



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy of Tocilizumab as a Remission-Induction and Glucocorticoid-Sparing Regimen in Subjects with New-Onset Polymyalgia Rheumatica (PMR-SPARE)

#### Summary

EudraCT number	2016-004990-42
Trial protocol	AT
Global end of trial date	02 June 2020

#### Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	PMR-SPARE
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Medical University Vienna, Department of Internal Medicine III
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Principal Investigator, Department of Medicine III, Division of Rheumatology, daniel.aletaha@meduniwien.ac.at
Scientific contact	Principal Investigator - Daniel Aletaha, Department of Medicine III, Division of Rheumatology, +43 4040043000, daniel.aletaha@meduniwien.ac.at

Notes:

#### Paediatric regulatory details

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

Notes:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2020
Global end of trial reached?	Yes
Global end of trial date	02 June 2020
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

Objectives: To assess the efficacy and safety of a tocilizumab-based regimen compared with placebo on top of rapidly tapered GC treatment in a double-blind, controlled fashion, focusing on GC-free remission of disease.

Methodology: In this double-blind, parallel group study, 36 patients with PMR will be recruited from three rheumatology centres and will be randomized in a 1:1 ratio to tocilizumab or placebo over the course of 16 weeks, accompanied by a rapid tapering GC scheme over 11 weeks in both arms. The primary endpoint is GC-free remission at week 16, and follow-up will be performed until week 24 for safety and sustained efficacy. Patients will receive either the subcutaneous preparation of 162 mg tocilizumab weekly or matching placebo injections.

Protection of trial subjects:

The investigator informed each subject comprehensively regarding the nature, significance, impact and risks of this clinical trial. During this instruction the subjects were made aware of the fact that they can withdraw their consent – without giving reasons – at any time without their further medical care being influenced in any way. In addition, subjects also received a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress. The patient information sheet was approved by ethics committee. The consent form was signed and dated by the subject and the physician who conducted the informed consent discussion before any study related procedure was performed. Additionally, the subjects were given a copy of the signed informed consent form.

The subjects had agreed to the possibility of study-related data being passed on to relevant authorities. According to the stipulations of the Austrian Data Protection Law, confidentiality and pseudonymity of the volunteers were assured. After giving written consent the subject underwent the first screening investigations.

During their participation in the clinical trial all subjects were insured as defined by legal requirements. The investigator of the clinical trial received a copy of the insurance conditions and filed the copy in the Investigator Site file for reference. The sponsor provided insurance to indemnify (legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries complied with the applicable regulations.

Background therapy:

All patients will be treated openly with 20 mg/day of prednisone at randomization. A pre-specified taper regimen will be followed over 11 weeks (for details on the taper regimen see Table 2).

In case of relapse (as defined by the investigators, who were all also blinded to CRP/ESR results), patients in either the tocilizumab or placebo group, should increase the prednisone dose by 5 mg for 1 week. Given remission is then re-achieved, the GC dose will be tapered within 4 weeks to the pre-relapse dose (within this 4-weeks period tapering is conducted at the discretion of the investigator). Subsequently, the pre-specified tapering protocol will be followed again. In case remission is not achieved by the dose increment of 5mg, or relapses occur on GC doses >5mg, the GC dose may be further increased at the discretion of the investigator. Subsequent tapering will also be at the discretion of the physician until the pre-relapse dose is achieved. Then, the pre-specified protocol will be followed.

Evidence for comparator: -

Actual start date of recruitment	01 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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Country: Number of subjects enrolled	Austria: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

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#### Subjects enrolled per age group

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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)	10
From 65 to 84 years	25
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Diagnosis of PMR (at, or up to 2 weeks before the screening visit) as confirmed by the investigator at screening and at baseline  
+ fulfilment of the provisional 2012 ACR-EULAR classification criteria + GC naïve or on GC treatment for a maximum of 2 weeks at screening with an initial dose between 12.5 and 25 mg/day prednisone.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Blinding was maintained throughout the 24-week treatment phase of this study by the provision of tocilizumab and matching placebo for tocilizumab in pre-filled syringes in a matching presentation for the first 16 weeks and maintenance of the blinding until week 24. The investigators involved in patient assessment remained blinded to the results of the fasting lipids, ALT/AST, CRP and ESR.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tocilizumab 162mg s.c. once weekly

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

162mg of Tocilizumab were administered subcutaneously via self-injection for 16 weeks.

<b>Arm title</b>	Placebo s.c. once weekly
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Arm description:

Placebo injections were administered via self-injection every week.

Arm type	Placebo
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly
Started	19	17
Completed	16	11
Not completed	3	6
Consent withdrawn by subject	2	-
Adverse event, non-fatal	-	4

Lost to follow-up	1	1
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Tocilizumab 162mg s.c. once weekly
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Reporting group description: -
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Reporting group title	Placebo s.c. once weekly
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Reporting group description:
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Placebo injections were administered via self-injection every week.
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Reporting group values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly	Total
Number of subjects	19	17	36
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	68.8	71.1	
standard deviation	± 9.0	± 9.0	-
Gender categorical			
Units: Subjects			
Female	10	9	19
Male	9	8	17
Disease duration at screening			
Units: day			
arithmetic mean	8	6	
standard deviation	± 5	± 3	-
C-reactive protein			
Units: mg/dL			
arithmetic mean	1.6	0.98	
standard deviation	± 2.4	± 1.5	-
Patients assessment of pain			
Units: millimeter(s)			
arithmetic mean	30.8	22.8	
standard deviation	± 26.0	± 16.7	-

## End points

### End points reporting groups

Reporting group title	Tocilizumab 162mg s.c. once weekly
Reporting group description:	-
Reporting group title	Placebo s.c. once weekly
Reporting group description:	Placebo injections were administered via self-injection every week.

### Primary: Patients in glucocorticoid-free remission at wk 16

End point title	Patients in glucocorticoid-free remission at wk 16
End point description:	The primary efficacy endpoint was the achievement of glucocorticoid-free remission at week 16.
End point type	Primary
End point timeframe:	at week 16

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Patients				
Glucocorticoid-free remission	12	2		

### Statistical analyses

Statistical analysis title	GC-free remission (wk 16)
Statistical analysis description:	The primary and key secondary endpoints were tested between the groups using either Fisher's exact tests for categorical variables, Kruskal-Wallis tests for non-normally distributed continuous data, or Kaplan-Meier estimator for time-to-event data. To control for type I error of the secondary endpoints, we applied a strategy of hierarchical testing, by which hypothesis testing continues until reaching the first non-significance.
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Fisher exact

### Secondary: Patients in glucocorticoid-free remission at wk 12

End point title	Patients in glucocorticoid-free remission at wk 12
End point description:	
To control for type I error of the secondary endpoints, we applied a strategy of hierarchical testing, by which hypothesis testing continues until reaching the first non-significance. The pre-determined hierarchy for testing secondary endpoints was: proportion of subjects in glucocorticoid-free remission at week 12 -> proportion of subjects in glucocorticoid-free remission at week 24 -> time to first relapse -> cumulative dose of prednisone at week 16 -> cumulative dose of prednisone at week 24 -> proportion of subjects with increased ESR >20mm/h, or increased CRP levels >5mg/L at week 24 -> patient pain (VAS) at week 16 -> patient global assessment of disease activity (VAS) at week 16 -> Evaluator global assessment (VAS) at week 16 -> SF-36 at week 16 -> HAQ at week 16.	
End point type	Secondary
End point timeframe:	
at week 12	

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Patients				
Glucocorticoid-free remission at week 12	11	3		

## Statistical analyses

<b>Statistical analysis title</b>	Glucocorticoid-free remission at week 12
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact

## Secondary: Patients in glucocorticoid-free remission at wk 24

End point title	Patients in glucocorticoid-free remission at wk 24
End point description:	
End point type	Secondary
End point timeframe:	
week 24	



<b>End point values</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Patients				
Glucocorticoid-free remission at week 24	11	3		

### Statistical analyses

<b>Statistical analysis title</b>	Glucocorticoid-free remission at week 24
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact

### Secondary: Time to first relapse (days)

End point title	Time to first relapse (days)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 24	

<b>End point values</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: day				
arithmetic mean (standard error)	130 (± 13)	82 (± 11)		

### Statistical analyses

<b>Statistical analysis title</b>	Time to first relapse (days)
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Kruskal-wallis

### Secondary: Cumulative prednisone dose (wk 16)

End point title	Cumulative prednisone dose (wk 16)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to week 16	

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	727 (721 to 842)	935 (861 to 1244)		

### Statistical analyses

<b>Statistical analysis title</b>	Cumulative prednisone dose at week 16
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Kruskal-wallis

### Secondary: Cumulative prednisone dose (wk 24)

End point title	Cumulative prednisone dose (wk 24)
End point description:	
End point type	Secondary
End point timeframe:	
baseline to week 24	

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	781 (721 to 972)	1290 (1106 to 1809)		

## Statistical analyses

Statistical analysis title	Cumulative prednisone dose at week 24
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Kruskal-wallis

## Secondary: subjects with increased ESR or CRP at wk 24

End point title	subjects with increased ESR or CRP at wk 24
End point description:	subjects with increased ESR (>20mm/h) or increased CRP (> 5mg/L)
End point type	Secondary
End point timeframe:	at week 24

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Patients				
Increased ESR (>20mm/h) at week 24	4	8		
Increased CRP (>5mg/L) at week 24	8	9		

## Statistical analyses

<b>Statistical analysis title</b>	Subjects with increased ESR (>20mm/h) at wk 24
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 <sup>[1]</sup>
Method	Fisher exact

Notes:

[1] - not significant

<b>Statistical analysis title</b>	subjects with increased CRP (> 5mg/L) at wk 24
Comparison groups	Tocilizumab 162mg s.c. once weekly v Placebo s.c. once weekly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 <sup>[2]</sup>
Method	Fisher exact

Notes:

[2] - not significant

### Secondary: Pain (VAS) at wk 16

End point title	Pain (VAS) at wk 16
End point description:	
End point type	Secondary
End point timeframe:	
at week 16	

<b>End point values</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	12 (4 to 29)	15 (1.5 to 45.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patient global assessment (VAS) at wk 16

End point title	Patient global assessment (VAS) at wk 16
End point description:	

End point type	Secondary
End point timeframe:	
at week 16	

<b>End point values</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	8 (3 to 25)	16 (3 to 50)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Evaluator global assessment (VAS) at wk 16

End point title	Evaluator global assessment (VAS) at wk 16
End point description:	

End point type	Secondary
End point timeframe:	
at week 16	

<b>End point values</b>	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	2 (0 to 6)	5 (1 to 30)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Short Form-36 (Physical Component Score) at wk 16

End point title	Short Form-36 (Physical Component Score) at wk 16
End point description:	

End point type	Secondary
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End point timeframe:  
at week 16

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Physical Component Score				
median (inter-quartile range (Q1-Q3))	56.3 (48.8 to 61.0)	46.9 (42.2 to 49.8)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Health Assessment Questionnaire (0-3) at wk 16

End point title	Health Assessment Questionnaire (0-3) at wk 16
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End point description:

End point type	Secondary
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End point timeframe:  
at week 16

End point values	Tocilizumab 162mg s.c. once weekly	Placebo s.c. once weekly		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: HAQ-DI				
median (inter-quartile range (Q1-Q3))	0 (0 to 0.5)	0.88 (0.13 to 1.13)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 weeks

Adverse event reporting additional description:

In total, 19 patients were exposed to tocilizumab treatment (162mg s.c. every week) and 17 patients received placebo treatment in the course of this study. As shown in Table 7, the total in-trial duration was 8.2 patient years for the tocilizumab group and 6.3 patient years for the placebo group.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	Tocilizumab 162mg s.c. every week
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Reporting group description: -

Reporting group title	Placebo s.c. every week
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Reporting group description: -

Serious adverse events	Tocilizumab 162mg s.c. every week	Placebo s.c. every week	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	5 / 17 (29.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heat stroke			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Pancreatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Tocilizumab 162mg s.c. every week	Placebo s.c. every week	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)	14 / 17 (82.35%)	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	3 / 19 (15.79%)	4 / 17 (23.53%)	
occurrences (all)	6	6	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder	Additional description: musculoskeletal complains not related to polymyalgia rheumatica disease activity by discretion of investigator		
subjects affected / exposed	0 / 19 (0.00%)	7 / 17 (41.18%)	
occurrences (all)	0	7	
Infections and infestations			
Infection			
subjects affected / exposed	12 / 19 (63.16%)	6 / 17 (35.29%)	
occurrences (all)	17	6	



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported