Clinical trial results:
Prospective randomized, double-blind, and placebo-controlled clinical trial with hydroxychloroquine (HCQ) in patients with erosive-inflammatory osteoarthritis (OA) of the finger joints (acronym: OA TREAT)

Summary

EudraCT number	2011-001689-16
Trial protocol	DE
Global end of trial date	05 July 2018

Results information

Result version number	v1 (current)
This version publication date	21 March 2022
First version publication date	21 March 2022

Trial information

Trial identification

Sponsor protocol code	20110531

Additional study identifiers

ISRCTN number	ISRCTN46445413
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1121-1623
Other trial identifiers	German Register of Clinical Trials: DRKS00000796

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dep. of Rheumatology, CC12, Charité - Universitätsmedizin Berlin, +49 30450513133, insider@charite.de
Scientific contact	Dep. of Rheumatology, CC12, Charité - Universitätsmedizin Berlin, +49 30450513133, insider@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	05 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2018
Global end of trial reached?	Yes
Global end of trial date	05 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate efficacy and safety of HCQ by clinical and radiological outcome compared to placebo in patients with severe and refractory inflammatory hand OA.

Protection of trial subjects:

Half-yearly visits to the ophthalmologist. Regular monitoring of liver and kidney values and blood count. Patients receive an NSAID/Cox-2 inhibitor in addition to the verum/placebo.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2013
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: 153
Worldwide total number of subjects	153
EEA total number of subjects	153

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)	153
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The subjects were recruited between 21.November 2013 to February 2017 in 47 study centres.

Pre-assignment

Screening details:

A total number of 220 subjects with clinical symptoms of inflammatory hand OA according the American College of Rheumatology classification and with hand radiographs showing radiological signs of digital erosive OA defined by grades 2 or higher, per Kellgren and Lawrence Scale.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum HCQ

Arm description:

Subjects received HCQ drom day 1 up to week 52

Arm type	Experimental
Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	6584604.00.00
Other name	Quensyl, Hydroxychloroquine sulfate
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Hydroxychloroquine sulfate 200mg/capsule, dose 200mg resp. 400 mg HCQ depending on weight of subjects

30 - 49 kg one capsule every day
50 - 64 kg one capsule day one, two capsules every other day
> 64 kg two capsules every day

Arm title	Placebo

Arm description:

Subjects were trated with placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo identical with study drug apart from the active ingredient, depending on weight of subjects

30 - 49 kg one capsule every day
50 - 64 kg one capsule day one, two capsules every other day
> 64 kg two capsules every day

Number of subjects in period 1	Verum HCQ	Placebo
Started	75	78
Completed	52	61
Not completed	23	17
Adverse event, serious fatal	7	-
Consent withdrawn by subject	7	4
Physician decision	3	1
Adverse event, non-fatal	3	12
Premature unblinding	1	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Verum HCQ
Reporting group description:	
Subjects received HCQ drom day 1 up to week 52	
Reporting group title	Placebo
Reporting group description:	
Subjects were trated with placebo	

Reporting group values	Verum HCQ	Placebo	Total
Number of subjects	75	78	153
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	75	78	153
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	68	60	128
Male	7	18	25

End points

End points reporting groups

Reporting group title	Verum HCQ
Reporting group description: Subjects received HCQ drom day 1 up to week 52	
Reporting group title	Placebo
Reporting group description: Subjects were trated with placebo	

Primary: Changes of AUSCAN Index for pain and hand disability from baseline to end of treatment (week 52)

End point title	Changes of AUSCAN Index for pain and hand disability from baseline to end of treatment (week 52)
End point description:	
End point type	Primary
End point timeframe: from baseline to week 52	

End point values	Verum HCQ	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: score				
arithmetic mean (full range (min-max))				
AUSCAN pain	26.65 (23.91 to 29.38)	26.47 (23.88 to 29.06)		
AUSCAN function	48.1 (43.03 to 53.18)	51.3 (46.58 to 56.01)		

Statistical analyses

Statistical analysis title	ANCOVA analyses
Statistical analysis description: the multiple endpoint test according to Läuter and O'Brien was applied to the 52 week outcome in the AUSCAN pain and hand function scales. To increase the accuracy, the Läuter SSsum test was applied to the baselineadjusted week 52 values of the two AUSCAN scales. The SS test is a onesided test. In the second step, a separate analysis of the AUSCAN pain and hand function scales was performed. These analyses were performed by an analysis of covariance (ANCOVA) with the corresponding AUSCAN	
Comparison groups	Verum HCQ v Placebo

Number of subjects included in analysis	153
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: change efficacy in measure HCQ between baseline and week 26

End point title	change efficacy in measure HCQ between baseline and week 26

End point description:

Efficacy of HCQ determined by AUSCAN score, patient's global assessment of disease activity, patient's assessment of stiffness and physician's global assessment of disease activity from baseline to week 26

End point type	Secondary

End point timeframe:

from baseline to week 26

End point values	Verum HCQ	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: score				
arithmetic mean (full range (min-max))				
AUSCAN pain	26.66 (24.36 to 28.95)	25.94 (23.77 to 28.12)		
AUSCAN function	51.07 (47.04 to 55.11)	51.35 (47.77 to 54.94)		
AUSCAN stiffness	4.82 (4.3 to 5.35)	5.06 (4.55 to 5.57)		
Physican global	3.35 (2.96 to 3.74)	3.88 (3.54 to 4.23)		
Patient global	4.87 (4.33 to 5.4)	5.34 (4.8 to 5.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic progression from baseline to week 52

End point title	Radiographic progression from baseline to week 52

End point description:

for p-value HCQ vs. placebo see attachment table 8

End point type	Secondary

End point timeframe:

from baseline to week 52

End point values	Verum HCQ	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: score				
arithmetic mean (full range (min-max))				
Kallmann score (modified)	53.59 (52.11 to 55.07)	52.8 (51.42 to 54.19)		
Erosion score (modified)	12.34 (11.65 to 13.04)	11.45 (10.79 to 12.1)		
Osteophytes	14.69 (14.31 to 15.06)	14.74 (14.39 to 15.1)		
Joint space narrowing	17.87 (17.42 to 18.32)	17.92 (17.5 to 18.34)		
Laterial deformity	2.57 (2.41 to 2.73)	2.57 (2.42 to 2.72)		
Subchondral cysts	3.67 (3.32 to 4.01)	3.84 (3.52 to 4.16)		
Sclerosis	2.41 (2.14 to 2.68)	2.32 (2.07 to 2.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: change quality of life in measure HCQ vs. placebo from baseline to week 26 and week 52

End point title	change quality of life in measure HCQ vs. placebo from baseline to week 26 and week 52
End point description:	
more results and details to SF36 and p-value, see attachment	
End point type	Secondary
End point timeframe:	
from baseline up to week 26 and from baseline up to week 52	

End point values	Verum HCQ	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: score				
arithmetic mean (full range (min-max))				
Health Assessment Questionaire (HAQ) 26 weeks	0.89 (0.81 to 0.97)	0.89 (0.81 to 0.97)		
Health Assessment Questionaire (HAQ) 52 weeks	0.86 (0.77 to 0.95)	0.81 (0.72 to 0.89)		
SF-SACRAH 26 weeks	4.19 (3.77 to 4.62)	4.2 (3.79 to 4.6)		

SF-SACRAH 52 weeks	3.99 (3.48 to 4.49)	4.29 (3.84 to 4.74)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the whole trial

Adverse event reporting additional description:

Events were reported to the sponsor close to the time of the visit, SAEs immediately after becoming known within 24 hours. The sponsor's pharmacovigilance department and the medical monitor are responsible for further monitoring. The Safety Monitoring Board decides annually or in case of serious events on the continuation of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Verum - HCQ
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Verum - HCQ	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 75 (9.33%)	15 / 78 (19.23%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Vascular disorder			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorder			

subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 75 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
congenital, familial and genetic disorder			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac disorders			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
nervous disorder			
subjects affected / exposed	1 / 75 (1.33%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear and labyrinth disorder			
subjects affected / exposed	0 / 75 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 75 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

gastrointestinal disorders			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	1 / 75 (1.33%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 32	0 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 46	0 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	Verum - HCQ	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 75 (92.00%)	23 / 78 (29.49%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 75 (6.67%)	2 / 78 (2.56%)	
occurrences (all)	7	2	
Nervous system disorders			

Migraine			
subjects affected / exposed	3 / 75 (4.00%)	2 / 78 (2.56%)	
occurrences (all)	6	2	
Headache			
subjects affected / exposed	9 / 75 (12.00%)	7 / 78 (8.97%)	
occurrences (all)	18	13	
Paraesthesia			
subjects affected / exposed	0 / 75 (0.00%)	3 / 78 (3.85%)	
occurrences (all)	0	5	
Dizziness			
subjects affected / exposed	5 / 75 (6.67%)	1 / 78 (1.28%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	12 / 75 (16.00%)	11 / 78 (14.10%)	
occurrences (all)	15	13	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 75 (1.33%)	4 / 78 (5.13%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 75 (5.33%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
Abdominal pain upper			
subjects affected / exposed	6 / 75 (8.00%)	5 / 78 (6.41%)	
occurrences (all)	10	6	
Diarrhoea			
subjects affected / exposed	7 / 75 (9.33%)	2 / 78 (2.56%)	
occurrences (all)	8	2	
Gastritis			
subjects affected / exposed	5 / 75 (6.67%)	2 / 78 (2.56%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	6 / 75 (8.00%)	2 / 78 (2.56%)	
occurrences (all)	8	2	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	4 / 75 (5.33%)	0 / 78 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 75 (4.00%)	2 / 78 (2.56%)	
occurrences (all)	3	7	
Back pain			
subjects affected / exposed	4 / 75 (5.33%)	10 / 78 (12.82%)	
occurrences (all)	4	12	
Joint effusion			
subjects affected / exposed	2 / 75 (2.67%)	1 / 78 (1.28%)	
occurrences (all)	4	1	
Muscle disorder			
subjects affected / exposed	7 / 75 (9.33%)	7 / 78 (8.97%)	
occurrences (all)	7	10	
Neck pain			
subjects affected / exposed	1 / 75 (1.33%)	2 / 78 (2.56%)	
occurrences (all)	1	4	
Osteoarthritis			
subjects affected / exposed	4 / 75 (5.33%)	8 / 78 (10.26%)	
occurrences (all)	6	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 75 (5.33%)	4 / 78 (5.13%)	
occurrences (all)	6	5	
Upper respiratory tract infection			
subjects affected / exposed	8 / 75 (10.67%)	10 / 78 (12.82%)	
occurrences (all)	8	12	
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	4 / 78 (5.13%)	
occurrences (all)	4	7	
Bronchitis			

subjects affected / exposed	9 / 75 (12.00%)	1 / 78 (1.28%)	
occurrences (all)	9	2	
Gastroenteritis			
subjects affected / exposed	2 / 75 (2.67%)	7 / 78 (8.97%)	
occurrences (all)	3	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2014	The main reason for the amendment was to clarify and to find better wordings for the inclusion and exclusion criteria.
25 June 2014	The primary reason for the amendment is the additional information about possible cardiomyopathy with resulting heart failure when taking HCQ (reason: Fachinformation/ Product information had been changed)
03 November 2014	The primary reason for the amendment is the change of production of the IMP by another pharmacy.
18 December 2015	The primary reason for the amendment was the adjustment of the primary and secondary outcome parameters and the resulting adjustment of the subject numbers. The coprimary outcome parameter of xray progression was changed into a secondary parameter. Therefore, the subject number was reduced to 220.

Notes:

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/34215704