Clinical trial results:
A pilot open-label study to assess the efficacy and safety of tocilizumab (TCZ) in patients with active Schnitzler's syndrome (SchS)

Summary

EudraCT number	2016-003828-23
Trial protocol	DE
Global end of trial date	10 April 2019

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022
Summary attachment (see zip file)	final report_ML39310 (Final report_ML39310.pdf)

Trial information

Trial identification

Sponsor protocol code	ML39310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03046381
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Karoline Krause, Charité - Universitätsmedizin Berlin; Dpt. of Dermatology and Allergy, 0049 30450518336, karoline.krause@charite.de
Scientific contact	Karoline Krause, Charité - Universitätsmedizin Berlin; Dpt. of Dermatology and Allergy, 0049 30450518336, karoline.krause@charite.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	10 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2019
Global end of trial reached?	Yes
Global end of trial date	10 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of TCZ on the clinical signs and symptoms of SchS. This study is a pilot study intended to provide efficacy, safety and tolerability data in a small patient population of SchS. With the small sample size and the unknown variability of the disease activity assessments in this population, statistical power considerations are unwarranted in principle. Due to the limited patient numbers with SchS, the sample size is not based on statistical methodology but reflects the number of patients that are currently treated at the Autoinflammation Reference Center Charité and thought to willing and suitable to participate in the study

Protection of trial subjects:

Safety parameters were documented at each study visit and reported accordingly. Safety parameters included adverse events, laboratory values, clinical monitoring, and prescribed clinic visits.

Background therapy:

Tocilizumab ((RoActemra®, L04AC07,Roche/Chugai, CH-4070 Basel, Switzerland) is a recombinant humanized, anti-human monoclonal antibody of the IgG1 sub-class directed against the soluble (sIL-6R) and membrane-bound interleukin-6 receptor (mIL-6R).
Interleukin-6 (IL-6) is a key mediator of local and systemic inflammatory reactions. The final tocilizumab drug has intravenous (IV) and subcutaneous (SC) formulations. Tocilizumab (IV and SC formulations) is indicated for adults for treatment of moderate to
severe active rheumatoid arthritis (RA) in E.U. and U.S.. Moreover, tocilizumab (IV formulation) is approved for children 2 years of age and older for treatment of polyarticularcourse juvenile idiopathic arthritis (pJIA) and systemic juvenile idiopathic arthritis (sJIA) in
E.U. and U.S.. In India and Japan, tocilizumab is approved for treatment of Castleman's disease. Clinical studies were conducted for Crohn's disease, multiple myeloma, systemic lupus erythematosus, ankylosing spondylitis and B-cell chronic lymphocytic leukemia, but
tocilizumab is no longer being developed for these indications. Moreover, tocilizumab has been shown to be effective in severe uveitis associated with Behçet's disease. Effective treatment of single patients with autoinflammatory diseases tumor necrosis factor
receptor-associated periodic syndrome (TRAPS) as well as Schnitzler's syndrome has been reported.

Evidence for comparator: -

Actual start date of recruitment	19 July 2017
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	Germany: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Germany, between July 2017 (first patient first visit) and March 2019 (last patient last visit).

Pre-assignment

Screening details:

Screening details:
N=9 patients entered the initial screening phase of the study. N=8 patients were eligible for the study and entered the treatment phase. N=4 patients discontinued the study. N=4 patients completed the study.

Period 1

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

Arms

Arm title	Tocilizumab 162mg

Arm description:

This study is a pilot study intended to provide efficacy, safety and tolerability data in a small patient population of SchS. With the small sample size and the unknown variability of the disease activity assessments in this population, statistical power considerations are unwarranted in principle. Due to the limited patient numbers with SchS, the sample size is not based on statistical methodology but reflects the number of patients that are currently treated at the Autoinflammation Reference Center Charité and thought to willing and suitable to participate in the study.

Arm type	Experimental
Investigational medicinal product name	Tocilizumab 162mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

162 mg subcutaneous injections every week within 52 weeks.

Number of subjects in period 1	Tocilizumab 162mg
Started	8
Completed	4
Not completed	4
Adverse event, non-fatal	2
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults over 18 years	8	8	
Gender categorical Units: Subjects			
Male/Female	8	8	

End points

End points reporting groups

Reporting group title	Tocilizumab 162mg

Reporting group description:

This study is a pilot study intended to provide efficacy, safety and tolerability data in a small patient population of SchS. With the small sample size and the unknown variability of the disease activity assessments in this population, statistical power considerations are unwarranted in principle. Due to the limited patient numbers with SchS, the sample size is not based on statistical methodology but reflects the number of patients that are currently treated at the Autoinflammation Reference Center Charité and thought to willing and suitable to participate in the study.

Subject analysis set title	Baseline (Week 0)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

For comparisons between baseline and tocilizumab treatment, primarily descriptive statistics will be used

Primary: PGA change in the open label phase

End point title	PGA change in the open label phase

End point description:

End point type	Primary

End point timeframe:

Week 20

End point values	Tocilizumab 162mg	Baseline (Week 0)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	8		
Units: PGA Score				
arithmetic mean (standard deviation)				
Total (0-20)	3.3 (± 3.6)	12.1 (± 2.5)		
Urticarial rash (0-4)	1.0 (± 1.5)	1.8 (± 1.5)		
Fatigue (0-4)	0.6 (± 0.5)	2.6 (± 0.7)		
Fever (0-4)	0 (± 0)	1.4 (± 1.3)		
Myalgia (0-4)	0.9 (± 1.1)	2.9 (± 0.8)		
Arthralgia /bone pain (0-4)	0.9 (± 1.2)	3.5 (± 0.5)		

Statistical analyses

Statistical analysis title	Descriptive statistics for comparison

Statistical analysis description:

For comparisons between baseline and tocilizumab treatment, primarily descriptive statistics will be used. For continuous variables, the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum, including confidence intervals where applicable, will be assessed. f a sufficient number of subjects is recruited, appropriate statistical tests will be advanced; otherwise, only descriptive statistics will be provided.

Comparison groups	Tocilizumab 162mg v Baseline (Week 0)
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - For comparisons between baseline and open-label treatment period with continuous variables and expected normal distribution, a paired t-test will be used. If parametric assumptions are unwarranted, non-parametric analogies such as the Wilcoxon signed rank test will be advanced.

Secondary: change of the inflammation marker levels

End point title	change of the inflammation marker levels

End point description:

see manuscript: Graphs for CRP, ESR, SAA and S100A8/9
CRP, C reactive Protein; ESR, Erythrocyte sedimentation rates;SAA, Serum Amyloid A;

End point type	Secondary

End point timeframe:

Week 20

End point values	Tocilizumab 162mg	Baseline (Week 0)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	8		
Units: mg/l, mm/h and µg/l				
arithmetic mean (standard deviation)				
CRP	0.6 (± 1.0)	31.67 (± 54.1)		
SAA	4.1 (± 3.5)	176 (± 260.2)		
ESR	12.6 (± 13.1)	37.6 (± 29.3)		
S100A8/9	2.4 (± 1.1)	6.6 (± 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of the SchAS score

End point title	Change of the SchAS score

End point description:

SchAS (Schnitzler’s syndrome activity score, 0-10);
Tocilizumab treatment resulted in reduction of mean total SchAS scores

End point type	Secondary

End point timeframe:

Week 20 (140 Days)

End point values	Tocilizumab 162mg	Baseline (Week 0)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	8		
Units: Score				
arithmetic mean (full range (min-max))				
SchAS	1.5 (0.25 to 2.8)	2.3 (0.7 to 4.0)		

Attachments (see zip file)	SchAS score/SchAS.pdf

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PGA change in the optional study extension

End point title	PGA change in the optional study extension

End point description:

Change in the investigator’s assessment of total disease activity (Physician global assessment [PGA], a composite score which includes the 5 key clinical symptoms of SchS) between baseline and TCZ treatment

End point type	Other pre-specified

End point timeframe:

52 weeks

End point values	Tocilizumab 162mg			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: PGA Score				
arithmetic mean (standard deviation)				
Total (0-20)	7 (± 4.5)			
Urticarial rash (0-4)	2 (± 1.4)			
Fatigue (0-4)	1.8 (± 1)			
Fever (0-4)	0 (± 0)			
Myalgia (0-4)	1.8 (± 1.3)			
Arthralgia /bone pain (0-4)	1.5 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

During the whole trial.

Adverse event reporting additional description:

Safety analysis will be performed on the safety population. Summary statistics for all safety variables will include the total number of subjects and the number experiencing the adverse event by body system using MedDRA terminology.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

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

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: for Safety Results see attachment: final report_ML39310

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33545397