Clinical trial results:
Rituximab (RTX) therapy in steroid resistant patients or patients relapsing after intravenous steroids with active TAO

Rescue RTX

Summary

EudraCT number	2011-000899-33
Trial protocol	SE
Global end of trial date	09 February 2024
Results information	
Result version number	v1 (current)
This version publication date	26 May 2024
First version publication date	26 May 2024

Trial information

Trial identification	
Sponsor protocol code	rescue RTX
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02378298
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Department of Endocrinology, Sahlgrenska University Hospital
Sponsor organisation address	Medicinmottagningen, Sahlgrenska Universitetssjukhus, Blå stråket 5, vån 1 , Gothenburg, Sweden, 413 45
Public contact	Helena Filipsson Nyström, Department of Endocrinology, Sahlgrenska University Hospital, 0046 31-7863398,
Scientific contact	Helena Filipsson Nyström, Department of Endocrinology, Sahlgrenska University Hospital, 0046 31-7863398,

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	09 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2024
Global end of trial reached?	Yes
Global end of trial date	09 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary scientific question

1. To evaluate the effect of RTX+MTX in patients with active TAO unresponsive to steroids or active TAO relapsing after steroid treatment.

Protection of trial subjects:

This study was approved by the Ethics committee in Göteborg and by the Swedish Medical Product Agency, Uppsala, Sweden, and was registered at www.clinicaltrials.gov (NCT02378298). Informed consent was received from all study participants. The retrospective data collection did not require individual informed consent. We adhered to the Declaration of Helsinki and the study conduct was closely followed by a monitor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	5

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study took place at the Departments of Ophthalmology, Endocrinology, and Rheumatology at Sahlgrenska University Hospital (SU) in Mölndal and Göteborg, Sweden. Eligible patients were consecutively asked by the ophthalmologist for participation.

Pre-assignment period milestones

Number of subjects started	37
Number of subjects completed	37

Period 1

Period 1 title	Run-In (0-4 WEEKS)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Non-responders RTX+MTX (NR-RTX)

Arm description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

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

Dosage and administration details:

methylprednisolone 500 mg once weekly

Arm title	Responders (R-CG)

Arm description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Arm type	Active comparator
Investigational medicinal product name	methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

methylprednisolone 500 mg once weekly

Arm title	Non-responders Control Group (R-C)

Arm description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Arm type	Active comparator
Investigational medicinal product name	methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

methylprednisolone 500 mg once weekly

Number of subjects in period 1	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Started	12	13	12
Completed	10	13	12
Not completed	2	0	0
Physician decision	2	-	-

Period 2

Period 2 title	Intervention (5-12 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Non-responders RTX+MTX (NR-RTX)

Arm description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Arm type	Experimental

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

Rituximab (1000 mg) was administered at 5 and 7 weeks after the baseline visit

Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravesical use

Dosage and administration details:

15–20 mg/week

Arm title	Responders (R-CG)

Arm description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Arm type	Active comparator
Investigational medicinal product name	methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

methylprednisolone 500 mg once weekly for 6 weeks followed by 250 mg once weekly for 2 weeks

Arm title	Non-responders Control Group (R-C)

Arm description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Arm type	Active comparator
Investigational medicinal product name	methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

methylprednisolone 500 mg once weekly for 6 weeks followed by 250 mg once weekly for 2 weeks

Number of subjects in period 2	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Started	10	13	12
Completed	10	13	11
Not completed	0	0	1
Physician decision	-	-	1

Period 3

Period 3 title	Follow-up (13-18 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Non-responders RTX+MTX (NR-RTX)

Arm description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Responders (R-CG)

Arm description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Non-responders Control Group (R-C)

Arm description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Started	10	13	11
Completed	10	13	11

Period 4

Period 4 title	Surveillance (19-68 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Non-responders RTX+MTX (NR-RTX)

Arm description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Responders (R-CG)

Arm description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Non-responders Control Group (R-C)

Arm description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Started	10	13	11
Completed	10	12	11
Not completed	0	1	0
Adverse event, serious fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Non-responders RTX+MTX (NR-RTX)

Reporting group description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Reporting group title	Responders (R-CG)

Reporting group description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Reporting group title	Non-responders Control Group (R-C)

Reporting group description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Reporting group values	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Number of subjects	12	13	12
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	52.8	54.6	57.5
standard deviation	± 9.1	± 6.9	± 12.0
Gender categorical Units: Subjects			
Female	6	12	7
Male	6	1	5
Thyroid-stimulating hormone receptor antibodies (TRAb) Units: IE/L			
median			
inter-quartile range (Q1-Q3)			

Reporting group values	Total		
Number of subjects	37		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	25		
Male	12		
Thyroid-stimulating hormone receptor antibodies (TRAb) Units: IE/L			
median			
inter-quartile range (Q1-Q3)	-		

Subject analysis sets	
Subject analysis set title	Non-responders RTX+MTX (NR-RTX)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Subject analysis set title	Responders (R-CG)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Subject analysis set title	Non-responders Control Group (R-C)
Subject analysis set type	Full analysis

Subject analysis set description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Reporting group values	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)
Number of subjects	12	13	12
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	52.8	54.6	57.5
standard deviation	± 9.1	± 6.9	± 12.0
Gender categorical			
Units: Subjects			
Female	6	12	7
Male	6	1	5
Thyroid-stimulating hormone receptor antibodies (TRAb)			
Units: IE/L			
median	28.6	11.4	9.7
inter-quartile range (Q1-Q3)	7.8 to 41.0	5.9 to 20.3	4.7 to 27.0

End points

End points reporting groups

Reporting group title	Non-responders RTX+MTX (NR-RTX)

Reporting group description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Reporting group title	Responders (R-CG)

Reporting group description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Reporting group title	Non-responders Control Group (R-C)

Reporting group description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Reporting group title	Non-responders RTX+MTX (NR-RTX)

Reporting group description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Reporting group title	Responders (R-CG)

Reporting group description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Reporting group title	Non-responders Control Group (R-C)

Reporting group description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Reporting group title	Non-responders RTX+MTX (NR-RTX)

Reporting group description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Reporting group title	Responders (R-CG)

Reporting group description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Reporting group title	Non-responders Control Group (R-C)

Reporting group description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Reporting group title	Non-responders RTX+MTX (NR-RTX)

Reporting group description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Reporting group title	Responders (R-CG)

Reporting group description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Reporting group title	Non-responders Control Group (R-C)

Reporting group description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Subject analysis set title	Non-responders RTX+MTX (NR-RTX)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with moderate-severe TAO with an inflammatory CAS of ≥ 4 that do not respond to iv GC (deltaCAS <2 compared to baseline after 4 weeks of iv GC) or do relapse (deltaCAS ≥2 and total CAS ≥4) after steroid treatment compared to previous CAS measurement at 12 weeks. Rituximab (1000 mg iv with 2 weeks in between) is combined with methotrexate (15-20 mg once a week) to minimize the risk of antibody developement. MTX is always combined with RTX and is never given as a monotherapy in this study.
rituximab and methotrexate

Subject analysis set title	Responders (R-CG)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients in the study have a 4 weeks period of 500 mg methylprednisolone iv/week. Depending of the response patients are classified as non- responders (and are given RTX and MTX) or responders. The responders continue with intravenous infusion of Methylprednisolone 500 mg /week in 2 weeks and thereafter 250 mg iv/week in 6 weeks.

Subject analysis set title	Non-responders Control Group (R-C)
Subject analysis set type	Full analysis

Subject analysis set description:

A retrospective group of non-responsive patients after 4 weeks with iv glucocorticoids, who received regular care, i.e. full 12-week treatment with glucocorticoids according to clinical praxis. This group was used as control and received the same therapy as Responders (R-CG).

Primary: Comparison of Clinical Activity Score (a Composite Measure of Ophthalmological Signs and Symptoms) Between Arms

End point title	Comparison of Clinical Activity Score (a Composite Measure of Ophthalmological Signs and Symptoms) Between Arms

End point description:

The primary outcome measurement is the responder analysis in Clinical activity score (CAS) according to Mouritz et al and the consensus statement from European Group of Graves orbitopathy (EUGOGO). CAS consists of 10 items: the first 7 items are evaluated at the first visit, and the remaining 3 items (change in motility, vision acuity, and change in proptosis) at return visits.

End point type	Primary

End point timeframe:

At 12,18 and 68 weeks

End point values	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	Non-responders Control Group (R-C)	Non-responders RTX+MTX (NR-RTX)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	13	12	10
Units: score on a scale				
arithmetic mean (standard deviation)	4.2 (± 1.03)	2.88 (± 1.33)	4.0 (± 1.41)	4.05 (± 1.23)

End point values	Responders (R-CG)	Non-responders Control Group (R-C)	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	11	10	13
Units: score on a scale				
arithmetic mean (standard deviation)	3.81 (± 1.35)	3.63 (± 1.60)	3.0 (± 1.39)	2.58 (± 1.4)

End point values	Non-responders Control Group (R-C)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: score on a scale				
arithmetic mean (standard deviation)	2.14 (± 2.12)			

Statistical analyses

Statistical analysis title	multivariable linear mixed models
Statistical analysis description: R version 4.3.2 package lme4 and marginal effects	
Comparison groups	Non-responders RTX+MTX (NR-RTX) v Responders (R-CG) v Non-responders Control Group (R-C) v Non-responders RTX+MTX (NR-RTX) v Responders (R-CG) v Non-responders Control Group (R-C) v Non-responders RTX+MTX (NR-RTX) v Responders (R-CG) v Non-responders Control Group (R-C)
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Regression, Linear

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Intervention phase = 4-12 weeks Follow-up phase: 13-18 weeks Surveillance phase: 19-68 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Non-responders RTX+MTX (NR-RTX)
Reporting group description: -	
Reporting group title	Responders (R-CG)
Reporting group description: -	

Serious adverse events	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	1 / 13 (7.69%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Nervous system disorders			
mental disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral aneurysm			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Non-responders RTX+MTX (NR-RTX)	Responders (R-CG)	
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 10 (80.00%)	11 / 13 (84.62%)	
Cardiac disorders High blood pressure subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 7	7 / 13 (53.85%) 11	
Hepatobiliary disorders Elevated liver blood tests subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1	
Endocrine disorders Positive oral glucose tolerance test subjects affected / exposed occurrences (all) Inadequate response to short ACTH subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4 0 / 10 (0.00%) 0	2 / 13 (15.38%) 4 1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported