



## Clinical trial results:

### COMBAT-MS (COMparison Between All immunoTherapies for Multiple Sclerosis)

**A prospective long-term cohort study of safety, efficacy and patient's satisfaction of MS disease modulatory treatments in relapsing-remitting multiple sclerosis**

#### Summary

EudraCT number	2016-003587-39
Trial protocol	SE
Global end of trial date	31 March 2022

#### Results information

Result version number	v1 (current)
This version publication date	23 May 2025
First version publication date	23 May 2025

#### Trial information

##### Trial identification

Sponsor protocol code	COMBAT-MS
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##### 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, Stockholm, Sweden, 17177
Public contact	Dept of Clinial Neuroscience, Karoloinska Institutet, 0046 08517 737 57, fredrik.piehl@ki.se
Scientific contact	Dept of Clinial Neuroscience, Karoloinska Institutet, 0046 08517 737 57, fredrik.piehl@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	25 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2022
Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The overarching goal of the study was to describe the effectiveness and safety of rituximab in comparison to other commonly used approved disease-modulatory therapies for relapsing-remitting MS in the setting of a population-based structured prospective follow-up cohort of patients being either treatment naïve or switching from a previous first MS therapy (escalation/second-line). In keeping with the non-interventional design and real-world setting, the main focus was to present point estimates and confidence limits for different outcome measures, with particular focus on long-term disability, quality of life scales and risk of serious adverse events.

Protection of trial subjects:

The study design was developed together with a Stakeholder Advisory Group (SAG) consisting of people with MS (PwMS), relatives to PwMS, patients' organization representatives, clinicians, and senior scientific consultants. They were selected to represent pwMS and caregivers from both USA and Sweden, advocacy and patient organizations (National MS Society, Neuro Sweden) and professional societies (American Academy of Neurology, Swedish MS Society). Quarterly conference calls with the SAG were held throughout the study to discuss study progress, provide feedback and address arising issues. To provide an additional communication channel for questions arising among study participants and provide consensus responses from the research team, our stakeholders initiated a Facebook COMBAT-MS group. The study design endorsed by the SAG was in the form of a prospective non-intervention cohort study where only additional patient-reported outcomes and a yearly biobanked blood sample deviated from clinical routine. No issues relating to safety or discomfort of participants due to the study itself were recorded during the study. Only two out of 3,522 participants initially consenting to participate chose to withdraw their consent and asked for their data to be deleted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2017
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	Sweden: 3764
Worldwide total number of subjects	3764
EEA total number of subjects	3764

Notes:

### Subjects enrolled per age group

In utero	0
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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)	3730
From 65 to 84 years	34
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited for prospective data collection between June 2, 2017 and June 30, 2019. Annual assessment of disability status and patient-reported outcomes were registered in the Swedish MS register, from the date of recruitment until March 31, 2022.

### Pre-assignment

Screening details:

CIS or RRMS; first or second ever MS DMT (2011–2018); followed at a Swedish university clinic; written consent; age 18–75; capacity to consent; if fertile, informed about DMT risks and contraception; no interfering conditions; no contraindications to trial drugs; no participation in other trials with blinded medication or conflicting protocols

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Rituximab (First DMT Cohort)

Arm description: -

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:

500 to 1000 mg

<b>Arm title</b>	Interferon (First DMT Cohort)
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	INTERFERON BETA-1B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25 mg, 30 mg, 44 mg, 125 mg;

<b>Arm title</b>	Glatiramer acetate (First DMT Cohort)
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	GLATIRAMER ACETATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

20 to 40 mg

<b>Arm title</b>	Dimethyl fumarate (First DMT Cohort)
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	DIMETHYL FUMARATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
240 mg	
<b>Arm title</b>	Natalizumab (First DMT Cohort)
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	NATALIZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
300 mg	
<b>Arm title</b>	Rituximab (Switch DMT Cohort)
Arm description: -	
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:	
500 to 1000 mg	
<b>Arm title</b>	Dimethyl fumarate (Switch DMT Cohort)
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	DIMETHYL FUMARATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
240 mg	
<b>Arm title</b>	Natalizumab (Switch DMT Cohort)
Arm description: -	
Arm type	Active comparator

Investigational medicinal product name	NATALIZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
300 mg	
<b>Arm title</b>	Fingolimod (Switch DMT Cohort)
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	FINGOLIMOD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
0.5 mg	
<b>Arm title</b>	Teriflunomide (Switch DMT Cohort)
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	TERIFLUNOMIDE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
14 mg	

<b>Number of subjects in period 1</b>	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)
Started	591	992	116
Completed	591	992	116

<b>Number of subjects in period 1</b>	Dimethyl fumarate (First DMT Cohort)	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)
Started	416	334	748
Completed	416	334	748

<b>Number of subjects in period 1</b>	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)	Fingolimod (Switch DMT Cohort)
Started	570	541	443
Completed	570	541	443

<b>Number of subjects in period 1</b>	Teriflunomide (Switch DMT Cohort)
Started	161

Completed	161
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## Baseline characteristics

### Reporting groups

Reporting group title	Rituximab (First DMT Cohort)
Reporting group description: -	
Reporting group title	Interferon (First DMT Cohort)
Reporting group description: -	
Reporting group title	Glatiramer acetate (First DMT Cohort)
Reporting group description: -	
Reporting group title	Dimethyl fumarate (First DMT Cohort)
Reporting group description: -	
Reporting group title	Natalizumab (First DMT Cohort)
Reporting group description: -	
Reporting group title	Rituximab (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Dimethyl fumarate (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Natalizumab (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Fingolimod (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Teriflunomide (Switch DMT Cohort)
Reporting group description: -	

Reporting group values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)
Number of subjects	591	992	116
Age categorical			
Units: Subjects			

Age continuous			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: years			
arithmetic mean	36.9	35.8	36.9
standard deviation	± 11.3	± 10.5	± 11.7
Gender categorical			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Female	399	705	90
Male	192	287	26
Born in Sweden			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total			



number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
born in Sweden (n)	494	782	98
not born in Sweden (n)	97	210	18
Education 12+ years			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
has 12+ years education (n)	310	545	61
does not have 12+ years education (n)	281	447	55
Any relapse last year			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
relapse last year (n)	367	648	62
no relapse last year (n)	224	344	54
Medical history - serious infection			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
serious infection reported (n)	15	21	1
no serious infection reported (n)	576	971	115
Medical history - cancer			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
cancer reported (n)	4	10	3
no cancer reported (n)	587	982	113
Medical history - major adverse cardiovascular event (MACE)			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
MACE reported (n)	9	10	4
no MACE reported (n)	582	982	112
Medical history - arrhythmia			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			

Arrhythmia reported (n)	10	7	0
no Arrhythmia reported (n)	581	985	116
Medical history - diabetes			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Diabetes reported (n)	13	17	2
no Diabetes reported (n)	578	975	114
Medical history - antidepressant use			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Antidepressant use (n)	88	98	25
no Antidepressant use (n)	503	894	91
Year of DMT start			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Year			
arithmetic mean	2016	2013	2013
inter-quartile range (Q1-Q3)	2015 to 2017	2012 to 2014	2012 to 2014
Years since MS diagnosis			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.3	0.9	1.7
standard deviation	± 4.0	± 3.1	± 4.5
EDSS mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	2.0	1.6	1.4
standard deviation	± 1.3	± 1.2	± 1.2
MSIS-29 physical mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.8	1.6	1.7
standard deviation	± 0.8	± 0.7	± 0.6
MSIS-29 psychological mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column			

automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: mean (SD)			
arithmetic mean	2.4	2.2	2.6
standard deviation	± 1.0	± 0.9	± 0.9
SDMT mean			

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: mean (SD)			
arithmetic mean	52.0	55.2	54.4
standard deviation	± 11.4	± 12.3	± 11.4

<b>Reporting group values</b>	Dimethyl fumarate (First DMT Cohort)	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)
Number of subjects	416	334	748
Age categorical			
Units: Subjects			

Age continuous			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: years			
arithmetic mean	34.4	31.6	39.0
standard deviation	± 9.7	± 9.2	± 10.5
Gender categorical			

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
Female	283	242	560
Male	133	92	188
Born in Sweden			

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
born in Sweden (n)	337	278	605
not born in Sweden (n)	79	56	143

Education 12+ years			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
has 12+ years education (n)	226	161	403

does not have 12+ years education (n)	190	173	345
Any relapse last year			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
relapse last year (n)	265	252	254
no relapse last year (n)	151	82	494
Medical history - serious infection			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
serious infection reported (n)	7	16	21
no serious infection reported (n)	409	318	727
Medical history - cancer			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
cancer reported (n)	4	3	10
no cancer reported (n)	412	331	738
Medical history - major adverse cardiovascular event (MACE)			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
MACE reported (n)	2	3	6
no MACE reported (n)	414	331	742
Medical history - arrhythmia			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Arrhythmia reported (n)	2	2	11
no Arrhythmia reported (n)	414	332	737
Medical history - diabetes			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Diabetes reported (n)	4	7	17
no Diabetes reported (n)	412	327	731
Medical history - antidepressant use			
Note that individual patients could contribute to more than one treatment group, both with their first			

line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Antidepressant use (n)	64	35	124
no Antidepressant use (n)	352	299	624
Year of DMT start			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Year			
arithmetic mean	2015	2014	2016
inter-quartile range (Q1-Q3)	2014 to 2017	2013 to 2016	2014 to 2017
Years since MS diagnosis			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	0.6	0.5	5.6
standard deviation	± 2.3	± 1.9	± 5.5
EDSS mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.5	2.1	2.0
standard deviation	± 1.1	± 1.3	± 1.3
MSIS-29 physical mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.7	2.0	1.7
standard deviation	± 0.8	± 0.9	± 0.8
MSIS-29 psychological mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	2.3	2.6	2.2
standard deviation	± 1.0	± 1.0	± 1.0
SDMT mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			

arithmetic mean	53.4	50.6	51.5
standard deviation	± 12.5	± 13.3	± 11.5

<b>Reporting group values</b>	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)	Fingolimod (Switch DMT Cohort)
Number of subjects	570	541	443
Age categorical			
Units: Subjects			

Age continuous			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: years			
arithmetic mean	40.6	35.1	37.3
standard deviation	± 10.6	± 9.6	± 9.4

Gender categorical			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
Female	418	406	292
Male	152	135	151

Born in Sweden			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
born in Sweden (n)	466	460	361
not born in Sweden (n)	104	81	82

Education 12+ years			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
has 12+ years education (n)	309	272	234
does not have 12+ years education (n)	261	269	209

Any relapse last year			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
relapse last year (n)	120	288	172
no relapse last year (n)	450	253	271

Medical history - serious infection			
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Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
serious infection reported (n)	17	21	12
no serious infection reported (n)	553	520	431

Medical history - cancer

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
cancer reported (n)	10	2	6
no cancer reported (n)	560	539	437

Medical history - major adverse cardiovascular event (MACE)

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
MACE reported (n)	6	5	1
no MACE reported (n)	564	536	442

Medical history - arrhythmia

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
Arrhythmia reported (n)	5	8	6
no Arrhythmia reported (n)	565	533	437

Medical history - diabetes

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
Diabetes reported (n)	12	6	5
no Diabetes reported (n)	558	535	438

Medical history - antidepressant use

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.

Units: Subjects			
Antidepressant use (n)	92	108	81
no Antidepressant use (n)	478	433	362

Year of DMT start

Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the

number of unique patients.			
Units: Year			
arithmetic mean	2015	2013	2013
inter-quartile range (Q1-Q3)	2014 to 2016	2012 to 2014	2012 to 2014
Years since MS diagnosis			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	7.1	4.7	5.6
standard deviation	± 5.9	± 4.8	± 4.8
EDSS mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.6	2.2	1.8
standard deviation	± 1.3	± 1.4	± 1.3
MSIS-29 physical mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.6	1.9	1.7
standard deviation	± 0.7	± 0.9	± 0.8
MSIS-29 psychological mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	2.0	2.4	2.2
standard deviation	± 0.9	± 1.0	± 0.9
SDMT mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	52.8	52.1	53.3
standard deviation	± 11.8	± 11.9	± 12.6
<b>Reporting group values</b>	Teriflunomide (Switch DMT Cohort)	Total	
Number of subjects	161	4912	
Age categorical			
Units: Subjects			



Age continuous			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: years			
arithmetic mean	46.3		
standard deviation	± 9.8	-	
Gender categorical			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Female	116	3511	
Male	45	1401	
Born in Sweden			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
born in Sweden (n)	139	4020	
not born in Sweden (n)	22	892	
Education 12+ years			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
has 12+ years education (n)	89	2610	
does not have 12+ years education (n)	72	2302	
Any relapse last year			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
relapse last year (n)	30	2458	
no relapse last year (n)	131	2454	
Medical history - serious infection			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
serious infection reported (n)	6	137	
no serious infection reported (n)	155	4775	
Medical history - cancer			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total			

number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
cancer reported (n)	7	59	
no cancer reported (n)	154	4853	
Medical history - major adverse cardiovascular event (MACE)			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
MACE reported (n)	4	50	
no MACE reported (n)	157	4862	
Medical history - arrhythmia			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Arrhythmia reported (n)	1	52	
no Arrhythmia reported (n)	160	4860	
Medical history - diabetes			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Diabetes reported (n)	2	85	
no Diabetes reported (n)	159	4827	
Medical history - antidepressant use			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Subjects			
Antidepressant use (n)	42	757	
no Antidepressant use (n)	119	4155	
Year of DMT start			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: Year			
arithmetic mean	2015		
inter-quartile range (Q1-Q3)	2015 to 2017	-	
Years since MS diagnosis			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	9.3		

standard deviation	$\pm 6.9$	-	
EDSS mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.8		
standard deviation	$\pm 1.6$	-	
MSIS-29 physical mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	1.7		
standard deviation	$\pm 0.7$	-	
MSIS-29 psychological mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	2.1		
standard deviation	$\pm 1.0$	-	
SDMT mean			
Note that individual patients could contribute to more than one treatment group, both with their first line and second line DMT, or exclusively in the first line or second line DMT group. The 'Total' column automatically sums observations across the first line and second line DMT groups. Therefore, the total number of participants reported in the total column of the descriptive table does not represent the number of unique patients.			
Units: mean (SD)			
arithmetic mean	53.3		
standard deviation	$\pm 9.9$	-	

## End points

### End points reporting groups

Reporting group title	Rituximab (First DMT Cohort)
Reporting group description: -	
Reporting group title	Interferon (First DMT Cohort)
Reporting group description: -	
Reporting group title	Glatiramer acetate (First DMT Cohort)
Reporting group description: -	
Reporting group title	Dimethyl fumarate (First DMT Cohort)
Reporting group description: -	
Reporting group title	Natalizumab (First DMT Cohort)
Reporting group description: -	
Reporting group title	Rituximab (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Dimethyl fumarate (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Natalizumab (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Fingolimod (Switch DMT Cohort)
Reporting group description: -	
Reporting group title	Teriflunomide (Switch DMT Cohort)
Reporting group description: -	

### Primary: Confirmed Disease Progression in Patients with Expanded Disability Status Scale (EDSS) <2.5 at Baseline

End point title	Confirmed Disease Progression in Patients with Expanded Disability Status Scale (EDSS) <2.5 at Baseline
End point description:	Data shown are adjusted difference in proportion, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.
End point type	Primary
End point timeframe:	Proportion of patients with baseline EDSS <2.5 progressing to 12 months confirmed EDSS ≥3 among those over 3 years of follow up.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	3.6	4.9	3.9	3.1

<b>End point values</b>	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	1.6	2.6	4.4	3.9

<b>End point values</b>	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	4.4	4.6		

### Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Statistical analysis description: Mean difference between Natalizumab to Rituximab at follow-up.	
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.43
Method	Regression, Linear

Notes:

[1] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0.43
Method	Regression, Linear

Notes:

[2] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.88
Method	Regression, Linear

Notes:

[3] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	= 0.57
Method	Regression, Linear

Notes:

[4] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	= 0.35
Method	Regression, Linear

Notes:

[5] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	= 0.76
Method	Regression, Linear

Notes:

[6] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)

Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	= 0.51
Method	Regression, Linear

Notes:

[7] - Comparative effectiveness analysis;

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[8]</sup>
P-value	= 0.66
Method	Regression, Linear

Notes:

[8] - Comparative effectiveness analysis;

### Primary: Confirmed Disease Progression in Patients with EDSS $\geq 2.5$ at Baseline

End point title	Confirmed Disease Progression in Patients with EDSS $\geq 2.5$ at Baseline
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End point description:

Data shown are adjusted difference in proportion, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Primary
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End point timeframe:

Proportion of patients with baseline EDSS  $\geq 2.5$  experiencing 12 months confirmed EDSS increase of 1 point among those over 3 years of follow up.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	8.8	11.4	9.4	6.5

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				

number (not applicable)	9.6	6.7	9.2	8.9
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End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	7.9	5.0		

## Statistical analyses

Statistical analysis title	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
P-value	= 0.99
Method	Regression, Linear

Notes:

[9] - Comparative effectiveness analysis;

Statistical analysis title	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[10]</sup>
P-value	= 0.83
Method	Regression, Linear

Notes:

[10] - Comparative effectiveness analysis

Statistical analysis title	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[11]</sup>
P-value	= 0.7
Method	Regression, Linear

Notes:

[11] - Comparative effectiveness analysis

Statistical analysis title	Rituximab vs Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)



Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[12]</sup>
P-value	= 0.78
Method	Regression, Linear

Notes:

[12] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[13]</sup>
P-value	= 0.82
Method	Regression, Linear

Notes:

[13] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[14]</sup>
P-value	= 0.49
Method	Regression, Linear

Notes:

[14] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[15]</sup>
P-value	= 0.85
Method	Regression, Linear

Notes:

[15] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)

Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[16]</sup>
P-value	= 0.64
Method	Regression, Linear

Notes:

[16] - Comparative effectiveness analysis

### Primary: Disease-related Impact on Daily Life, Physical

End point title	Disease-related Impact on Daily Life, Physical
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End point description:

Change in the MSIS-29 physical subscale (change from baseline; mean value).

Data shown are adjusted mean difference, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Primary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	-1.5	1.3	-5.0	-1.1

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	-6.2	-0.3	-0.5	-1.9

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				

number (not applicable)	-1.4	2.7		
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## Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[17]</sup>
P-value	= 0.57
Method	Regression, Linear

Notes:

[17] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[18]</sup>
P-value	= 0.23
Method	Regression, Linear

Notes:

[18] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[19]</sup>
P-value	= 0.96
Method	Regression, Linear

Notes:

[19] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[20]</sup>
P-value	= 0.05
Method	Regression, Linear

Notes:

[20] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[21]</sup>
P-value	= 0.5
Method	Regression, Linear

Notes:

[21] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[22]</sup>
P-value	= 0.11
Method	Regression, Linear

Notes:

[22] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[23]</sup>
P-value	= 0.07
Method	Regression, Linear

Notes:

[23] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[24]</sup>
P-value	= 0.13
Method	Regression, Linear

Notes:

[24] - Comparative effectiveness analysis

### Primary: Disease-related Impact on Daily Life, Psychological

End point title	Disease-related Impact on Daily Life, Psychological
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End point description:

Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of

antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Primary
End point timeframe:	
Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.	

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	-8.4	-5.3	-16.8	-6.6

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	-12.1	-3.9	-1.8	-6.0

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	-4.7	-0.8		

## Statistical analyses

Statistical analysis title	Rituximab vs. Interferon (First DMT Cohort)
Statistical analysis description:	
Change in the MSIS-29 psychological subscale (change from baseline; mean value).	
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)

Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[25]</sup>
P-value	= 0.37
Method	Regression, Linear

Notes:

[25] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value)

Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[26]</sup>
P-value	= 0.31
Method	Regression, Linear

Notes:

[26] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[27]</sup>
P-value	= 0.65
Method	Regression, Linear

Notes:

[27] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Natalizumab (First DMT Cohort) v Rituximab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[28]</sup>
P-value	= 0.14
Method	Regression, Linear

Notes:

[28] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch
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	DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[29]</sup>
P-value	= 0.98
Method	Regression, Linear

Notes:

[29] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Natalizumab (Switch DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[30]</sup>
P-value	= 0.3
Method	Regression, Linear

Notes:

[30] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[31]</sup>
P-value	= 0.28
Method	Regression, Linear

Notes:

[31] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
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Statistical analysis description:

Change in the MSIS-29 psychological subscale (change from baseline; mean value).

Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[32]</sup>
P-value	= 0.26
Method	Regression, Linear

Notes:

[32] - Comparative effectiveness analysis

## Secondary: Annualized Relapse Rate

End point title	Annualized Relapse Rate
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**End point description:**

Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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**End point timeframe:**

Comparison of mean number of relapses per year between the different treatments.

<b>End point values</b>	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	0.08	0.59	0.47	0.26

<b>End point values</b>	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	0.26	0.09	0.22	0.30

<b>End point values</b>	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	0.30	0.25		

**Statistical analyses**

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)



Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[33]</sup>
P-value	< 0.001
Method	Regression, Linear

Notes:

[33] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[34]</sup>
P-value	= 0.0005
Method	Regression, Linear

Notes:

[34] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[35]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[35] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[36]</sup>
P-value	= 0.23
Method	Regression, Linear

Notes:

[36] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[37]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[37] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[38]</sup>
P-value	= 0.02
Method	Regression, Linear

Notes:

[38] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[39]</sup>
P-value	= 0.0002
Method	Regression, Linear

Notes:

[39] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[40]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[40] - Comparative effectiveness analysis

## Secondary: Remaining on Therapy

End point title	Remaining on Therapy
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End point description:

Proportion remaining on the index DMT after 3 years.

Data shown are adjusted differences in percentage points, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: percentage				
number (not applicable)	89.1	30.2	34.5	45.8

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: percentage				
number (not applicable)	50.0	88.5	53.9	55.2

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: percentage				
number (not applicable)	58.7	47.5		

## Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[41]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[41] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[42]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[42] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[43]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[43] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[44]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[44] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[45]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[45] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[46]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[46] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[47]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[47] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[48]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[48] - Comparative effectiveness analysis

## Secondary: Change in EDSS

End point title	Change in EDSS
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End point description:

Comparison of yearly increase in mean EDSS between the different treatments.

Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	-0.2	0.1	0.2	-0.2

<b>End point values</b>	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	-0.4	-0.0	0.1	-0.1

<b>End point values</b>	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	0.1	0.3		

### Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Interferon (First DMT Cohort) v Rituximab (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[49]</sup>
P-value	= 0.2
Method	Regression, Linear

Notes:

[49] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[50]</sup>
P-value	= 0.81
Method	Regression, Linear

Notes:

[50] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)

Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[51]</sup>
P-value	= 0.36
Method	Regression, Linear

Notes:

[51] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[52]</sup>
P-value	= 0.6
Method	Regression, Linear

Notes:

[52] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[53]</sup>
P-value	= 0.98
Method	Regression, Linear

Notes:

[53] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[54]</sup>
P-value	= 0.53
Method	Regression, Linear

Notes:

[54] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[55]</sup>
P-value	= 0.94
Method	Regression, Linear

Notes:

[55] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[56]</sup>
P-value	= 0.19
Method	Regression, Linear

Notes:

[56] - Comparative effectiveness analysis

## Secondary: Proportion of Patients With at Least 1 Step Increase in EDSS

End point title	Proportion of Patients With at Least 1 Step Increase in EDSS
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End point description:

Comparison of yearly proportion of patients with at least 1 step increase in EDSS between the different treatments.

Data shown are adjusted differences in proportion, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

<b>End point values</b>	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	17.6	28.1	35.9	19.3

<b>End point values</b>	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	13.4	18.1	20.5	21.3



<b>End point values</b>	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	20.7	25.2		

## Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[57]</sup>
P-value	= 0.046
Method	Regression, Linear

Notes:

[57] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[58]</sup>
P-value	= 0.13
Method	Regression, Linear

Notes:

[58] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Dimethyl fumarate (First DMT Cohort) v Rituximab (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[59]</sup>
P-value	= 0.92
Method	Regression, Linear

Notes:

[59] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)

Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[60]</sup>
P-value	= 0.74
Method	Regression, Linear

Notes:

[60] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[61]</sup>
P-value	= 0.44
Method	Regression, Linear

Notes:

[61] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[62]</sup>
P-value	= 0.37
Method	Regression, Linear

Notes:

[62] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[63]</sup>
P-value	= 0.94
Method	Regression, Linear

Notes:

[63] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)

Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[64]</sup>
P-value	= 0.28
Method	Regression, Linear

Notes:

[64] - Comparative effectiveness analysis

## Secondary: Proportion of Patients With No Evidence of Disease Activity (NEDA) -2

End point title	Proportion of Patients With No Evidence of Disease Activity (NEDA) -2
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End point description:

Comparison of yearly proportion of patients with No Evidence of Disease Activity (NEDA) -2 (free of exacerbations, new/enlarged T2-lesions and occurrence of CEL) between the treatments.

Data shown are adjusted differences in proportion, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	77.6	33.8	34.1	52.6

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	58.5	81.4	60.6	58.4

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		

Units: mean				
number (not applicable)	48.6	58.5		

## Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[65]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[65] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[66]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[66] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[67]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[67] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[68]</sup>
P-value	= 0.048
Method	Regression, Linear

Notes:

[68] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[69]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[69] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[70]</sup>
P-value	= 0.0004
Method	Regression, Linear

Notes:

[70] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[71]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[71] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[72]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[72] - Comparative effectiveness analysis

## Secondary: Proportion of Patients With NEDA-3

End point title	Proportion of Patients With NEDA-3
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End point description:

Comparison of yearly proportion of patients with NEDA-3 (NEDA-2 plus no confirmed worsening of EDSS from baseline).

Data shown are adjusted differences in proportion, stratified by DMT line with rituximab as reference,

from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
End point timeframe:	
Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.	

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	75.1	33.1	33.2	51.7

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	57.2	78.9	57.5	56.0

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	47.6	57.0		

## Statistical analyses

Statistical analysis title	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)

Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[73]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[73] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[74]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[74] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[75]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[75] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[76]</sup>
P-value	= 0.07
Method	Regression, Linear

Notes:

[76] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[77]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[77] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[78]</sup>
P-value	= 0.0007
Method	Regression, Linear

Notes:

[78] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[79]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[79] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Teriflunomide (Switch DMT Cohort) v Rituximab (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[80]</sup>
P-value	< 0.0001
Method	Regression, Linear

Notes:

[80] - Comparative effectiveness analysis

## Secondary: Quality of Life Assessments

End point title	Quality of Life Assessments
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End point description:

Comparison of health related quality of life measured by EQ-5D. European Quality of Life Five Dimension (EQ-5D) measures health-related quality of life.

Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.



End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	0.77	0.77	0.74	0.81

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	0.76	0.76	0.80	0.74

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	0.79	0.77		

### Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[81]</sup>
P-value	= 0.1
Method	Regression, Linear

Notes:

[81] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)

Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[82]</sup>
P-value	= 0.52
Method	Regression, Linear

Notes:

[82] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[83]</sup>
P-value	= 0.997
Method	Regression, Linear

Notes:

[83] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[84]</sup>
P-value	= 0.66
Method	Regression, Linear

Notes:

[84] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[85]</sup>
P-value	= 0.46
Method	Regression, Linear

Notes:

[85] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[86]</sup>
P-value	= 0.13
Method	Regression, Linear

Notes:

[86] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[87]</sup>
P-value	= 0.04
Method	Regression, Linear

Notes:

[87] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[88]</sup>
P-value	= 0.69
Method	Regression, Linear

Notes:

[88] - Comparative effectiveness analysis

## Secondary: Fatigue

End point title	Fatigue
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End point description:

Comparison of fatigue measured by the Fatigue Scale for Motor and Cognitive Functions (FSMC).

Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.

End point type	Secondary
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End point timeframe:

Observed treatment effectiveness and adjusted difference compared to RTX, among Swedish MS patients 3 years after starting a first ever DMT (groups 1-5) and first DMT switch (groups 6-10) 2011-2018.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	55.3	51.7	55.2	48.4

<b>End point values</b>	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	53.1	53.3	49.6	56.0

<b>End point values</b>	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	48.7	53.2		

### Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[89]</sup>
P-value	= 0.98
Method	Regression, Linear

Notes:

[89] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[90]</sup>
P-value	= 0.79
Method	Regression, Linear

Notes:

[90] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)

Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[91]</sup>
P-value	= 0.35
Method	Regression, Linear

Notes:

[91] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)
Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[92]</sup>
P-value	= 0.19
Method	Regression, Linear

Notes:

[92] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[93]</sup>
P-value	= 0.82
Method	Regression, Linear

Notes:

[93] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[94]</sup>
P-value	= 0.55
Method	Regression, Linear

Notes:

[94] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[95]</sup>
P-value	= 0.04
Method	Regression, Linear

Notes:

[95] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Teriflunomide (Switch DMT Cohort) v Rituximab (Switch DMT Cohort)
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[96]</sup>
P-value	= 0.45
Method	Regression, Linear

Notes:

[96] - Comparative effectiveness analysis

## Secondary: Treatment Satisfaction

End point title	Treatment Satisfaction
End point description: Data shown are adjusted mean differences, stratified by DMT line with rituximab as reference, from multivariable linear regression adjusted for age, sex, year of treatment start, country of birth, geographical region, education level, duration since MS diagnosis, baseline EDSS and MSIS-29 scores, history of serious infection, malignancy, major adverse cardiovascular event, arrhythmia, use of antidepressants, diabetes. Confidence intervals are based on robust (Huber-White) standard errors.	
End point type	Secondary
End point timeframe: Comparison of patient satisfaction with their treatment using the Treatment Satisfaction Questionnaire (TSQ), items 1-9, restricted to patients remaining on index DMT at 3 years.	

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: mean				
number (not applicable)	50.0	44.5	42.3	48.3

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: mean				
number (not applicable)	49.6	49.4	49.0	49.8

End point values	Fingolimod (Switch DMT)	Teriflunomide (Switch DMT)		
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	Cohort)	Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: mean				
number (not applicable)	51.7	51.6		

## Statistical analyses

<b>Statistical analysis title</b>	Rituximab vs. Interferon (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Interferon (First DMT Cohort)
Number of subjects included in analysis	1583
Analysis specification	Pre-specified
Analysis type	other <sup>[97]</sup>
P-value	= 0.0008
Method	Regression, Linear

Notes:

[97] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Glatiramer acetate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Glatiramer acetate (First DMT Cohort)
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	other <sup>[98]</sup>
P-value	= 0.09
Method	Regression, Linear

Notes:

[98] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Dimethyl fumarate (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Dimethyl fumarate (First DMT Cohort)
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	other <sup>[99]</sup>
P-value	= 0.004
Method	Regression, Linear

Notes:

[99] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (First DMT Cohort)
Comparison groups	Rituximab (First DMT Cohort) v Natalizumab (First DMT Cohort)

Number of subjects included in analysis	925
Analysis specification	Pre-specified
Analysis type	other <sup>[100]</sup>
P-value	= 0.88
Method	Regression, Linear

Notes:

[100] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs Dimethyl fumarate (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Dimethyl fumarate (Switch DMT Cohort)
Number of subjects included in analysis	1318
Analysis specification	Pre-specified
Analysis type	other <sup>[101]</sup>
P-value	= 0.31
Method	Regression, Linear

Notes:

[101] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Natalizumab (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Natalizumab (Switch DMT Cohort)
Number of subjects included in analysis	1289
Analysis specification	Pre-specified
Analysis type	other <sup>[102]</sup>
P-value	= 0.08
Method	Regression, Linear

Notes:

[102] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Fingolimod (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Fingolimod (Switch DMT Cohort)
Number of subjects included in analysis	1191
Analysis specification	Pre-specified
Analysis type	other <sup>[103]</sup>
P-value	= 0.0018
Method	Regression, Linear

Notes:

[103] - Comparative effectiveness analysis

<b>Statistical analysis title</b>	Rituximab vs. Teriflunomide (Switch DMT Cohort)
Comparison groups	Rituximab (Switch DMT Cohort) v Teriflunomide (Switch DMT Cohort)



Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	other <sup>[104]</sup>
P-value	= 0.04
Method	Regression, Linear

Notes:

[104] - Comparative effectiveness analysis

## Secondary: Rate of Serious Infections

End point title	Rate of Serious Infections
End point description:	
Descriptive analysis (Regression, Cox)	
End point type	Secondary
End point timeframe:	
Rate of serious infections, defined as hospitalizations where the main diagnosis included an ICD-10 diagnosis code in the national patient register in the 3 years after initiating index DMT	

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: Incident rate (IR) per 1000 pyrs				
number (not applicable)	12.7	6.8	5.8	9.8

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: Incident rate (IR) per 1000 pyrs				
number (not applicable)	12.2	20.2	5.9	6.2

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: Incident rate (IR) per 1000 pyrs				
number (not applicable)	10.7	14.9		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Rate of Major Adverse Cardiovascular Events (MACE)

End point title	Rate of Major Adverse Cardiovascular Events (MACE)
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End point description:

Descriptive analysis (Regression, Cox)

End point type	Secondary
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End point timeframe:

Rate of MACE, defined as acute coronary syndrome, stroke or death from any cardiovascular cause based on corresponding ICD-codes in the national patient and cause of death registries in the 3 years after initiating index DMT.

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	1.7	1.4	0.0	0.81

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	0.0	1.3	0.6	1.2

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	0.0	4.2		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Rate of Invasive Cancer

End point title	Rate of Invasive Cancer
End point description:	
Descriptive analysis (Regression, Cox)	
End point type	Secondary
End point timeframe:	
Rate of incident invasive cancer, defined as invasive cancers based on corresponding ICD-codes in the national cancer registry in the 3 years after initiating index DMT.	

End point values	Rituximab (First DMT Cohort)	Interferon (First DMT Cohort)	Glatiramer acetate (First DMT Cohort)	Dimethyl fumarate (First DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	591	992	116	416
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	0.6	2.4	2.9	0.0

End point values	Natalizumab (First DMT Cohort)	Rituximab (Switch DMT Cohort)	Dimethyl fumarate (Switch DMT Cohort)	Natalizumab (Switch DMT Cohort)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	334	748	570	541
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	3.0	1.3	3.0	1.2

End point values	Fingolimod (Switch DMT Cohort)	Teriflunomide (Switch DMT Cohort)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	161		
Units: Incident Rate (IR) per 1000 Pyrs				
number (not applicable)	4.6	0.0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

3 years.

Assessment type	Non-systematic
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### Dictionary used

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Dictionary name	N/A
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Dictionary version	0
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Frequency threshold for reporting non-serious adverse events: 0 %

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### 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: Serious and non-serious Adverse Events were not monitored. Other safety outcomes, collected retrospectively from national registers, are presented under secondary endpoints.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2021	Update in the informed consent to indicate that the last date for clinical visits is set to 2022, and the database will be locked on 2022-09-01.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported