Clinical trial results:
Phase II Trial of low-dose Sandimmun Optoral ® (Cyclosporine A) for the treatment of primary Sjögren's syndrome (pSS)

Summary

EudraCT number	2009-013976-38
Trial protocol	DE
Global end of trial date	11 February 2015

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information

Trial identification

Sponsor protocol code	COLO400BDE02T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01693393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr. Jan Zernicke, Medizinische Klinik m.S. Rheumatologie und Klinische Immunologie - Forschung, +49 030450 513025, jan.zernicke@charite.de
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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	11 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of efficacy of low-dose Cyclosporine A in patients with primary Sjögren's Syndrome and joint involvement after 16 week treatment period.

Protection of trial subjects:

The study was reviewed and approved by the Independent Ethics Committee of Berlin (Landesamt für Gesundheit und Soziales (LaGeSo)) and conducted according to the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2009
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

patients were recruited during a period of symptoms, the observed improvement could also be influenced by the variation of intensity of symptoms

Pre-assignment

Screening details:

Key inclusion criteria: a minimum of three tender joints and/or three swollen joints at screening and baseline, normal hematological, renal and liver lab results, stable treatment of Sjögren's syndrome meaning stable doses of nonsteroidal anti-inflammatory drug and glucocorticoid.
36 Patients screened
6 screening failures
30 Patients randomized

Period 1

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

Arms

Arm title	Cyclosporine A

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sandimmun Optoral
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Treatment consisted of the intake of low-dose CyA (approximately 2 mg kg−1 body weight day−1 divided in two intakes) over a period of 16 weeks

Number of subjects in period 1	Cyclosporine A
Started	30
Completed	22
Not completed	8
Adverse event, non-fatal	6
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Cyclosporine A

Reporting group description: -

Reporting group values	Cyclosporine A	Total	
Number of subjects	30	30	
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	54.9		
full range (min-max)	29 to 70	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	1	1	
Disease duration Units: Years			
arithmetic mean	6.1		
standard deviation	± 5.7	-	
GC dose			
Current background medication			
Units: milligram(s)			
arithmetic mean	5.9		
standard deviation	± 3.8	-	

End points

End points reporting groups

Reporting group title	Cyclosporine A
Reporting group description: -	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

All statistical analyses were performed in the intention to treat (ITT) collective. Twenty-eight (including six patients who dropped out during the study) had an EOT visit. For the two patients who were lost to follow-up (LTFU) after the baseline visit, the last observation carried forward (LOCF) method was used to impute the missing data.

Primary: Change of the joints (tender/swollen)

End point title	Change of the joints (tender/swollen)

End point description:

Comparison between Baselin (BL) and end of treatment (EOT);
TJC tender joint count, SJC swollen joint count,

End point type	Primary

End point timeframe:

16 Weeks

End point values	Cyclosporine A	Baseline		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	30		
Units: Score				
arithmetic mean (standard deviation)				
TJC /28	6.8 (± 6.9)	10.7 (± 7.3)		
TJC /68	10.4 (± 11.9)	16.2 (± 13.2)		
SJC /28	1.0 (± 2.3)	2.7 (± 2.6)		
SJC /66	1.3 (± 3.2)	3.2 (± 3.3)		

Attachments (see zip file)	Joint count/TJC.pdf

Statistical analyses

Statistical analysis title	improvement of number of swollen and tender joint

Statistical analysis description:

All statistical analyses were performed in the intention to treat (ITT) collective. Twenty-eight (including six patients who dropped out during the study) had an EOT visit. For the two patients who were lost to follow-up (LTFU) after the baseline visit, the last observation carried forward (LOCF) method was used to impute the missing data. Figure 1 summarizes the flow of patients.

Comparison groups	Cyclosporine A v Baseline

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes of the safety profile in patients

End point title	Changes of the safety profile in patients

End point description:

DAS28 disease activity score using the 28 joint count, CRP C-reactive Protein, ESR erythrocyte sedimentation rate, ESSDAI EULAR Sjögren's Syndrome Disease Activity Index, SF36 Short Form with 36 questions, MHD mental health domain, PHD physical health domain, HAQ-DI health assessment questionnaire disability index.
For more detailed Secondary Endpoints see attachment

End point type	Secondary

End point timeframe:

16 weeks

End point values	Cyclosporine A	Baseline		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	30		
Units: Score				
arithmetic mean (standard deviation)				
DAS28 CRP	3.4 (± 1.4)	4.2 (± 0.9)		
DAS28 ESR	4.3 (± 1.4)	5.1 (± 1.0)		
ESSDAI (0–123)	3.9 (± 4.2)	5.5 (± 3.3)		
ESSDAI articular (0–3)	1.0 (± 0.96)	2.0 (± 0.53)		
Physician's disease activity (0–100)	26.0 (± 19.1)	50.4 (± 13.4)		
Patient's disease activity (0–100)	53.2 (± 27.0)	58.7 (± 21.0)		
Pain (0–100)	52.5 (± 27.9)	63.2 (± 20.9)		
Fatigue (0–100)	32.2 (± 20.5)	28.7 (± 18.3)		
SF36 MHD	42.2 (± 20.5)	39.3 (± 16.4)		
SF36 PHD	33.8 (± 20.2)	27.7 (± 15.1)		
SF36 total	38.1 (± 21.0)	33.9 (± 15.0)		
HAQ-DI	1.2 (± 0.7)	1.3 (± 0.6)		

Attachments (see zip file)	Changes from BL to EOT/BL and EOT comparison.pdf DAS28/DAS28.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

16 weeks

Adverse event reporting additional description:

No new or unexpected safety observations were made. Among the 30 patients, all had experienced at least one adverse event (AE). Gastrointestinal disorders were the most common AEs. All AEs were mild or moderate with exception of one serious AE (hypertension).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Cyclosporine A

Reporting group description: -

Serious adverse events	Cyclosporine A		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 30 (3.33%)		
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	Cyclosporine A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
overall			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			

Congenital cardiovascular disorders			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	14		
General disorders and administration site conditions			
nonspecific disorders that impact several body systems or sites			
subjects affected / exposed	12 / 30 (40.00%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Pleural infections and inflammations; Upper/ Lower respiratory tract disorders			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Psychiatric disorders			
overall			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Investigations			
clinical laboratory test and radiologic test concept	Additional description: clinical laboratory test and radiologic test concept		
subjects affected / exposed	13 / 30 (43.33%)		
occurrences (all)	16		
Injury, poisoning and procedural complications			
overall			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Nervous system disorders			
Spinal cord and nerve root disorders Cranial nerve disorders			
subjects affected / exposed	16 / 30 (53.33%)		
occurrences (all)	23		
Ear and labyrinth disorders			
Ocular infections, irritations and inflammations and Ocular neoplasms			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Eye disorders			
Ocular infections, irritations and inflammations and Ocular neoplasms			

subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 5		
Gastrointestinal disorders Gastrointestinal motility and defaecation conditions subjects affected / exposed occurrences (all)	 21 / 30 (70.00%) 41		
Skin and subcutaneous tissue disorders Angioedema and urticaria, Pigmentation disorders subjects affected / exposed occurrences (all)	 10 / 30 (33.33%) 18		
Renal and urinary disorders Bladder infections and inflammations/ Bladder reflux condition subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 3		
Musculoskeletal and connective tissue disorders Infectious arthritis Bone disorders Muscle disorders subjects affected / exposed occurrences (all)	 20 / 30 (66.67%) 29		
Infections and infestations Bacterial infectious disorders, fungal infectious disorders, Ectoparasitic disorders subjects affected / exposed occurrences (all)	 9 / 30 (30.00%) 13		
Metabolism and nutrition disorders Purine and pyrimidine metabolism disorders; Inborn errors of metabolism subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2		

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/27470087