



## Clinical trial results:

### Efficacy of Rituximab at low doses in Multiple Sclerosis – A prospective, randomized, double-blind, active controlled, pilo trial

#### Summary

EudraCT number	2017-000426-35
Trial protocol	AT
Global end of trial date	31 January 2025

#### Results information

Result version number	v1 (current)
This version publication date	16 March 2025
First version publication date	16 March 2025

#### Trial information

##### Trial identification

Sponsor protocol code	1.0
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Office of the Dept. of Neurology, Medical University of Vienna - Department of Neurology, +43 1 4040031230, neurologie-sekretariat@meduniwien.ac.at
Scientific contact	Office of the Dept. of Neurology, Medical University of Vienna - Department of Neurology, +43 1 4040031230, neurologie-sekretariat@meduniwien.ac.at

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2025
Global end of trial reached?	Yes
Global end of trial date	31 January 2025
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial is to investigate whether 100mg rituximab every 10-12 weeks are equally effective compared to other, currently used dosing regimens. This will be evaluated by the annualized relapse rate at 48 weeks

Protection of trial subjects:

Only patients with already existing treatment with rituximab or patients in whom physicians intended to use rituximab were included in the study. More frequent control visits were conducted compared to the clinical routine. Emergency treatment (additional doses) were possible in the interventional group.

Background therapy:

Regular treatment for Multiple was possible and this study did not interfere with the physicians decision to treat patients.

Evidence for comparator:

standard dose rituximab was the comparator. As mentioned only patients in whom physicians intended rituximab treatment were included to reduce the risks for participants.

Actual start date of recruitment	26 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	23

From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All 24 patients were recruited at the Department of Neurology, Medical University of Vienna, Austria, between 26.3.2019 and 5.8.2021.

### Pre-assignment

Screening details:

The study population consisted of patients with a diagnosis of MS and an already existing treatment with rituximab, or an intended treatment with rituximab. The plan was to recruit both, treatment naive and pretreated patients.

### Period 1

Period 1 title	Active Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Intervention

Arm description:

Treatment with 100mg Rituximab at week 0, 10-12, 20-24 and 30-36

Arm type	Experimental
Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100mg intravenous infusion over 60 minutes, after dilution of the appropriate amount to 20mL (Infusion speed 20mL/h) for the 100mg dose

<b>Arm title</b>	Control
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Arm description:

Standard dose rituximab 375mg/m<sup>2</sup> at Week 0 and Week 24

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 375mg/m<sup>2</sup> at Week 0 and at Week 24

<b>Number of subjects in period 1</b>	Intervention	Control
Started	16	8
Completed	12	7
Not completed	4	1
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	-

## Baseline characteristics

### Reporting groups

Reporting group title	Intervention
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Reporting group description:

Treatment with 100mg Rituximab at week 0, 10-12, 20-24 and 30-36

Reporting group title	Control
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Reporting group description:

Standard dose rituximab 375mg/m2 at Week 0 and Week 24

Reporting group values	Intervention	Control	Total
Number of subjects	16	8	24
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	8	23
From 65-84 years	1	0	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	43.4	38.4	-
standard deviation	± 10.3	± 12.1	-
Gender categorical			
Units: Subjects			
Female	9	4	13
Male	7	4	11
pretreatment			
Number of patients pretreated with rituximab			
Units: Subjects			
pretreatment	6	3	9
treatment-naive	10	5	15

### Subject analysis sets

Subject analysis set title	mITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All patients who received at least one infusion of rituximab

<b>Reporting group values</b>	mITT		
Number of subjects	24		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	23		
From 65-84 years	1		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	41.7		
standard deviation	± 10.9		
Gender categorical			
Units: Subjects			
Female	11		
Male	13		
pretreatment			
Number of patients pretreated with rituximab			
Units: Subjects			
pretreatment	9		
treatment-naive	15		

## End points

### End points reporting groups

Reporting group title	Intervention
Reporting group description: Treatment with 100mg Rituximab at week 0, 10-12, 20-24 and 30-36	

Reporting group title	Control
Reporting group description: Standard dose rituximab 375mg/m <sup>2</sup> at Week 0 and Week 24	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients who received at least one infusion of rituximab	

### Primary: CD20+ suppression

End point title	CD20+ suppression
End point description: The primary endpoint are CD20+ cell counts at week 48 -successful suppression is defined as an >90% reduction from baseline	
End point type	Primary
End point timeframe: week 48	

End point values	Intervention	Control	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	7	19	
Units: subjects				
successful suppression	10	6	16	
unsuccessful suppression	2	1	3	

### Statistical analyses

Statistical analysis title	primary endpoint analysis Intervention
Statistical analysis description: Mean and 95% confidence intervals, a descriptive comparison of the control group and the intervention group is performed in a pilot non-inferiority study	
Comparison groups	Intervention v Control



Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	mean (%) and 95% CI
Point estimate	83
Confidence interval	
level	95 %
sides	2-sided
lower limit	61
upper limit	100

Notes:

[1] - pilot study, not powered for non-inferiority/superiority

<b>Statistical analysis title</b>	Primary Endpoint Analysis Control group
Statistical analysis description:	
Mean and 95% confidence intervals, a descriptive comparison of the control group and the intervention group is performed in a pilot non-inferiority study	
Comparison groups	Control v Intervention
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
Method	95% confidence intervals
Parameter estimate	mean (%) and 95% Confidence Intervals
Point estimate	86
Confidence interval	
level	95 %
sides	2-sided
lower limit	58
upper limit	100

Notes:

[2] - pilot study, not powered for non-inferiority/superiority

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening to End of Study Visit (approximately 48 weeks)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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### Reporting groups

Reporting group title	Intervention Group
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Reporting group description:

all patients receiving low-dose rituximab: 100mg at week 0, week 10-12, week 20-24, week 30-36

Reporting group title	Control Group
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Reporting group description:

patients receiving standard dose rituximab 375mg/m<sup>2</sup> at week 0 and 24

Serious adverse events	Intervention Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Cardiac disorders			
Myocardial infarction	Additional description: one patient suffered from myocardial infarction and was hospitalized		
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ulcus ventriculi	Additional description: Patient required surgery and was hospitalized		
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide	Additional description: suicide of a patient with a pre-existing depression		
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Intervention Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	4 / 8 (50.00%)	
Vascular disorders			
arterial hypertension			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
fatigue			
subjects affected / exposed	3 / 16 (18.75%)	2 / 8 (25.00%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
anterior cruciate ligament tear			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

COVID-19 subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 8 (12.50%) 1	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated because of recruitment problems during the covid-19 pandemic. The study would have required immunocompromised patients to visit the hospital more often than necessary, which was against their best interest.
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Notes: