirheumatic drug (bDMARD) rituximab in patients with RA.
Primary objective	To investigate the long-term patient-reported impact of rituximab tapering based on disease activity-guided dose reduction compared to tapering based on interval prolongation in patients with RA.
Secondary objective(s)	The main secondary objective is to compare the long-term clinical effectiveness (disease activity measured by the Disease Activity Score 28 – C-reactive protein (DAS28-CRP)) of tapering rituximab based on disease activity-guided dose reduction compared to interval prolongation. Other secondary objectives: - Compare the cumulative dose of rituximab in the two trial arms over 104 weeks.

	- Compare the cumulative dose of glucocorticoids in the two trial arms over 104 weeks. - Determine the proportion of patients who tapered their rituximab dose to 200 or 500 mg in the group that tapered based on dose reduction (experimental arm) over 104 weeks. - Determine the mean/median interval between rituximab administrations in the group that tapered based on interval prolongation (active control arm). - Determine the proportion of patients achieving a good/moderate EULAR response 12 weeks after a rituximab infusion per cycle/per dose. - Compare the maintenance of disease control between the two groups. - Compare the disease activity according to the simplified disease activity index (SDAI) score between the two groups. - Compare the drug retention rate between the two groups. - Compare the proportion of serious adverse events/reactions between the two groups. - Compare the proportion of patients with (serious) infections between the two groups.
Trial Design	Open-label, multicentre, randomised controlled pragmatic trial This is a superiority trial consisting of 2 arms: • Active control arm: arm in which patients taper rituximab in a fixed dose of 1000 mg intravenously (IV) administered based on interval prolongation (treatment according to the current reimbursement criteria for retreatment with rituximab: retreatment in case of a relapse of RA with a DAS28 score ≥3.2 and last administration of rituximab at least 24 weeks before). • Experimental arm: arm in which patients taper rituximab based on disease activity-guided dose reduction. Patients in this arm will receive rituximab at fixed intervals of 24 weeks, and the administered dose of rituximab will be reduced in case of a DAS28 score ≤3.2 in the following sequence: 1 x 1000 mg IV (maximum), 1 x 500 mg IV, 1 x 200 mg IV (minimum). In case of a DAS28 score >3.2, the last effective dose will be administered. The trial duration is 2 years (104 weeks), with a 1 year inclusion period. Trial visits are planned every 12 weeks. Additional unscheduled visits are optional.
Endpoints	Primary Endpoint: Difference in Rheumatoid Arthritis Impact of Disease (RAID) score area under the curve (AUC) over 2 years in the two trial arms. Main Secondary Endpoint: Difference in DAS28-CRP AUC over 2 years in the two trial arms. Other Secondary Endpoints: - Difference in SDAI AUC over 2 years in both study arms. - Cumulative dose of glucocorticoids over 104 weeks in the two trial arms. - Cumulative dose of rituximab over 104 weeks in the two trial arms.

	- Proportion of patients who tapered the rituximab dose to 200 mg or 500 mg in the experimental arm (tapering based on disease-acitivy guided dose reduction). - Mean/median interval between rituximab administrations in the active control arm (tapering based on interval prolongation) - Proportion of patients achieving a good or moderate EULAR response (good response: decrease in DAS28-CRP >1.2 with present DAS28-CRP ≤3.2; moderate response: decrease in DAS28-CRP >0.6 to ≤1.2 with present DAS28-CRP ≤5.1, or decrease in DAS28-CRP >1.2 with present DAS28-CRP >3.2) 12 weeks after administration of rituximab (1). - Proportion of patients maintaining disease control in both study arms (losing disease control is defined as having a DAS28-CRP >3.2 with a previous DAS28-CRP ≤3.2). - Rituximab drug-retention rates in both study arms. - Proportion of patients with serious adverse events/reactions in both study arms. - Proportion of patients with (serious) infections in both study arms.
Sample Size	134
IMP, dosage and route of administration	IMP: rituximab Dosage: either 1x1000 mg, 1x500 mg, or 1x200 mg Route of administration: intravenous
Active comparator product(s)	Not applicable
Maximum duration of treatment and Follow Up of a Participant	2 years
Maximum duration of entire Trial	3 years (1 year inclusion period + 2 year trial)
Date anticipated First Patient First Visit (FPFV)	Q4 of 2023
Date anticipated Last Patient Last Visit (LPLV)	Q3 of 2026
Third parties	Fonds voor Wetenschappelijk ReumaOnderzoek (FWRO): research grant for financial support. The pharmaceutical company Celltrion Healthcare provides support for the provision of rituximab administered outside of the Belgian reimbursement criteria in the experimental arm (see point 2.4). Fonds academische studies: application for research grant from UZ Leuven.

TRIAL FLOWCHART

Schedule of Events – Trial specific Procedures / Assessments

Table 1: Flowchart of the RITUXERA trial

	SCR/ BL◊	W12	W24	W36	W48	W60	W72	W84	W96	W104	Flare/ Unsch§
ICF	x										
In- and exclusion criteria	x										
Randomisation	x										
Demographics*	x										
Weight	x				x					x	
Medical history	x										
66/68 Joint count	x	x	x	x	x	x	x	x	x	x	x
RF and ACPA status	x										
CRP and ESR	x	x	x	x	x	x	x	x	x	x	x
DAS28	x	x	x	x	x	x	x	x	x	x	x
SDAI	x	x	x	x	x	x	x	x	x	x	x
RAID	x	x	x	x	x	x	x	x	x	x	x
PGA	x	x	x	x	x	x	x	x	x	x	x
PhGA	x	x	x	x	x	x	x	x	x	x	x
EQ-5D	x	x	x	x	x	x	x	x	x	x	
VAS pain	x	x	x	x	x	x	x	x	x	x	x
VAS fatigue	x	x	x	x	x	x	x	x	x	x	x
HAQ	x	x	x	x	x	x	x	x	x	x	
ASES	x	x	x	x	x	x	x	x	x	x	
WPAI	x	x	x	x	x	x	x	x	x	x	
Immunoglobulin count£	x		(x)	(x)	(x)	(x)	(x)	(x)	(x)	x	(x)
CD19+ and memory B-cells count£	x		(x)	(x)	(x)	(x)	(x)	(x)	(x)	x	(x)
Concomitant medication†	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x

Rituximab infusion (active control arm: interval prolongation)°	x		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Rituximab infusion (Experimental arm: dose reduction)$	x		x (x)		x (x)		x (x)		x (x)		

SCR: *screening*, BL: *baseline*, W: *week*, Unsch: *unscheduled visit*, ICF: *informed consent form*, RF: *rheumatoid factor*, ACPA: *anti-citrullinated protein antibody*, CRP: *C-reactive protein*, ESR: *erythrocyte sedimentation rate*, DAS28: *Disease Activity Score in 28 joints*, SDAI: *Simple Disease Activity Index*, RAID: *Rheumatoid Arthritis Impact of Disease questionnaire*, PGA: *Patient Global Assessment*, PhGA: *Physician Global Assessment*, EQ-5D: *EuroQuol-5-Dimensions questionnaire*, VAS: *visual analogue scale*, HAQ: *Health Assessment Questionnaire*, ASES: *Arthritis Self-Efficacy Scale,* WPAI: *Work Productivity and Activity Impairment questionnaire,* CD: *cluster of differentiation.*

Orange: procedures performed specifically for the Trial (thus not considered standard of care).

◊ Screening and baseline procedures will be conducted during the same visit, if possible. If this is not feasible, a window of 2 weeks is allowed between screening and baseline.

* Demographics: age, gender, date of birth, date of diagnosis of rheumatoid arthritis, start date of rituximab treatment for rheumatoid arthritis, smoking status, alcohol consumption, length, prior use of bDMARDs and tsDMARDs, number of previous rituximab cycles, and employment status.

§ Flare/unscheduled visit: unscheduled visits can take place according to the investigator's decision.

£ Immunoglobulin count (IgG, IgA and IgM) and $CD19^+$/memory B cell count will only be determined at baseline, W104 and on the moment (or just before) each new rituximab infusion. Therefore, this is indicated as "(x)" in the flowchart.

† Collection of concomitant medication with specific attention to the glucocorticoid dose, frequency and duration.

° The active control arm will be retreated with 1x1000 mg rituximab IV in case the DAS28-CRP score is ≥3.2 at least 24 weeks after the previous rituximab cycle, unless there are contraindications. Therefore, this is indicated as "(x)" in the flowchart.

$ The experimental group will be retreated every 24 weeks in a dose depending on the current DAS28-CRP. If treated with a current DAS28-CRP ≥3.2, retreatment falls under the current Belgian reimbursement criteria for treatment with rituximab in rheumatoid arthritis, and therefore this administration will be considered to be part of the standard of care. When treated outside the Belgian reimbursement criteria, this is not considered to be standard of care, therefore indicated with (x).

NB. A visit window of 4 weeks (2 weeks before and after the predefined date) is allowed.

1 Background and Rationale

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. According to the European Alliance of Associations for Rheumatology (EULAR) recommendations, RA should be treated first with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), preferably methotrexate (MTX), combined with a short-term step-down scheme of glucocorticoids. In case patients with RA are insufficiently controlled with csDMARDs, a biologic DMARD (bDMARD) or a targeted synthetic DMARD tsDMARD), i.e. Janus kinase (JAK) inhibitor, should be added to the therapy (2). Moreover, in Belgium, patients should have failed two csDMARDs before they can receive reimbursement for bDMARDs or JAK inhibitors.

Several bDMARDs are available as treatment for RA, such as rituximab (RTX). Rituximab has a B-cell depleting mechanism of action and is approved and reimbursed in Belgium after failing a bDMARD targeting tumour necrosis factor (TNF). The original treatment regimen of rituximab in RA consisted of two infusions of 1000 mg with an interval of two weeks. However, evidence has shown that a lower dose (e.g. one infusion of 1000 mg) could be equally effective as the original dose (3–10). Consequently, a cycle consisting of one infusion of 1000 mg is increasingly being used in daily clinical practice. Furthermore, the REDO trial showed that rituximab might be even lowered to an ultra-low dose, namely one infusion of 500 mg or even 200 mg (11). In Belgium, a subsequent rituximab cycle is reimbursed in case of an increase in disease activity, defined as a disease activity score in 28 joints (DAS28) of at least 3.2, as well as a previous rituximab cycle administered at least 24 weeks ago. This retreatment strategy could be called an "on-flare retreatment strategy". The reimbursement criteria clearly contribute to a decreased risk of overtreatment. However, a loss of disease control could have a major impact on the quality of life of the patient and may contribute to progressive structural joint damage. Furthermore, disease progression may potentially lower the chances of re-achieving disease control.

As bDMARDs are expensive drugs and might be accompanied by a dose-dependent increased risk of infections (12), decreasing the dose has the advantage of potential cost-savings and a decreased risk of serious infections (13,14). Therefore, EULAR recommends to consider tapering of bDMARDs when patients have a controlled disease activity (2). Tapering can be either done by increasing the time between administrations (also called "spacing") or by reducing the dosage of the drug based on disease activity. However, there is still a need to determine which tapering strategy would be the best fit for the drug rituximab, reducing side effects and costs and taking into account patient preferences. Furthermore, as we hypothesize that administering rituximab at a fixed interval in tapered doses guided by disease activity may prevent flares of disease acitivity, this strategy might result in a better benefit/risk balance. In the RITUXERA trial, we hope to obtain answers regarding the optimal tapering strategy for rituximab in rheumatoid arthritis, which we will subsequently try to implement in daily practice.

2 Trial Objectives and Design

2.1 Trial objectives

Primary research question:
What is the optimal treatment/tapering strategy for rituximab in patients with rheumatoid arthritis in terms of reducing patient reported disease impact?

Specific hypothesis:
Tapering rituximab in dose guided by disease activity results in lower patient reported disease impact in comparison to tapering rituximab by interval prolongation.

The primary objective of this trial is to investigate the long-term patient-reported impact of rituximab tapering based on disease activity-guided dose reduction compared to tapering based on interval prolongation in patients with rheumatoid arthritis.

The main secondary objective is to compare the long-term clinical effectiveness of tapering rituximab based on disease activity-guided dose reduction compared to interval prolongation.

2.2 Primary Endpoints

The primary endpoint is the comparison of the area under the curve (AUC) of the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire over 104 weeks between patients tapering rituximab based on dose or based on interval prolongation.

2.3 Secondary Endpoints

The main secondary endpoint is to compare the AUC of the disease activity score in 28 joint – C-reactive protein (DAS28-CRP) over 104 weeks between patients tapering rituximab based on dose or based on interval prolongation.

Other secondary outcomes:

- Compare the cumulative dose of rituximab in the two trial arms over 104 weeks.
- Compare the cumulative dose of glucocorticoids in the two trial arms over 104 weeks.
- Determine the proportion of patients who tapered their rituximab dose to 200 or 500 mg in the group that tapered based on dose reduction (experimental arm) over 104 weeks.
- Determine the mean/median interval between rituximab administrations in the group that tapered based on interval prolongation (active control arm).
- Proportion of patients achieving a good/moderate EULAR response 12 weeks after a rituximab infusion per cycle/per dose (good response: decrease in DAS28-CRP >1.2 with present DAS28-CRP ≤3.2; moderate response: decrease in DAS28-CRP >0.6 to ≤1.2 with present DAS28-CRP ≤5.1, or decrease in DAS28-CRP >1.2 with present DAS28-CRP >3.2) (1).
- Compare the maintenance of disease control between the two groups. Loss of disease control is defined as having a DAS28-CRP >3.2 with previous DAS28-CRP ≤3.2.
- Compare the disease activity according to the simplified disease activity index (SDAI) score between the two groups (SDAI AUC over 104 weeks).
- Compare the rituximab drug retention rate between the two groups.
- Compare the proportion of serious adverse events/reactions between the two groups.
- Compare the proportion of patients with (serious) infections between the two groups.

Other exploratory outcomes:

- Compare the evolution and fluctuations over time of functionality (Health assessment questionnaire (HAQ)) between the two groups.
- Compare the evolution and fluctuations over time of pain, fatigue, and patient global assessment (PGA) (visual analogue scales (VAS)) between the two groups.
- Compare the evolution and fluctuations over time of self-efficacy (Arthritis self-efficacy scale (ASES) questionnaire) between the two groups.
- Evaluation of cluster of differentiation (CD) 19^{+} counts and memory B-cells.
- Evaluation of the immunoglobulin (Ig) counts (IgA, IgG, IgM).
- Compare professional and vocational participation (Work Productivity and Activity Impairment questionnaire (WPAI)) over time between the two groups.

- Compare quality of life (EuroQol 5 Dimensions (EQ-5D)) over time between the two groups.

2.4 Trial Design

In this two-year, multicentre, open-label, pragmatic randomised controlled trial, patients with RA previously treated with at least one succesful cycle of RTX will be included if they are in need of a subsequent treatment cycle (i.e. DAS28 score ≥3.2 and previous treatment with rituximab at least 24 weeks before, in accordance with the Belgian reimbursement criteria).

Included patients will be 1:1 randomised into 2 treatment arms (Figure 1):
Patients who are randomised to the active control arm will taper rituximab based on interval prolongation, which reflects the current standard of care. They will receive rituximab cycles consisting of 1 infusion of 1000 mg IV. A subsequent cycle will be administered based on the presence of a flare (according to the current Belgian reimbursement criteria: DAS28 score ≥3.2 and previous treatment with rituximab at least 24 weeks before).
Patients who are randomised to the experimental arm will receive rituximab at fixed intervals of 24 weeks, and will taper the dose guided by disease activity, whenever possible. Patients will taper their rituximab dose according to the following predefined sequence: 1x 1000 mg IV (maximum) → 1x 500 mg IV → 1x 200 mg (minimum) if the DAS28 score is ≤3.2. If at any 24 week interval visit the patient experiences a loss of disease control (DAS28 score is >3.2) and consequently the Belgian reimbursement criteria for rituximab retreatment are met, the previously effective dose will be administered.

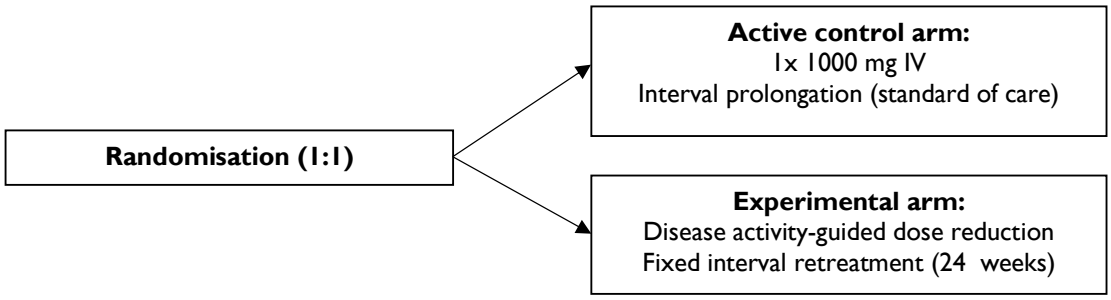


Figure 1: The RITUXERA trial consists of 2 treatment groups. Patients from the active control arm will taper based on interval prolongation and patients from the experimental arm will taper based on disease activity-guided dose reduction.

2.4.1 Tapering based on interval prolongation (active control arm)

In this group patients are retreated with 1 infusion of 1000 mg rituximab when the DAS28-CRP score is ≥3.2 at least 24 weeks following the previous rituximab administration. The choice of this cut-off is based on the Belgian reimbursement criteria for rituximab retreatment. Subsequently, patients in this arm will be retreated with 1x 1000 mg IV rituximab in case the DAS28-CRP score is ≥3.2 at least 24 weeks since the previous rituximab cycle, unless there are contraindications.

2.4.2 Tapering based on disease activity-guided dose optimisation (experimental arm)

In this group, patients are retreated based on a fixed interval (every 24 weeks) unless contraindicated. At baseline, the patients are treated with one infusion of 1000 mg rituximab. If patients are in remission or low disease activity according to the DAS28-CRP (i.e. score ≤3.2) at the time of retreatment, the dose shall be tapered down. The tapering sequence will be as followed: 1x 1000 mg IV (maximum) → 1x 500 mg IV → 1x 200 mg IV (minimum). In case patients do not achieve low disease activity with the tapered dose (i.e. disease control = DAS28-CRP score >3.2), they fullfill the Belgian reimbursement criteria and

will be treated with the last effective dose (previous step in the tapering sequence) during the subsequent retreatment and glucocorticoid bridging can be considered until the next infusion. The dosage of glucocorticoids (GCs) should be kept as stable as possible and in case of chronic use the dose should not exceed the baseline dose between week 8 and 12 and between week 20 and week 24 following the last RTX infusion.

2.4.3 Potential Risks associated with Tapering

As in this trial, rituximab is used within its registered indication, and the doses that will be administered as dictated by the study protocol will never exceed doses used in line with the standard of care, we do not expect an increase of adverse events attributable to rituximab. As patients who are randomised to the experimental arm may receive lower doses of rituximab, fewer adverse events may even be expected in this study group.

The lower doses of rituximab administered in the experimental tapering strategy may be associated with an increased risk of RA symptom recurrence. However, there is sufficient evidence that this risk is acceptable (11). Moreover, we hypothesize that the systematic administration of rituximab according to this strategy may actually increase disease stability, potentially preventing relapses of disease and associated symptom recurrences. If, however, lower doses of rituximab are insufficient to control active disease in a participant (regardless of study group), rescue medication may be considered, as defined in section 5.4, which is consistent with the current standard of care.

2.4.4 Randomisation

At baseline, patients will be randomised to either group 1 or 2 according to a 1:1 ratio. Randomisation will be stratified based on study centre and the number of previous rituximab cycles (≤2 or >2), to ensure the comparability of the two treatment groups.

2.4.5 Trial Visits

Study visits are planned every 12 weeks, with a window of 4 weeks (2 weeks before or after the predefined date) in both study arms, starting from baseline. This interval was chosen as a reflection of current clinical practice. In case of an increase in disease activity or other unforeseen circumstances (investigator's decision), the site can schedule an additional visit (flare/unscheduled visit).

2.4.5.1 Screening/Baseline Visit

- Informed consent form (ICF)
- Inclusion and exclusion criteria
- Randomisation procedure
- Demographics (age, gender, date of birth, date of diagnosis, start date of rituximab treatment, smoking status, alcohol consumption, length, prior bDMARDs and tsDMARDs, number of previous rituximab cycles, and employment status)
- Medical history
- Weight
- Clinical examination
- 68/66 joint count
- RF and ACPA status
- CRP and ESR (Erythrocyte sedimentation rate)
- Patient reported outcomes (RAID, patient global assessment (PGA), EuroQol 5D (EQ-5D), VAS fatigue, VAS pain, HAQ, Arthritis self-efficacy scale (ASES), Work productivity and activity impairment questionnaire (WPAI))
- DAS28 and SDAI
- Physician global assessment (PhGA)
- Immunoglobulin count (IgG, IgA and IgM)

- $CD19^+$ count and memory B-cells
- Adverse events (after informed consent has been obtained but prior to initiation of Trial treatment, only adverse events caused by a Trial specific procedure and serious adverse events of special interests should be recorded in the electronic case report form. See 6.3)
- Prescription of rituximab treatment consisting of 1 infusion of 1000 mg for both group 1 and 2 (the infusion itself should be given as soon as possible after the study visit, within a 3 week window of the study visit)

It is highly recommended to do the screening and baseline on the same visit. If this is not feasible, a window of 2 weeks is allowed between screening and baseline.

2.4.5.2 Week 12

- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, EQ-5D, VAS fatigue, VAS pain, HAQ, ASES, WPAI)
- PhGA
- DAS28 and SDAI
- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)
- Adverse events

2.4.5.3 Week 24

- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, EQ-5D, VAS fatigue, VAS pain, HAQ, ASES, WPAI)
- PhGA
- DAS28 and SDAI
- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)
- Adverse events
- Prescription of rituximab treatment consisting of a tapered dose for group 2 (the infusion itself should be given as soon as possible after the study visit, within a window of 3 weeks following the study visit)
- *(Prescription of rituximab treatment consisting of 1x 1000 mg for group 1 - only if the DAS28-CRP is ≥3.2 and the previous infusion is at least 24 weeks ago)*
- *(Immunoglobulin count (IgG, IgA and IgM) – should only be determined at the moment (or just before) each new rituximab infusion)*
- *($CD19^+$ count and memory B-cells – should only be determined at the moment (or just before) each new rituximab infusion)*

2.4.5.4 Week 36, 60 and 84

- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, EQ-5D, VAS fatigue, VAS pain, HAQ, ASES, WPAI)
- PhGA
- DAS28 and SDAI
- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)

- Adverse events
- *(Prescription of rituximab treatment consisting of 1x 1000 mg for group 1 - only if the DAS28-CRP is ≥3.2 and the previous infusion is at least 24 weeks ago)*
- *(Immunoglobulin count (IgG, IgA and IgM) – should only be determined at the moment (or just before) each new rituximab infusion)*
- *(CD19$^+$ count and memory B-cells – should only be determined at the moment (or just before) each new rituximab infusion)*

2.4.5.5 Week 48, 72 and 96

- Weight (only required at the Week 48 visit)
- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, EQ5D, VAS fatigue, VAS pain, HAQ, ASES, WPAI)
- PhGA
- DAS28 and SDAI
- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)
- Adverse events
- Prescription of rituximab treatment for group 2 (the infusion itself should be given as soon as possible after the study visit, within a window of 3 weeks following the study visit)
- *(Immunoglobulin count (IgG, IgA and IgM) – should only be determined at the moment (or just before) each new rituximab infusion)*
- *(CD19$^+$ count and memory B-cells – should only be determined at the moment (or just before) each new rituximab infusion)*
- *(Prescription of rituximab treatment consisting of 1x 1000 mg for group 1 - only if the DAS28-CRP is ≥3.2 and the previous infusion is at least 24 weeks ago)*

2.4.5.6 Week 104

- Weight
- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, EQ5D, VAS fatigue, VAS pain, HAQ, ASES, WPAI)
- PhGA
- DAS28 and SDAI
- Immunoglobulin count (IgG, IgA and IgM)
- CD19$^+$ count and memory B-cells
- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)
- Adverse events
- *(Prescription of rituximab treatment consisting of 1x 1000 mg for group 1 - only if the DAS28-CRP is ≥3.2 and the previous infusion is at least 24 weeks ago)*

2.4.5.7 Flare/Unscheduled Visit

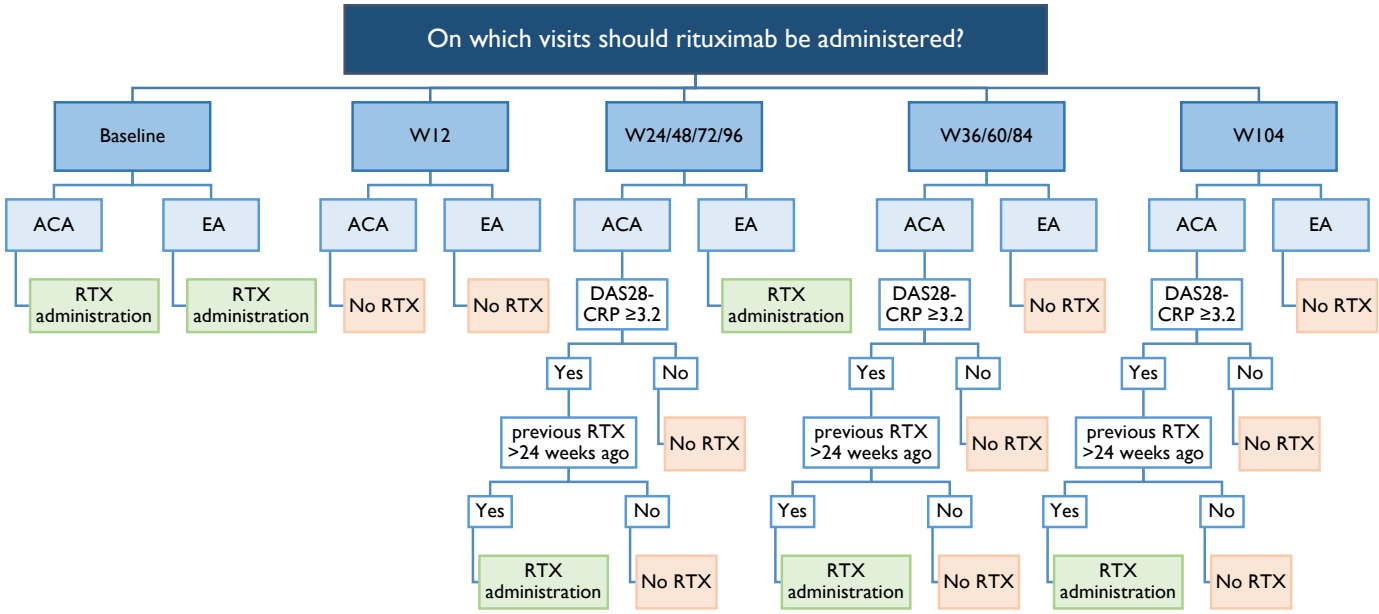
- Clinical examination
- 68/66 joint count
- CRP and ESR
- Patient reported outcomes (RAID, PGA, VAS fatigue, VAS pain)
- PhGA
- DAS28 and SDAI

- Concomitant medication (with specific attention to the glucocorticoid dose, frequency and duration)
- Adverse events
- *(Immunoglobulin count (IgG, IgA and IgM) – should only be determined at the moment (or just before) each new rituximab infusion)*
- *(CD19$^+$ count and memory B-cells – should only be determined at the moment (or just before) each new rituximab infusion)*
- *(Prescription of rituximab treatment consisting of 1x 1000 mg for group 1 - only if the DAS28-CRP is ≥3.2 and the previous infusion is at least 24 weeks ago)*

Patients randomised to the active control arm will receive rituximab (1 infusion of 1000 mg) according to the Belgian reimbursement criteria, namely at baseline and whenever the DAS28-CRP score is ≥3.2 and the previous infusion is at least 24 weeks ago.

Patients randomised to the experimental arm will receive rituximab based on a fixed retreatment schedule, namely at baseline, week 24, week 48, week 72 and week 96. If patients are in remission or low disease activity according to the DAS28-CRP (≤3.2) at the time of retreatment, the dose must be further tapered down. The tapering sequence will be as follows: 1x 1000 mg IV (maximum) → 1x 500 mg IV → 1x 200 mg IV (minimum). In case patients do not achieve low disease activity with the tapered dose (i.e., DAS28-CRP >3.2), they fullfill the Belgian reimbursement criteria for retreatment and will be treated with the last effective dose (previous step in the tapering sequence).

In case of a toxicity, actions will be taken according to good clinical practice. Toxicities will be documented and followed up as closely as possible.



Active control arm (ACA): patients will receive 1 infusion of 1000 mg rituximab for retreatment.

Experimental arm (EA): patients will receive rituximab every 24 weeks, but will reduce their dose according to the sequence 1x 1000 mg IV (maximum) → 1x 500 mg IV → 1x 200 mg IV (minimum). The next reduction step will be taken if the patients are in remission or at least in low disease activity at the moment of retreatment (DAS28-CRP score ≤3.2). In case low disease activity is not achieved, patients will return to their last effective dose.

2.5 Expected Duration of the Trial

The duration of the trial will be 3 years: 1 year inclusion period and 2 year trial.

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Diagnosis of rheumatoid arthritis (according to the 2010 ACR/EULAR Classification Criteria for RA) (15)
2. Current treatment with rituximab
3. Previous response to rituximab, defined as a minimum of one successful rituximab cycle (= a moderate/good EULAR response 16 weeks after the first RTX administration) (1,16)
4. Need for a subsequent rituximabh cycle according to the Belgian reimbursement criteria (i.e. DAS28 score ≥3.2)
5. If patients are treated with methotrexate or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), this should be at a stable dose for at least 4 weeks prior to baseline
6. Age ≥ 18 years old
7. Understanding and able to write Dutch or French
8. Able and willing to give written informed consent and participate in the study before any study procedure

All participants that are considered for Trial participation, per the above criteria will be documented on the Screening Log, including Screen Failures.

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Current treatment with a bDMARD other than rituximab
2. Current treatment with a targeted synthetic disease-modifying antirheumatic drug (tsDMARD)
3. Pregnancy or pregnancy wish
4. Presence of an absolute contraindication to treatment with rituximab, according to the label of rituximab and according to medical judgement*

*Based on the summary of product characteristics (SmPC) of Mabthera, Ruxience, Rixathon, and Truxima, absolute contraindications to treatment with rituximab are:

- Hypersensitivity to the active substance (rituximab) or to excipients;
- Active severe infections;
- Severe immune deficiency;
- Severe heart failure (New York Heart Association (NYHA) Class IV) or other severe uncontrolled cardiac conditions.

We do acknowledge that trial participants may develop exclusion criteria while being treated with rituximab. If the patient develops a contraindication to treatment with rituximab during the course of the study (exclusion criterion 4), a medical professional will judge whether the contraindication to the use of rituximab is temporary/reversible, and whether further treatment with rituximab is acceptable considering the benefit/risk balance, in line with the standard of care (see also 4.10).

Every effort will be made to gather a representative sample of patients, reflecting a normal distribution of patients with established RA treated with rituximab. We therefore chose to conduct a multicentric trial using inclusion and exclusion criteria which are not too restrictive.

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomised in the Trial and will be identified on the Screening Log as Screen Failure.

4 Trial Procedures

All Trial related procedures will take place at the participating site where the subject was included for study, with the exception of the administration of rituximab outside the Belgian reimbursement criteria for patients who were randomised to the experimental arm and who were not included at either University Hospitals Leuven or Cliniques Universitaires Saint-Luc Bruxelles. Administrations of rituximab in this specific case will take place at University Hospitals Leuven Campus Gasthuisberg (see point 5.1). In this specific situation, after evaluating the patient as in the standard of care, the consulting rheumatologist at the participating site will contact the rheumatologist responsible for the day care hospital of University Hospital Leuven to schedule an appointment for retreatment with rituximab, specifying the patient's name and the dose of rituximab to be administered according to the study protocol. Administrations of rituximab at UZ Leuven will be medically supervised according to standard of care. After administration of rituximab, the medical supervisor(s) from UZ Leuven (thus having a therapeutic relationship with the participant) will disclose all relevant medical information about the administration to the treating rheumatologist of the participating site in a medical report, after which the eCRF can be completed at the participating site. This procedure is clearly explained and described in the informed consent, so all patients participating will confirm their agreement as part of the informed consent procedure.

4.1 Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

Special attention during the consent process will be given to explain patients that when randomized to the experimental arm, if the reimbursement criteria for rituximab are not fulfilled, the administration of the medication will be done at UZ Leuven, except for patients treated at UCL.

4.2 Selection of Participants / Recruitment

In every participating site, patients with RA currently treated with rituximab may be approached for screening if a new cycle of rituximab is deemed necessary by the rheumatologist. In this case, the rheumatologist shall inform the patient about the planned trial, in collaboration with a clinical research associate (CRA) or investigator, and start the screening process.

4.3 Randomisation Procedure / Blinding (if applicable)

To ensure the integrity of the Trial, the following randomisation procedures have been established:

Participants will be randomised in a 1:1-ratio during the screening visit, based on stratified randomisation by study center and number of previous rituximab cycles (≤2 or >2), to either the active control arm (tapering by interval prolongation) or the experimental arm (tapering by dose adjustment guided by disease activity).

The randomisation schedule will be based on centre-specific, computer-generated sequences programmed in Research Electronic Data Capture (REDCap), ensuring allocation concealment.

As this is an open-label trial, no placebo/blinding procedures are involved.

4.4 Laboratory tests

A routine blood sample will be performed at each visit according to daily clinical practice (if not available from the general practitioner within 5 days of the study visit). The routine laboratory test should minimally require CRP and ESR.
At screening/baseline the RF and ACPA status is asked. If this is not yet known, this should be determined.
The immunoglobulin (IgA, IgG and IgM), $CD19^{+}$ and memory B cell counts should only be determined at baseline, week 104 and at the moment of (or just before) each new rituximab infusion.
No samples will be stored for further analysis within this protocol.

4.5 Medical history

At screening/baseline, the medical history will be collected. This will be done using a predefined comorbidity list consisting of check boxes for cardiovascular, respiratory, gastrointestinal, renal, neurological, cancer, endocrine, musculoskeletal, psychiatric disorders, metabolic disturbances, extra-articular manifestations of RA, and other relevant conditions.

4.6 Clinical and rheumatological examination

At every visit, a routine clinical and rheumatologic examination will be done. A complete 68/66 joint count will be done at each visit based on a present/absent-score for pain and swelling. Nocturnal pain (present/not) and morning stiffness will be evaluated (yes/no; with further specification when present).
A VAS global assessment of the disease activity by the physician will be scored (PhGA).

4.7 Patient reported outcomes

During the trial, Patient Reported Outcomes (PROs) will be gathered by means of self-reported patient questionnaires. Many of these PROs are collected routinely as part of good clinical practice by Belgian rheumatologists. The collected questionnaires are RAID, PGA, EQ-5D, VAS fatigue, VAS pain, HAQ, ASES, and WPAI.
The PROs will preferably be collected via REDCap to minimise the risk of incompleteness or transcription errors. The PROs can be accessed via a link, which will be send to the patient's email address, or via a QR-code during the study visit. The email address will only be accessible by the site staff so anonymity can be guaranteed. If patients are not able to complete the PROs online, a paper alternative will be provided.

4.8 Composite indices

On every Trial visit, the DAS28-CRP and SDAI scores will be calculated.

4.9 End of Trial

The maximal duration of the Trial is 2 years (104 weeks).
The end of the trial is defined as the last visit of the last patient.

4.10 Premature discontinuation of Trial treatment

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant. Similarly, the Sponsor, CA/EC can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when the integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Safety concerns related to IMP or unacceptable intolerability
- Trial participation while in violation of the inclusion and/or exclusion criteria*

*As stated in section 3.2 concerning exclusion criterion 4, trial participants may develop a contraindication to treatment with rituximab during the course of the study in line with the SmPC of Mabthera/Ruxience/Truxima/Rixathon. In this case, a medical professional will judge whether the contraindication to treatment with rituximab is temporary/reversible, and whether further treatment with rituximab is acceptable considering the benefit/risk balance, in line with the standard of care. This may result in treatment interruption or discontinuation of trial participation.

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up.

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g. dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

Participants who no longer want to adhere to the study protocol but do not withdraw their consent will continuously be monitored, and efforts will be made that they will receive the best possible care.

5 Trial Medication / Drug

Generic Drug Name (& company brand name)	IMP or non-IMP	Used within Indication? (Y or N)	Route of administration (po,sc,iv,…)	Dose/dosage and units
rituximab (Mabthera, Truxima, Rixathon, Ruxience)	IMP	Y (rheumatoid arthritis)	IV	1 x 1000 mg or 1 x 500 mg or 1 x 200 mg
paracetamol (Dafalgan)	non-IMP	Y*	IV	1 x 1000 mg
cetirizine (Zyrtec)	non-IMP	Y*	PO	1 x 10 mg
levocetirizine (Xyzall)	non-IMP	Y*	PO	1 x 5 mg
methylprednisolone (Solu-Medrol) §	non-IMP	Y*	IV	1 x 125 mg in 50 mL NaCl 0.9%

* medication co-administered with rituximab (either cetirizine or levocetirizine).

§ or equivalent.

5.1 Investigational Medicinal Product (IMP) and Dosing Regimen

In this trial, all patients will receive rituximab, administered by health care professionals.
Rituximab can be prescribed as Mabthera (the bio-originator) or as biosimilars available on the market, which currently include Truxima, Rixathon, and Ruxience.

License for the bio-originator (Mabthera) is held by Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany, filed under numbers EU/1/98/067/001 and EU/1/98/067/002. First date of MA: June 2nd 1998.

License for the biosimilar (Truxima) is held by Celltrion Healthcare Hungary Kft., Váci út 1-3. WestEnd Office Building B torony, 1062 Budapest, Hungary, filed under numbers EU/1/16/1167/002.

License for the biosimilar (Rixathon) is held by Sandoz GmbH, Biochemiestr. 10, 6250 Kundl, Austria, filed under numbers EU/1/17/1185/001, EU/1/17/1185/002, EU/1/17/1185/003 and EU/1/17/1185/004.

License for the biosimilar (Ruxience) is held by Pfizer Europe MA E.E.I.G., Pleinlaan 17, 1050, Brussels, Belgium, filed under numbers EU/1/20/1431/002.

Either the bio-originator of the biosimilar can be used for intravenous administration.

Rituximab is administrated together with premedication: 1 g paracetamol, an antihistaminic (either cetirizine 10 mg PO or levocetirizine 5 mg PO) and 125 mg methylprednisolone IV in 50 ml NaCl 0.9%; or equivalent. Rituximab can be used in combination with another csDMARD and/or glucocorticoids. Depending on the trial arm, retreatment with rituximab will be done based on DAS28-CRP ≥3.2 (at least 24 weeks after the previous cycle, active control arm) or at a fixed interval every 24 weeks (experimental arm). The active control arm will receive rituximab cycles consisting of 1 infusion of 1000 mg and the experimental arm will taper the rituximab dose according to a predefined schedule (see 2.4.2), with a maximum of 1 x 1000 mg IV and a minimum of 1 x 200 mg IV. The tapered doses used in group 2 have shown to be effective in previous studies (11).

All medications used in this protocol have Marketing Authorization (MA) to be used in RA. As the IMP will be prescribed on-label within this trial, they will be used within the MA.

Patients who are randomised to the active control arm (tapering based on interval) will receive rituximab in line with the Belgian reimbursement criteria.
It is possible that patients randomised to the experimental arm (tapering based on disease activity-guided dose reduction) will not fulfil Belgian reimbursement criteria, as retreatment will take place at fixed time points of 24 weeks, even if the DAS28-score is <3.2. For administration of rituximab in those situations, the pharmaceutical company Celltrion Healthcare provides support for provision of rituximab to the hospital pharmacies of University Hospitals Leuven and Cliniques Universitaires Saint-Luc Bruxelles. As a consequence, patients who are not in follow-up at either one of these two centres and require an administration of rituximab outside of the Belgian reimbursement criteria will receive rituximab at University Hospitals Leuven Campus Gasthuisberg.

5.2 Drug Accountability

Rituximab will be stored at temperatures between 2°C – 8°C in outer packaging protected from light, in accordance with the SmPC. All medications used in this trial will be prepared by the corresponding hospital or private practice. The SmPC of rituximab can be found at http://bijsluiters.fagg-afmps.be/ or www.ema.europa.eu.

All patients included in this study will have received previous approval by the RIZIV/INAMI for use of rituximab for RA. In case of loss of disease control at least 24 weeks after a previous infusion, prolongation of reimbursement for rituximab will be applied for according to the Belgian criteria (i.e. DAS28-CRP ≥3.2).

The pharmaceutical company Celltrion Healthcare provides support for the provision of rituximab according to the protocol but outside the reimbursement criteria to the hospital pharmacies of University Hospitals Leuven and Cliniques Universitaires Saint-Luc Bruxelles. Patients from the experimental arm (tapering according to disease-activity guided dose reduction) who are not in follow-up at either University Hospitals Leuven or Cliniques Universitaires Saint-Luc Bruxelles will receive rituximab at the University Hospitals Leuven (Campus Gasthuisberg) in case they have a DAS28-CRP score <3.2 at the week 24 interval visit and therefore do not fulfill the Belgian reimbursement criteria.

Day-care hospitalizations and administrations of rituximab are considered to be standard of care when the Belgian reimbursement criteria are fulfilled, regardless of the study arm, and will be charged to the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI).

5.3 Concomitant / Prohibited Medication / Treatment

As previously stated in the exclusion criteria (see 3.2), no concomitant therapy with other bDMARDs aside from rituximab, or tsDMARDs are allowed throughout this trial. If either one of these medications are used, it is considered to be a protocol violation and will result in Trial discontinuation.

Concomitant use of glucorticoids and csDMARDs is allowed. However, the dosage of glucocorticoids should be kept as stable as possible, and in case of chronic use the dose should not exceed the baseline dose between week 8 and 12 and between week 20 and week 24 following the last rituximab infusion. In addition, csDMARDs should be at a stable dose for at least 4 weeks prior to baseline.

5.4 Rescue Medication

In the case of insufficient control of disease activity despite treatment with rituximab in accordance with the study protocol, (temporary) use/bridging of glucocorticoids is advised until the next infusion. The dosage of glucocorticoids should be kept as stable as possible and in case of chronic use the dose should not exceed the baseline dose between week 8 and 12 and between week 20 and week 24 following the last RTX infusion.

If this does not result in sufficient control of disease activity, a change of DMARD therapy may be considered, in accordance with the standard of care. If this action results in a switch to a bDMARD other than rituximab, or a switch to a tsDMARD, this will count to a protocol violation, resulting in Trial discontinuation.

6 Safety reporting

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during a trial, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

6.1.2 Adverse Reaction (AR) or Adverse Drug Reaction (ADR)

An AR is any noxious and unintended responses to an investigational medicinal product or to a trial and, when an investigational product is concerned, related to any dose administered.

6.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Inpatient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- A life-threatening* experience
- Death
- Important medical events may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

** The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.*

6.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product reference safety information (e.g. investigator's brochure for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product).

6.1.5 Adverse Events of Special Interest (AESI)

AESI are defined by the protocol as major cardiac and cerebrovascular events, non-traumatic bone fractures, malignancies, serious infections, COVID19-infections, a negative outcome of a pregnancy, and death.

6.1.6 Unexpected events that might influence the benefit-risk balance

The following unexpected events that might materially influence the benefit-risk balance, and which are not considered SUSARs, should be reported to the Member States:

- Increase in rate of occurrence of expected serious adverse events which may be clinically important
- Significant hazard to patient population

Unexpected events that are likely to seriously affect the benefit-risk balance and emergency safety measures which have been taken to protect the subjects are considered urgent safety measures.

6.2 Adverse Events that do not require reporting

In general, the following should not be recorded as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness). However, in case the pre-existing condition appears to be enhanced by the IMP, this should be reported as an AE.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

In addition, the following AEs should not be recorded in the eCRF:

- (S)AEs that are not possibly related to RA or the treatment of RA.
- Laboratory findings that are not deemed clinically significant.
- Laboratory findings that are deemed clinically significant, but are not possiblty related to RA or the treatment of RA.

An AE that should not be recorded in the eCRF according to the above criteria may nonetheless be reported if deemed indicated/necessary according to medical judgement.

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and, if appropriate as stated in the previous sections, in the eCRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE to be recorded in the eCRF:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the Investigational Medicinal Product (IMP) and/or Trial procedures
- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
  - *None* – An AE which is not related to the IMP or the Trial
  - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
  - *Possible* – An AE which might be due to the use of the IMP or Trial participation. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
  - *Probable* - An AE which might be due to the use of the IMP or Trial participation. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
  - *Definitely* – An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

6.3.2 Timelines for reporting

- After informed consent has been obtained but prior to initiation of Trial treatment, only adverse events caused by a Trial specific procedure and AESI should be recorded in the eCRF.
- After initiation of trial treatment, adverse events will be recorded in the eCRF as follows:
    - All AEs and SAEs related to RA or the treatment of RA/ trial medication, or deemed signicifcant based on medical judgement and AESIs will be reported until 30 days after last trial treatment administration or until last follow-up visit (whichever occurs first).

All serious AE/ARs and AESIs as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. In this case, after assessment and recording of the seriousness criteria in the eCRF, a SAE-form should be completed by the investigator. This SAE report will then be electronically signed and automatically emailed to the Department of Rheumatology of the University Hospitals Leuven. In case the electronic system is unavailable, a paper copy can be used. Once the eCRF is again available the information should be completed as soon as possible.

The investigator or site must complete the SAE-form within 24 hours (immediately) after becoming aware of the SAE, SAR or AESI. If the investigator is not available at the time of reporting, the report without causality and expectedness will be provided by site staff within the prescribed timeframe and must be followed-up by medical assessment as soon as possible thereafter. Follow-up information must be submitted promptly within the electronic template available in the eCRF.

Unexpected events affecting the benefit-risk balance must be reported ad hoc to the sponsor as soon as possible after becoming aware of the event.

Staff of the coordinating center (University Hospitals Leuven) will be available to provide guidance regarding (S)AE, SAR or AESI reporting.

Contact Information:
Johan Joly, project manager (PM)
Department of Rheumatology, University Hospitals Leuven
Herestraat 49, B-3000 Leuven, Belgium
Telephone number: [redacted]
Fax number: [redacted]
Email address: [redacted]

In case the PM is not available, the CI can be contacted instead:
Prof. Dr. Patrick Verschueren
Department of Rheumatology, University Hospitals Leuven
Herestraat 49, B-3000 Leuven, Belgium
Telephone number: [redacted]
Fax number: [redacted]
Email address: [redacted]

6.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the eCRF. The worst case severity and seriousness of an event must be kept throughout the trial.

Follow-up information for SAEs, SARs and AESIs should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs, ARs or AESIs which subsequently become serious.

- All *serious AEs, ARs and AESIs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due

to the serious AE, AR or AESIs) and until all related queries have been resolved, or until end of trial (whichever occurs first).

- *Non-serious AEs* must be followed up until the patient's last Trial visit, and until all related queries have been resolved.

SAEs after the end of the Trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMP or the Trial after the subject has ended the Trial, the Investigator should report this SAE within the same timelines as for SAEs during the Trial.

6.3.4 Pregnancy and Lactation

As treatment with rituximab is contraindicated in pregnancy, female patients who are pregnant or who wish to become pregnant are excluded from this study (see 3.2 for exclusion criteria). In line with the SmPC of Mabthera, Rixathon, Ruxience and Truxima, woman of childbearing potential should use effective contraceptive methods during and for 12 months after treatment with rituximab. Furthermore, breastfeeding is not recommended during treatment with rituximab until 6 months after the last administration of rituximab. Contraceptive measures and advice on breastfeeding will be discussed with female patients, as part of the standard of care.

Female subjects must be instructed to notify the Investigator if they do become pregnant during the trial. The Investigator must report any pregnancy in subjects who have received Trial product(s) to the Sponsor within 24 hours of becoming aware of the event. Pregnant patients will not receive further administations of rituximab, but will be followed up for safety reasons.

6.3.5 Technical Complaints

Technical complaints should be reported to the Marketing Authorisation Holder (eg. change in color, unequal sizes, broken vials/pills, sedimentation, …).

6.3.6 Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, the IMP, Trial procedure or is an unrelated event).

6.4 Reporting requirements to the Member states

The Investigator is responsible for ensuring that all safety events are recorded in the eCRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SARs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to the Investigators.

6.4.1 Sponsor's reporting of Suspected Unexpected Serious Adverse Reactions (=SUSARs)

After receiving the SAE report form with causality (relationship) assessment from the Investigator, the sponsor can also make a causality assessment. The term SADR (Serious Adverse Drug Reaction) is to be used whenever either the Investigator or the Sponsor deems the SAE as possibly or probably related to the IMP.

The Sponsor must evaluate (and document the evaluation of) the expectedness for each SADR against the Reference Safety Information, e.g. in the Investigator's Brochure or applicable product information. In case the event is Unexpected (= a SUSAR) it must be reported by the Sponsor to Member states (through the EudraVigilance database) and other participating Investigators within the following timelines:

- **7** calendar days if fatal or life-threatening event (follow-up information within an additional 8 days)
- **15** calendar days if non-fatal or non-life-threatening event (follow-up information as soon as possible)

Other participating investigators should be notified of safety profile changes via investigators' letters, not of individual SUSAR reports.

For reporting to the EudraVigilance database, all information related to the SUSAR should be provided by the Sponsor to the CTC of UZ Leuven as soon as possible. Contact details: CTC.safety@uzleuven.be and tel. 016 34 19 98.

6.4.2 Sponsor's reporting of unexpected events that might influence the benefit-risk balance

The sponsor has the obligation to notify the Member states through the EU portal (CTIS) for all unexpected events, that are not SUSARs, and which affect the benefit-risk balance within the following timelines:

- **7** calendar days for serious urgent safety measures
- **15** calendar days for other events

6.4.3 Temporary halt or early termination of the clinical Trial for reasons of subject safety

The sponsor has the obligation to notify the concerned Member States through the EU portal (CTIS) in case of early termination of the clinical Trial for safety reasons. The notification (containing information on the reasons for such action and follow-up measures) should be made immediately, but not later than 15 calendar days after the temporary halt or termination.

6.4.4 Annual reporting

The Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a Development Safety Update Report (DSUR) through the EU portal (CTIS), taking into account all new available safety information received during the reporting period.

6.4.5 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	(S)AE (related to RA or the treatment of RA, or based on medical judgement)	AE form	sponsor	as defined in protocol
	AESI	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event)
	Serious AR	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event)
	death	SAE form	sponsor	asap
	Unexpected events affecting the benefit-risk balance	ad hoc	sponsor	asap
Sponsor	SUSAR	EudraVigilance	**unblinded:** - Member states (via EudraVigilance)	asap, but no later than

			- MAH **Safety profile changes:** - PIs of participating sites	- 7 calendar days (in case of fatal or life-threatening SUSAR) - 15 calendar days (other SUSAR)
	Unexpected events affecting the benefit-risk balance	EU portal (CTIS)	EU portal (CTIS)	asap, but not later than - 7 calendars days (serious urgent safety measures) - 15 calendar days (other unexpected events)
	Annual Progress/ Development Safety Update Report	DSUR template	EU portal (CTIS)	annually

6.5 Trial Steering Committee (TSC)

The TSC will be composed of the coordinating investigator, the project manager, the trial data manager, 2 experts and a patient research partner.

The TSC will overview the Trial on regular meetings (3x/year during 3 years) based on reports prepared by the CI and PM. This committee will monitor the course of the trial logistically, but also in terms of safety, and will advise the CI and PM if required.

All remarks and decisions of the TSC will be documented in a report that will be stored at the department of Rheumatology, University Hospitals Leuven and will be shared with the Sponsor. The summary will be shared with all participating investigators.

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

7.1 Sample Size Calculation for the Primary Outcome

This trial is a superiority trial aiming to investigate the long-term patient-reported impact of rituximab tapering by reducing the dose of rituximab compared to tapering by prolonging the interval. The primary outcome is based on the AUC of the RAID score over the whole duration of the trial, namely 104 weeks. We expect that patients who taper treatment based on disease activity-guided dose reduction and fixed retreatment will do better compared to tapering based on interval prolongation. Therefore, we consider a reduction in RAID AUC of at least 20% over 104 weeks of treatment, as an important decrease of the overall disease burden. We used the data of Salaffi et al. (17) as the reference data for sample size calculation. In this study 151 patients with RA were in remission and had a median RAID score of 2.43 (95% confidence interval (C.I.) 2.26 – 2.63) and 111 patients were in low disease activity with a median RAID score of 3.35 (95% C.I. 3.20 – 3.53) (14). The data of the patients in remission and low disease activity (LDA) were pooled together to yield the RAID AUC for the sample size calculation.

Patients in remission:

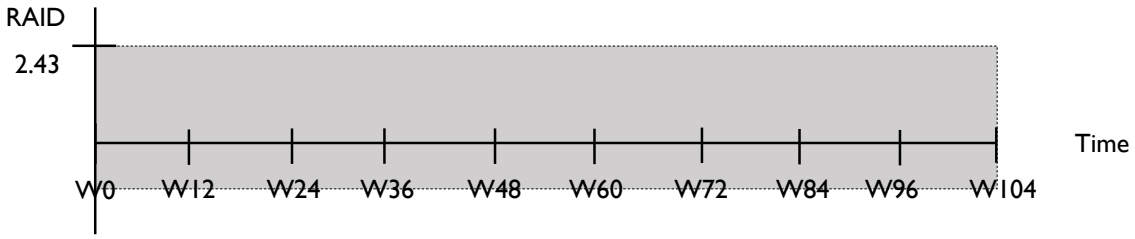
Number of patients	151
Median RAID score	2.43
95% C.I.	2.26 – 2.63

Calculation of standard deviation (SD) from the 95% C.I.:

$$SD = \sqrt{number\ patients} * \frac{(upper\ limit\ CI\ - lower\ limit\ CI)}{3.92}$$

$$SD = \sqrt{151} * \frac{(2.63 - 2.26)}{3.92} = 1.16$$

Calculation of the RAID AUC:



$$AUC = \frac{1}{2} * (value1 + value2) * (time2\ - time1)$$

Median RAID AUC:

$$AUC = 0.5\ * (2.43 + 2.43) * (104\ - 0) = 252.72$$

SD RAID AUC:

$$AUC = 0.5\ * (1.16 + 1.16) * (104\ - 0) = 120.64$$

Patients in LDA:

Number of patients	111
Median RAID score	3.35
95% C.I.	3.20 – 3.53

Calculation of SD from the 95% C.I.:

$$SD = \sqrt{number\ patients} * \frac{(upper\ limit\ CI\ - lower\ limit\ CI)}{3.92}$$

$$SD = \sqrt{111} * \frac{(3.53 - 3.20)}{3.92} = 0.89$$

Calculation of AUC:

$$AUC = \frac{1}{2} * (value1 + value2) * (time2\ - time1)$$

Media RAID AUC:

$$AUC = 0.5\ * (3.35 + 3.35) * (104\ - 0) = 348.4$$

SD RAID AUC:

$$AUC = 0.5\ * (0.89 + 0.89) * (104\ - 0) = 92.56$$

Pooling remission and LDA:

	Group 1 (RA patients in remission)	**Group 2 (RA patients in LDA)**
Sample size	N_1 (151)	N_2 (111)
Median	M_1 (252.72)	M_2 (348.4)
Standard Deviation (SD)	SD_1 (120.64)	SD_2 (92.56)

Combined sample size:

$$N_1 + N_2$$
$$= 151 + 111 = 262$$

Combined mean:

$$\frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$
$$= \frac{151 * 252.72 + 111 * 348.4}{151 + 111} = 293.26$$

Combined SD:

$$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$
$$= \sqrt{\frac{(151 - 1)120.64^2 + (111 - 1)92.56^2 + \frac{151 * 111}{151 + 111}(252.72^2 + 348.4^2 - 2 * 252.72 * 348.4)}{151 + 111 - 1}}$$
$$= 119.24$$

This yielded a pooled mean RAID AUC of 293.26 (SD 119.24) over a period of 104 weeks.

Calculation of the 20% superiority margin:

Pooled mean	293.26
- 20% margin	293.26 * 0.8 = 234.60

A 20% reduction in RAID AUC would reflect a mean RAID AUC of 234.60.

For a superiority design, with a two-sided alpha of 0.05, the null and alternative hypothesis are:

Null hypothesis: Tapering rituximab based on dose reduction leads to the same RAID AUC compared to tapering rituximab based on interval prolongation in patients with rheumatoid arthritis. H_0: $\delta = 0$

Alternative hypothesis: Tapering rituximab based on dose reduction can be considered superior to tapering based on interval prolongation in patients with rheumatoid arthritis. H_1: $\delta \neq 0$

These are the parameters taken into account for the sample size calculation (using a web-based sample size calculator, https://riskcalc.org/samplesize/):

- Calculation of superiority
- Allocation 1:1
- Power of 0.80
- Alpha of 0.05 (two-sided)
- Primary outcome is RAID AUC over 104 weeks, with a mean AUC of 293.26 (SD 119.24) for the reference group (based on data of Salaffi et al. (17))
- We assumed a superiority margin of 20%, resulting in a mean outcome of 234.60
- Drop-out of 20% over the duration of the trial

According to the sample size calculation for a superiority trial, to have a 80% chance of detecting a decrease in primary outcome measure from 293.26 in the control group to 234.60 in the experimental group with a significance level of 5% and a drop-out rate of 20%, 134 patients are required. This means that 67 patients must be included in group 1 and 67 patients in group 2.

In this randomised controlled trial, an intention to treat, a per protocol and a safety analysis will be performed.

Intention to treat analysis: This includes all randomised patients and they will be analysed according to the treatment they are randomised to.

Per protocol analysis: This includes all randomised patients that followed the randomised treatment regimen and received the rituximab administrations according to the protocol.

Safety analysis: This includes all treated patients, while taking into account the treatment that they actually received. Any subject randomised into the study that received at least one dose of study drug will be included in this analysis.

7.2 Sample Size Calculation for the Main Secondary Outcome

The randomised controlled SMART trial of Mariette et al. (3) was a non-inferiority trial that examined 2 dosing regimens (2x 1000mg IV and 1x 1000mg IV) over a duration of 2 years. All patients received in the beginning of the trial the standard dose of 2x 1000mg IV and were thereafter randomised to one of the 2 dosing regimens. Their primary outcome was DAS28-CRP AUC over 104 weeks with a non-inferiority margin of 20%. This trial was able to show a non-inferiority of the lower dose, with a mean AUC DAS28-CRP of 2761 (SD 508) for the 1x 1000mg arm and 2666 (SD 490) for the 2x 1000mg arm, resulting in an adjusted difference of 51.4 (95% CI -131.22 – 233.98). We used the 1x 1000 mg arm as a reference arm for our sample size calculation of the main secondary outcome.
A reduction in DAS28-CRP AUC of more than 20% over the first 104 weeks of treatment would reflect an important decrease of the overall impact of disease.
These were the parameters taken into account for the sample size calculation:

- Calculation of superiority
- Allocation 1:1
- Power of 0.80
- Alpha of 0.05 (two-sided)
- Main secondary outcome is DAS28-CRP AUC after 104 weeks, with a mean AUC of 2761 (SD 508) for the reference group treated with 1x 1000 mg (based on the SMART trial of Mariette et al.).
- We assumed a superiority margin of 20%, resulting in a mean outcome of 2208.8.
- Drop-out of 20% over the trial duration.

According to the sample size calculation for the main secondary outcome, to have a 80% chance of detecting a decrease in main secondary outcome measure from 2761 in the control group to 2208.8 in the experimental group with a significance level of 5% and a drop-out rate of 20%, 28 patients are required. This means that 14 patients must be included in group 1 and 14 patients in group 2.

7.3 Statistical Analysis

7.3.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Difference in RAID AUC over 2 years in the two trial arms will be evaluated with an independent t-test (parametric test) or Mann-Whitney U test (non-parametric test) depending on distribution of the RAID AUC. A parametric tests will be used if data comply to a normal distribution. When this is not the case, a non-parametric test will be used.
Main Secondary	The difference in DAS28-CRP AUC over 2 years in the two trial arms will be evaluated with an independent t-test or Mann-Whitney U test depending on distribution of the DAS28-CRP AUC.
Secondary	Demographic data will be analysed descriptively. Categorical variables will be based on numbers and proportions. Continuous variables will be analysed by mean, medians, standard deviations and IQR depending on the data distribution. The difference in cumulative dose of rituximab over 104 weeks will be compared between the two trial arms using an independent t-test or Mann-Whitney U test, depending on the distribution of data.

	The difference in cumulative dose of glucocorticoids over 104 weeks will be compared between the two trial arms using an independent t-test or Mann-Whitney U test, depending on the distribution. The proportion of patients who tapered their rituximab dose to 200 or 500 mg in the group that tapered based on disease activity-guided dose reduction (group 2) over 104 weeks will be analysed descriptively. The mean/median interval between rituximab administrations in the group that tapered based on interval prolongation (group 1) will be analysed descriptively. The proportion of patients achieving a good/moderate EULAR response 12 weeks after a rituximab infusion will be analysed descriptively. A good EULAR response is defined as a decrease in DAS28-CRP >1.2 with present DAS28-CRP ≤3.2. A moderate EULAR response is defined as a decrease in DAS28-CRP >0.6 to ≤1.2 with present DAS28-CRP ≤5.1, or a decrease in DAS28-CRP >1.2 with present DAS28-CRP >3.2. The maintenance of disease control (i.e. DAS28-CRP ≤3.2) will be determined using Kaplan-Meier survival analysis. The two groups will be compared with a log-rank test. The difference in SDAI AUC over 2 years in the two arms will be evaluated with an independent t-test or Mann-Whitney U test depending on distribution of the SDAI AUC. The rituximab drug retention rate will be compared between the two arms using a Kaplan-Meier survival analysis and log-rank test. The proportion of patients with serious adverse events/reactions will be compared between the two groups using a Chi squared test. The proportion of patients with (serious) infections will be compared between the two groups using a Chi squared test.
Exploratory	A correlations matrix will be calculated using appropriate methods (e.g. Pearson, Spearman) between HAQ and possible confounders (e.g. age, disease duration). The changes over time of the HAQ will be determined using a linear mixed model with as dependent variable the HAQ over time and as independent variables clinical relevant variables, such as age, gender, disease duration, previous number of rituximab cycles, and treatment arm. Furthermore, interactions between the independent variables will be checked. The same procedure will be done with VAS pain, VAS fatigue, and ASES as dependent variable. $CD19^+$ counts, memory B-cells and immunoglobulin counts, professional and vocational participation, and quality of life will first be analysed descriptively. If differences between the groups are shown by a descriptive analysis and if feasible, a data driven analysis may be carried out.

7.3.2 Other Analyses

A health economic analysis might be conducted depending on the results of the primary outcome, but will not fit in the scope of the present study. Quality of life (EQ5D) data and information on professional and vocational participation (Work Productivity and Activity Impairment (WPAI) questionnaire) are systematically collected in this trial for this reason. In future research, differences in costs, disease activity

and quality-adjusted life years (QALYs) could be compared between the two groups using an independent t-test of Mann-Whitney U test, depending on the distribution of the data. An incremental cost-effectiveness ratio and incremental net monetary benefit could be calculated between the disease activity-guided dose reduction group and interval prolongation group.

7.4 Final Database Lock

The final database lock is planned after the last visit of the last patient participating in the Trial, after completion of all eCRFs and monitoring.

8 Data handling

Data handling and data flows for the Trial are summarized below and will be described in more detail in the Trial-specific Data Management Plan (DMP).

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection tools and source document identification

Source data will be collected and recorded in the study participants' files/medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfil the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore source documentation will be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of relevant adverse events and follow-up of adverse events as required by the protocol; administration of medication as prescribed for the study and relevant concomitant medication will be documented in the source data; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents could be reviewed by the clinical team to ensure that they are accurate and complete.

As defined in section 1.52 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes,…).

8.1.1.2 Case Report Form (CRF)

The CRF used in this study is created in REDCap and will be provided for each subject in electronic format (eCRF). The study data will be transcribed on a regular basis by study personnel (i.e. the principal investigator and/or clinical research associates of the participating site where the patient was included for study) from the source documents onto an eCRF in a pseudonymized manner, and transmitted in a secure manner to the CI within the timeframe agreed upon between CI and the participating sites.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets (including but not limited to copies of the eCRF) will become part of the study participant's source documentation. All data relating to the study must be recorded in eCRFs prepared by the investigator. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. Proper audit trails are available to demonstrate the validity of the trial data. A copy of the completed eCRFs will be archived at the study site.

8.1.1.3 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any eCRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.4 Data Management

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed.

8.1.1.5 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2 legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the GDPR and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed eCRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled “Essential Documents for the Conduct of a Clinical Trial”, and as specified by applicable regulatory requirement(s).
The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such eCRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

UZ Leuven Clinical Trial Center (CTC) performs a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as 'higher risk', as the potential risks associated to study procedures and protocol design are higher to that of standard medical care since the standard dosage schedule treatment of the patient population might be modified in comparison with the standard care treatment duration. However:

- The IMP is already widely used as standard treatment for rheumatoid arthritis in the appointed goal population.
- The study-specific intervention will be the comparison of the long-term patient-reported impact of rituximab tapering based on disease activity-guided dose reduction compared to tapering based on interval prolongation in patients with rheumatoid arthritis. Hence, the tapering of the dosage is not the study intervention itself.
- This is an open-label trial, no placebo/blinding procedures are involved.
- The study design is fairly straightforward and minimal study-specific interventions will take place, as majority of the study procedures are part of the standard care of the patient population.

Hence, based on the above risk assessment and as permitted by ICH-GCP (r2) section 5.0.4, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by ICH-GCP E6(r2) §1.38) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data. Nonetheless, within the Department of Rheumatology of University Hospitals Leuven risk-based monitoring will be performed from a distance on a data management level. All possible measures will be taken to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in ICH-GCP(r2).

8.4 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final eCRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the eCRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any modifications thereto, the final Clinical Study Report (CSR) and the Trial database) according to ICH-GCP E6(R2). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 CA/EC review & reports

Before the start of the Trial, this protocol and other related documents (e.g. ICF, advertisements, IB, etc.) will be submitted through the CTIS portal for review to the CA/EC for Trial authorization. The Trial shall not commence until such approvals have been obtained and until other relevant essential Trial documents, such as duly signed contract agreements, evidence of adequate Trial financing etc. are in place.

It is the responsibility of the CI to produce the Development Update Safety Report (DSUR) and submit to the EC/CA through CTIS within 30 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

The CI shall notify the CA/EC of the end of the Trial using the CTIS portal. Should the Trial be temporarily suspended or, ended prematurely, the CI will notify the CA/EC and include the reasons for suspension/premature termination within 15 days of the decision. The CI will submit a final report with the results of the study, including any publications/abstracts, to the CA/EC within 1 year of trial termination or within 6 months for paediatric Trials. The CTIS portal will be used for communication with the CA/EC of all participating Member States.

9.2 Peer review

This Trial protocol was peer reviewed by 2 independent patient research partners (PRPs) and one emeritus professor in Rheumatology.

9.3 Regulatory Compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for the CTR and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use and with the GDPR, the relevant Belgian laws implementing the GDPR, including the Belgian Law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data and the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

9.4 Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible. The coordinating investigator and all principal investigators are currently certified in GCP practice and agree to renew training should their certification expire during the course of this study. The CI and PIs vouch for adequate training on this matter of study personnel/CRAs.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the DSUR). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

9.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR including the Belgian Law of July 30th 2018 on the protection of natural persons with regard to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area (which is not intented), safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Art 12 of the Belgian Law of May 7th 2017 on clinical Trials with medicinal products for human use applies. Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 12 of the said law.

9.7 Modifications

During the Trial the Sponsor may modify the Trial. It is the Sponsor's responsibility to assess whether a modification is substantial or non-substantial, a change relevant to the the supervision of the Trial, or whether a substantial modification leads to changes in the Trial to an extent that it has to be considered as a completely new clinical trial.

A "substantial modification" is defined as any change of the Trial which is made after a decision is issued on a previously submitted application and that is likely to substantially impact the subjects' safety or rights or the reliability and robustness of the data generated in the Trial. A non exhaustive list of examples of substantial and non-substantial modifications is available in Annex III of the CTR Q&A document in Eudralex volume 10. The Sponsor shall submit the substantial modifications in CTIS which will be evaluated by the CA/EC. A substantial modification may only be implemented if it has been approved by the CA/EC with no prejudice to the right of Sponsor and the Principal Investigator to take urgent safety measures without awaiting prior authorisation. In that case, the event and the measures taken should be reported in CTIS without undue delay but no later than 7 days from the date the measures have been taken.

A "change which is not a substantial modification but relevant to the supervision of the Trial by the CA/EC" shall be permanently updated in CTIS by the Sponsor, in line with article 81(9) of the CTR. An example of such change is an update of sponsor or CRO contact details.

A "non-substantial modification" is any change outside the scope of a substantial modification and irrelevant to the supervision of the Trial. A non-substantial modification should not be notified as such. These changes

should be implemented during the next substantial modification. Non-substantial modifications need to be listed and identified as such in the cover letter of the substantial modification application.

9.8 Post-Trial activities

As explained in section 7.3.2, future health economic analysis may be considered depending on the result of the primary outcome of the present study.

If participants from either study arm are in need of a subsequent treatment with rituximab after termination of this Trial, they will be treated according to the Belgian reimbursement criteria for treatment with rituximab in RA.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

Every participating centre that includes at least one patient in this trial, will be assured one authorship.

As this is a multicentre Trial, it is anticipated that the primary results of the overall Trial shall be published in a multicentre publication. Participating Sites are not allowed to publish any subset data or results from the Trial prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least thirty (30) calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 Joint Commission International (JCI)

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by the Sponsor in its regular activities, and in accordance with JCI standards, the Sponsor shall comply with the following obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Trial; (b) the Sponsor will ensure that multi-center Trial reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsor will not grant

incentives, other than standard compensations and reimbursement of costs, to Trial participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Trial and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the Trial participants in accordance with all applicable laws.

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APPENDICES

14 Appendix I: Clinical trial protocol history

Version	Date	Author(s)	Comments
1.0	23/06/20	DB	Initial draft of the protocol.
1.1	17/02/22	DB	Adaptations after discussing the trial design in depth.
1.2	7/04/22	DB, JJ, PV and RW	Implementation of suggestions of PV, RW and JJ.
1.3	06/09/2022	DB	Updated information on rituximab samples and general adaptations.
1.4	09/11/2022	DB, PV, EDM	Incorporation of suggestions of the research team.
1.5	03/02/2023	EDM, PV, DB, JJ	Update on monitoring of trial.
1.6	25/04/2023	EDM, PV, JJ, DB	Update on study protocol document lay-out, financial compensation of trial participants, rescue medication, interim analysis, trial steering committee and post-trial activities.
1.7	30/06/2023	EDM, PV, JJ	Update on sections IMP and Safety Reporting, TSC, third party sponsoring, and exclusion criteria.
1.8	09/08/2023	EDM, PV, JJ	Update on compliance with GDPR and GCP, financial compensation of trial participants, definition of study procedures within standards of care, and secondary outcomes.
2.0	13/11/2023	EDM, PV, JJ	Update on the study's exclusion criteria, secondary and explory outcomes/endpoints, monitoring of patients after trial discontinuation, definition of the end of the trial, assessment of potential risks associated with tapering strategies, and information regarding pregnancy and breastfeeding.

DB: Delphine Bertrand, JJ: Johan Joly, PV: Patrick Verschueren, RW: Rene Westhovens, EDM: Elias De Meyst

15 Appendix 2: Data Processing Annex (DPA) between Sponsor and Participating Site(s)

Definitions:

- "Protocol" means the document entitled Tapering of rituximab based on interval prolongation compared to disease activity-guided dose reduction in patients with rheumatoid arthritis: Protocol of the RITUXERA Trial (version 2.0) containing the details of the academic Trial as developed by the Sponsor and approved by the relevant CA/EC.
- "Sponsor" means University Hospitals Leuven (UZ Leuven).
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
    a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
    b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
    (i) accidentally or unlawfully destroyed, lost or altered,
    (ii) disclosed or made available without authorization, or
    (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:
    (i) the current state of the art,
    (ii) the cost of their implementation, and
    (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)
7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.
8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.
9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.
10. The Data Processor must without undue delay in writing notify the Data Controller about:
    (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
    (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
    (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.
11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:
    (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
    (ii) the likely consequences of the Personal Data breach;
    (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by

implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.

14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.

16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.

17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.