Clinical trial results:
RItuximab versus FUmarate in Newly Diagnosed Multiple Sclerosis – RIFUND-MS
A randomized phase 3 study comparing Rituximab with Dimethyl Fumarate in early Relapsing-Remitting Multiple Sclerosis

Objective: To compare the efficacy of rituximab on the ability to prevent relapses in early RRMS and CIS compared with dimethyl fumarate (DMF), which is an approved first-line medication for RRMS today, using a phase 3 design.
Population: Patients with newly diagnosed RRMS or CIS with no more than 10 years disease duration (since diagnosis), 18 – 50 years of age and previously not treated with immunomodulating drugs OR treated with first-line injectables. Patients should display protocol-defined clinical or radiological disease activity during the preceding year before screening for inclusion.
Intervention: Treatment with rituximab (Mabthera®) with an initial dose of 1000 mg intravenously (iv) followed by 500 mg iv every six months.
Control: Treatment with DMF (Tecfidera®) 240 mg twice daily. The two treatments are randomised in a 1:1 proportion.
Outcome: Primary outcome is the relative risk of experiencing a relapse during the two–year period for either compound. As secondary endpoints worsening on neurological disability, magnetic-resonance imaging-defined disease activity and effect on cerebrospinal fluid biomarkers will be analysed. In addition, health-economic evaluations of using rituximab as first-line treatment for RRMS will be performed.

Summary

EudraCT number	2015-004116-38
Trial protocol	SE
Global end of trial date	21 April 2021
Results information	
Result version number	v1 (current)
This version publication date	20 April 2025
First version publication date	20 April 2025

Trial information

Trial identification	
Sponsor protocol code	RIFUND-MS
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Nobels väg 6, Solna, Sweden, 17177
Public contact	Department of Clinical Sciences, KI, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, 46 8123 555 33, anders.svenningsson@ki.se
Scientific contact	Department of Clinical Sciences, KI, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, 46 8123 555 33, anders.svenningsson@ki.se

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	08 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 April 2021
Global end of trial reached?	Yes
Global end of trial date	21 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is
• To compare clinical efficacy between rituximab administered according to a Swed-ish treatment schedule and dimethyl fumarate administered according to label

Protection of trial subjects:

All participants provided written informed consent at enrolment. The study protocol was approved by the ethical review board in Stockholm (reference number 2016/473-32) and the Swedish Medical Products Agency. The trial was monitored for compliance with Good Clinical Practice standards by an external monitor (Karolinska Trial Alliance) and was conducted in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	200
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial performed at 17 Swedish university and community hospitals. Eligible participants were aged 18–50 years with a diagnosis of relapsing-remitting multiple sclerosis, according to the prevailing McDonald criteria or with a demyelinating episode in conjunction with at least one asymptomatic lesion compatible with multiple sclerosis.

Pre-assignment

Screening details:

Key inclusion criteria for participants were: age 18–50 years; relapsing-remitting multiple sclerosis or clinically isolated syndrome according to prevailing McDonald criteria; 10 years or less since diagnosis; untreated or only exposed to interferons or glatiramer acetate; and with clinical or neuroradiological disease activity in the past year.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Data analyst, Assessor, Investigator[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	Dimethyl Fumarate (DMF)

Arm description:

oral dimethyl fumarate 240 mg twice daily

Arm type	Active comparator
Investigational medicinal product name	DIMETHYL FUMARATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

240 mg twice daily

Arm title	Rituximab

Arm description:

intravenous rituximab 1000 mg followed by 500 mg every 6 months

Arm type	Experimental
Investigational medicinal product name	RITUXIMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

intravenous rituximab 1000 mg followed by 500 mg every 6 months

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: All roles selected as blinded (investigator, data analyst, and assessor) are part of the researcher/staff group, which is in line with a single-blinded trial.
[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was a rater-blinded study where the investigator, data analyst, and assessor roles

were blinded. Participants were not blinded because we were unable to obtain placebo capsules identical to dimethyl fumarate.

Number of subjects in period 1	Dimethyl Fumarate (DMF)	Rituximab
Started	100	100
Completed	97	98
Not completed	3	2
Consent withdrawn by subject	1	1
Lost to follow-up	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description: oral dimethyl fumarate 240 mg twice daily	
Reporting group title	Rituximab
Reporting group description: intravenous rituximab 1000 mg followed by 500 mg every 6 months	

Reporting group values	Dimethyl Fumarate (DMF)	Rituximab	Total
Number of subjects	100	100	200
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)	100	100	200
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.7	34.1	
standard deviation	± 7.9	± 7.8	-
Gender categorical Units: Subjects			
Female	64	68	132
Male	36	32	68
number of treatment naïve patients Units: Subjects			
Treatment naive	95	98	193
Not treatment naive	5	2	7
Multiple sclerosis duration Units: years			
arithmetic mean	1.7	1.8	
standard deviation	± 2.5	± 3.4	-
EDSS score Units: score			
arithmetic mean	1.7	1.6	
standard deviation	± 1.0	± 1.2	-

End points

End points reporting groups	
Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description: oral dimethyl fumarate 240 mg twice daily	
Reporting group title	Rituximab
Reporting group description: intravenous rituximab 1000 mg followed by 500 mg every 6 months	

Primary: Patients with any protocol-defined relapse	
End point title	Patients with any protocol-defined relapse
End point description:	
End point type	Primary
End point timeframe: Start of study until 24 months	

End point values	Dimethyl Fumarate (DMF)	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: participant number				
number (n)	16	3		
percentage (%)	16	3		

Statistical analyses

Statistical analysis title	Risk Ratio
Comparison groups	Rituximab v Dimethyl Fumarate (DMF)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.006
Method	Log-binomial regression analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.62

Notes:
[1] - Log-binomial regression analysis

Secondary: Patients with any new T2 lesion or contrast-enhancing lesion

End point title	Patients with any new T2 lesion or contrast-enhancing lesion

End point description:

End point type	Secondary

End point timeframe:
between baseline and month 24

End point values	Dimethyl Fumarate (DMF)	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: participant number				
number (n)	36	21		
percentage (%)	37	21		

Statistical analyses

Statistical analysis title	Risk Ratio
Comparison groups	Dimethyl Fumarate (DMF) v Rituximab
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.019
Method	Log-binomial regression analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.91

Notes:
[2] - Log-binomial regression analysis

Post-hoc: Patients who discontinued drug

End point title	Patients who discontinued drug

End point description:

End point type	Post-hoc

End point timeframe:
between baseline and 24 months

End point values	Dimethyl Fumarate (DMF)	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: participant number				
number (n)	48	3		
percentage (%)	49	3		

Statistical analyses

Statistical analysis title	Risk Ratio
Comparison groups	Dimethyl Fumarate (DMF) v Rituximab
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Log-binomial regression analysis
Parameter estimate	Risk ratio (RR)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.19

Notes:

[3] - Log-binomial regression analysis

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 01/07/16 – 21/04/21	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE (27/11/17)
Dictionary version	5

Reporting groups	
Reporting group title	Rituximab
Reporting group description: -	
Reporting group title	Dimethyl Fumarate (DMF)
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Data is not available. See article (https://pubmed.ncbi.nlm.nih.gov/35841908/) for info about occurrences för non-serious adverse events.

Serious adverse events	Rituximab	Dimethyl Fumarate (DMF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 100 (8.00%)	5 / 100 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
accident			
subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
sinus tachycardia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
extrauterine pregnancy			
subjects affected / exposed	0 / 100 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

neutropenia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
bleeding ulcer			
subjects affected / exposed	2 / 100 (2.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
bronchiectasis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholecystitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
suicide attempt or depression			
subjects affected / exposed	0 / 100 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
pneumonia, pyelonephritis, or SARS-CoV-2			
subjects affected / exposed	2 / 100 (2.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab	Dimethyl Fumarate (DMF)	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 100 (0.00%)	0 / 100 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2017	- Extended inclusion age from 18 – 40 years of age (YOA) to 18 – 50 YOA; - Extended inclusion from 5 years disease duration to 10 years disease duration
30 March 2020	- The protocol was adapted to the emerging COVID-19 pandemic allowing longer infusion intervals in the rituximab arm and consequently prolongation of the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35841908