Clinical trial results:
Sequential B cell/T cell therapy to re-induce humoral immune tolerance in ACPA-positive Rheumatoid Arthritis (TOLERA): a prospective randomized controlled open-label single-centre clinical trial in adult subjects with active ACPA-positive Rheumatoid Arthritis failing Methotrexate

Summary

EudraCT number	2018-003877-91
Trial protocol	DE
Global end of trial date	28 June 2022

Results information

Result version number	v1 (current)
This version publication date	22 June 2024
First version publication date	22 June 2024

Trial information

Trial identification

Sponsor protocol code	TOLERA

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Erlangen
Sponsor organisation address	Maximiliansplatz 2, Erlangen, Germany, 91054
Public contact	Medizinische Klinik 3, Universitätsklinikum Erlangen, arnd.kleyer@extern.uk-erlangen.de
Scientific contact	Medizinische Klinik 3, Universitätsklinikum Erlangen, arnd.kleyer@extern.uk-erlangen.de

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	23 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2022
Global end of trial reached?	Yes
Global end of trial date	28 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of a sequential Rituximab/Abatacept treatment on auto-antibody production and thereby determine its potential to lower ACPA levels and to induce a potential seroconversion and thus an immunological remission

Protection of trial subjects:

Vigorous inclusion and exclusion criteria; close monitoring visits for patients on drug

Background therapy:

Methotrexate (maximal tolerated dose, range 0-25 mg/week)

Evidence for comparator: -

Actual start date of recruitment	01 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	15
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient recruitment was performed in the outpatient and inpatient ward of the department of Internal Medicine 3, Universitätsklinikum Erlangen

Pre-assignment

Screening details:

ACR-EULAR criteria of Rheumatoid Arthritis fulfilled, SDAI >= 11, ACPA positive, inadequate treatment response / intolerance to cDMARDs or bDMARDs

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab + best medical care

Arm description:

Control group: rituximab 1000 mg week 0 and week 2 i.v., followed by best medical care until week 52

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

Dosage and administration details:

1000 mg i.v. at week 0 and week 2

Arm title	Rituximab + Abatacept

Arm description:

Treatment group: rituximab 1000 mg week 0 and week 2 i.v., followed by abatacept 125 mg s.c. from week 8 until week 52 once weekly (44 weeks)

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

Dosage and administration details:

1000 mg i.v. at week 0 and week 2

Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

125 mg s.c. once weekly from week 8 until week 52 (44 weeks)

Number of subjects in period 1	Rituximab + best medical care	Rituximab + Abatacept
Started	10	10
Completed	9	9
Not completed	1	1
worsening of disease	1	-
incompliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	20	20	
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	53.2		
full range (min-max)	22 to 77	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	11	11	
Disease duration Units: year			
arithmetic mean	7.8		
full range (min-max)	1 to 39	-	
ACPA level Units: unit(s)/millilitre			
arithmetic mean	252.7		
standard deviation	± 341.8	-	
SDAI Units: none			
arithmetic mean	24.6		
standard deviation	± 10.9	-	
CDAI Units: none			
arithmetic mean	22.2		
standard deviation	± 9.2	-	
DAS-28 ESR Units: none			
arithmetic mean	4.8		
standard deviation	± 1.4	-	

DAS-28 CRP Units: none arithmetic mean standard deviation	 4.6 ± 1.1	 -	
CRP Units: milligram(s)/litre arithmetic mean standard deviation	 24.4 ± 40.8	 -	
ESR Units: millimetre(s)/hour arithmetic mean standard deviation	 29.7 ± 25.2	 -	

End points

End points reporting groups

Reporting group title	Rituximab + best medical care
Reporting group description:	
Control group: rituximab 1000 mg week 0 and week 2 i.v., followed by best medical care until week 52	
Reporting group title	Rituximab + Abatacept
Reporting group description:	
Treatment group: rituximab 1000 mg week 0 and week 2 i.v., followed by abatacept 125 mg s.c. from week 8 until week 52 once weekly (44 weeks)	

Primary: Proportion of anti CCP2 antibody seroconversions

End point title	Proportion of anti CCP2 antibody seroconversions[1]
End point description:	
defined as lowering of anti-CCP2 antibodies below 5 RE/ml	
End point type	Primary
End point timeframe:	
week 52	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: descriptive analysis

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti CCP2 antibody levels

End point title	Change in anti CCP2 antibody levels
End point description:	
End point type	Secondary
End point timeframe:	
week 52 compared to baseline	

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: unit(s)/millilitre				
arithmetic mean (confidence interval 95%)	-71.03 (-157.09 to -12.25)	-2.83 (-67.58 to 60.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IgA

End point title	Change in IgA

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: milligram(s)/dl				
arithmetic mean (confidence interval 95%)	-31.07 (-60.27 to -7.73)	34.60 (0.51 to 69.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IgG

End point title	Change in IgG

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: millligram(s)/dl				
arithmetic mean (confidence interval 95%)	-34.31 (-85.02 to 19.30)	49.01 (-53.88 to 167.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IgM

End point title	Change in IgM

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: milligram(s)/dl				
arithmetic mean (confidence interval 95%)	-34.46 (-78.65 to -3.59)	-12.09 (-27.41 to 1.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in number of CCP+ B Cells

End point title	Change in number of CCP+ B Cells

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: /millilitre				
arithmetic mean (confidence interval 95%)	-15.11 (-26.89 to -2.22)	-5.80 (-30.20 to 15.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SDAI

End point title	Change in SDAI

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: none				
arithmetic mean (confidence interval 95%)	-13.64 (-21.69 to -5.66)	-16.70 (-23.38 to -9.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDAI

End point title	Change in CDAI

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: none				
arithmetic mean (confidence interval 95%)	-11.36 (-17.87 to -5.01)	-16.47 (-23.06 to -8.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DAS28 (CRP)

End point title	Change in DAS28 (CRP)

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: none				
arithmetic mean (confidence interval 95%)	-1.38 (-2.03 to -0.79)	-1.88 (-2.68 to -1.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DAS28 (ESR)

End point title	Change in DAS28 (ESR)

End point description:

End point type	Secondary

End point timeframe:

week 52 compared to baseline

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: none				
arithmetic mean (confidence interval 95%)	-1.57 (-2.24 to -0.90)	-1.74 (-2.54 to -0.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 remission

End point title	DAS28 remission
End point description: number of patients in DAS28 remission at week 52	
End point type	Secondary
End point timeframe: week 52	

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: SDAI remission

End point title	SDAI remission
End point description: number of patients in SDAI remission at week 52	
End point type	Secondary
End point timeframe: week 52	

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subject	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Boolean remission

End point title	Boolean remission

End point description:

number of patients in Boolean remission at week 52

End point type	Secondary

End point timeframe:

week 52

End point values	Rituximab + best medical care	Rituximab + Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: subject	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

V1 (enrolment) - V9 (EoS)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	All subjects enrolled

Reporting group description: -

Serious adverse events	All subjects enrolled		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
hand fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shoulder operation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All subjects enrolled		
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 20 (95.00%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Surgical and medical procedures Hip arthroplasty subjects affected / exposed occurrences (all) Skin lesion removal subjects affected / exposed occurrences (all) Tendon operation subjects affected / exposed occurrences (all) Tooth extraction subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Impaired healing subjects affected / exposed occurrences (all) Injection site reaction subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Reproductive system and breast			

disorders Breast disorder subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Throat tightness subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Psychiatric disorders Listless subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Injury, poisoning and procedural complications Eye injury subjects affected / exposed occurrences (all) Hand fracture subjects affected / exposed occurrences (all) Infusion related reaction subjects affected / exposed occurrences (all) Meniscus injury subjects affected / exposed occurrences (all) Tibia fracture subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Eye disorders Cataract subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Gastrointestinal disorders Aphthous ulcer subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Diverticulum subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		

Mouth ulceration subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Blister subjects affected / exposed occurrences (all) Night sweats subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Renal and urinary disorders Leukocyturia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bursitis subjects affected / exposed occurrences (all) Enthesopathy subjects affected / exposed occurrences (all) Intervertebral disc protrusion subjects affected / exposed occurrences (all)	 5 / 20 (25.00%) 7 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		

Muscle spasms subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Infections and infestations Asymptomatic bacteriuria subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
COVID-19 subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 4		
Fungal infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Metabolism and nutrition disorders Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2019	anti-CCP2 antibody test system changed
15 April 2020	Clarification: in case of MTX intolerance Rituximab / Abatacept can be used as monotherapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 April 2020	Recruitment stop due to COVID-19 pandemia	04 May 2020

Notes:

Limitations and caveats

None reported