Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CDZ173 in patients with primary Sjögren's syndrome.

Summary

EudraCT number	2014-004616-12
Trial protocol	DE HU PL
Global end of trial date	17 May 2017

Results information

Result version number	v1 (current)
This version publication date	31 May 2018
First version publication date	31 May 2018

Trial information

Trial identification

Sponsor protocol code	CCDZ173X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02775916
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	17 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of CDZ173 in patients with primary Sjögren's syndrome. To compare the effect of CDZ173 versus placebo on the patient reported outcome of primary Sjögren's syndrome patients after 12 weeks of treatment (study Week 13 (Day 85)).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
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: 22
Country: Number of subjects enrolled	Hungary: 8
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)	26
From 65 to 84 years	4

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 30 patients were randomized in a ratio of 2:1 to receive either CDZ173 or placebo (twice daily at approximately 12 hour intervals) during the 12-week treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CDZ173

Arm description:

Capsule

Arm type	Experimental
Investigational medicinal product name	CDZ173
Investigational medicinal product code	CDZ173
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CDZ173 70mg oral capsule twice a day for 12 weeks

Arm title	Placebo

Arm description:

Capsule matching Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	CDZ173
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo oral capsule twice a day for 12 weeks

Number of subjects in period 1	CDZ173	Placebo
Started	20	10
Completed	17	10
Not completed	3	0
Adverse event, non-fatal	1	-

Subject/Guardian Decision	2	-

Baseline characteristics

Reporting groups	
Reporting group title	CDZ173
Reporting group description:	
Capsule	
Reporting group title	Placebo
Reporting group description:	
Capsule matching Placebo	

Reporting group values	CDZ173	Placebo	Total
Number of subjects	20	10	30
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)	17	9	26
From 65-84 years	3	1	4
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	48.7	44.7	
standard deviation	± 13.85	± 11.58	-
Sex: Female, Male			
Units: Subjects			
Female	17	9	26
Male	3	1	4
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	20	10	30
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	CDZ173
Reporting group description: Capsule	
Reporting group title	Placebo
Reporting group description: Capsule matching Placebo	

Primary: Safety and tolerability of CDZ173 in patients with primary Sjögren’s syndrome up to Day 85
No statistical analysis was planned for this primary outcome.

End point title	Safety and tolerability of CDZ173 in patients with primary Sjögren’s syndrome up to Day 85 No statistical analysis was planned for this primary outcome.[1]
End point description: Safety and tolerability of CDZ173 in patients with primary Sjögren’s syndrome up to End of Treatment Day 85	
End point type	Primary
End point timeframe: up to Day 85	

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: No statistical analysis was planned for this primary outcome

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: count of participants				
Participants with at least one AE|	20	8		
Participants with at least one SAE|	1	0		
Death|	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) after 12 weeks of Treatment Day 85

End point title	Change from Baseline in the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) after 12 weeks of Treatment Day 85

End point description:

The ESSPRI is an established disease outcome measure for Sjögren’s syndrome. It consists of a questionnaire developed to assess the patients' symptoms in primary Sjögren's syndrome and covered the three key subjective areas of discomfort, i.e., dryness, pain and fatigue. The full questionnaire had 21 questions. Subsequently, it was noted that the first three questions, Likert scales ranging from 0 –

10, captured the essence of the ESSPRI. This abbreviated version was used to define the "minimal clinically important improvement" (0.67 – 1) and the "patient-acceptable symptom state" (<5) Patients were asked to complete the full ESSPRI questionnaire. However, the mean of the first three questions was used for the primary analysis and for the assessment of eligibility. A reduction from baseline (or, a negative change from baseline) in ESSPRI indicates improvement in patients.

End point type	Primary

End point timeframe:

Baseline and 12 weeks (Day 85)

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
arithmetic mean (standard deviation)	-1.778 (± 2.4509)	-0.741 (± 1.3517)		

Statistical analyses

Statistical analysis title	Change from Baseline in the ESSPRI at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.343
upper limit	1.937
Variability estimate	Standard deviation
Dispersion value	1.332

Secondary: Change from Baseline in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks of Treatment Day 85

End point title	Change from Baseline in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks of Treatment Day 85

End point description:

The ESSDAI is an established disease outcome measure for Sjögren's syndrome. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score. A reduction from baseline (i.e., a negative change from baseline) in the ESSDAI score is indicative of improvement in a patient.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks (Day 85)

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
least squares mean (standard error)	-2.82 (± 1.165)	-3.34 (± 1.168)		

Statistical analyses

Statistical analysis title	Change from Baseline in the ESSDAI at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	3.55
Variability estimate	Standard error of the mean
Dispersion value	1.466

Secondary: Change from Baseline in the Short Form (36) Health Survey (SF-36) after 12 weeks of Treatment Day 85

End point title	Change from Baseline in the Short Form (36) Health Survey (SF-36) after 12 weeks of Treatment Day 85

End point description:

The Short Form Health Survey is a survey evaluating individual patient's health status which also monitors and compares patients' disease burden. The SF-36 consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section. An increase in SF-36 score from baseline (i.e., a positive change from baseline) indicates improvement in patients

End point type	Secondary

End point timeframe:

Baseline and 12 weeks (Day 85)

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
least squares mean (standard error)				
Physical Component Summary Score|	4.82 (± 2.235)	4.42 (± 2.425)		
Mental Component Summary Score|	5.43 (± 3.415)	1.10 (± 3.792)		

Statistical analyses

Statistical analysis title	Change from Baseline in SF-36 Physical at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.08
upper limit	6.89
Variability estimate	Standard error of the mean
Dispersion value	3.119

Statistical analysis title	Change from Baseline in SF-36 Mental at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	4.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.27
upper limit	13.93
Variability estimate	Standard error of the mean
Dispersion value	4.615

Secondary: Change in Baseline in Multidimensional Fatigue Inventory (MFI) after 12 weeks of Treatment (Day 85)

End point title	Change in Baseline in Multidimensional Fatigue Inventory (MFI) after 12 weeks of Treatment (Day 85)

End point description:

The Multidimensional Fatigue Inventory is a 20-item self-report instrument designed to measure fatigue that covered the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. A reduction from baseline (i.e., a negative change from baseline) in MFI indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks (Day 85)

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
least squares mean (standard error)	-8.80 (± 5.557)	-2.25 (± 5.774)		

Statistical analyses

Statistical analysis title	Change in Baseline in MFI at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-6.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.76
upper limit	8.66
Variability estimate	Standard error of the mean
Dispersion value	7.27

Secondary: Change from Baseline in Physician global assessment of the patient's overall disease activity (Physician VAS) after 12 weeks of Treatment Day 85

End point title	Change from Baseline in Physician global assessment of the patient's overall disease activity (Physician VAS) after 12 weeks of Treatment Day 85

End point description:

A reduction from baseline (i.e., a negative change from baseline) in physician global VAS assessment score indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks (Day 85)

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
least squares mean (standard error)	-10.06 (± 6.584)	0.91 (± 7.699)		

Statistical analyses

Statistical analysis title	Change from Baseline in Physician VAS at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-10.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.94
upper limit	9
Variability estimate	Standard error of the mean
Dispersion value	9.626

Secondary: Change from Baseline in Patient's global assessment of their disease activity (VAS) after 12 weeks of treatment Day 85

End point title	Change from Baseline in Patient's global assessment of their disease activity (VAS) after 12 weeks of treatment Day 85

End point description:

A reduction from baseline (or, a negative change from baseline) in patient global VAS assessment score indicates improvement in patients.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	CDZ173	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: total score				
least squares mean (standard error)	-4.83 (± 7.268)	2.87 (± 8.412)		

Statistical analyses

Statistical analysis title	Change from Baseline in VAS at Day 85
Comparison groups	CDZ173 v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-7.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.75
upper limit	14.37
Variability estimate	Standard error of the mean
Dispersion value	10.595

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	70 mg CDZ173 bid
Reporting group description:	
70 mg CDZ173 bid	
Reporting group title	Placebo bid
Reporting group description:	
Placebo bid	

Serious adverse events	70 mg CDZ173 bid	Placebo bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	70 mg CDZ173 bid	Placebo bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	8 / 10 (80.00%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	7 / 20 (35.00%)	1 / 10 (10.00%)	
occurrences (all)	11	3	
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Feeling Cold			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Eye disorders			
Dry Eye			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Diarrhoea			
subjects affected / exposed	5 / 20 (25.00%)	1 / 10 (10.00%)	
occurrences (all)	7	1	
Flatulence			
subjects affected / exposed	1 / 20 (5.00%)	3 / 10 (30.00%)	
occurrences (all)	5	3	
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Nasal Congestion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oropharyngeal Pain			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Eczema			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Hyperhidrosis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	10 / 20 (50.00%)	1 / 10 (10.00%)	
occurrences (all)	13	2	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Back Pain			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Sjogren's Syndrome			
subjects affected / exposed	2 / 20 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Infected Bite			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Tooth Infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 20 (15.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Vaginal Infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 20 (35.00%)	4 / 10 (40.00%)	
occurrences (all)	9	5	

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 2	 0 / 10 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2016	Amendment 1: The main purpose of this amendment was to include changes in contraceptive requirements based on results from drug-drug interaction study CCDZ173X2104 on hormonal contraception. Exclusion criterion #12 was modified to allow enrolment of women of child-bearing potential using hormonal contraception. In addition, changes were made in the Introduction, and Risks and Benefits sections to reflect the updates in the latest Investigator Brochure. Finally, specifications in inclusion and exclusion criteria, some minor changes, including clarifications on stopping rules, biomarkers assessments, infection monitoring, and typographical corrections, were made to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported