

**Clinical trial results:**

**A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety, and tolerability of ACZ885 (canakinumab) in patients with pulmonary sarcoidosis**

**Summary**

EudraCT number	2016-001255-49
Trial protocol	DE NL
Global end of trial date	04 March 2019

**Results information**

Result version number	v1 (current)
This version publication date	15 March 2020
First version publication date	15 March 2020

**Trial information****Trial identification**

Sponsor protocol code	CACZ885X2205
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, novartis.email@novartis.com

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	04 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 March 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective for this trial was to determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) [F-18]FDG-PET in nodules (nodular uptake regions) after 12 weeks of treatment, compared to placebo.

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	30 December 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: 20
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	40
EEA total number of subjects	34

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)	39

From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Safety Analysis set : 20 patients ACZ885 and 20 patients Placebo

PK Analysis set : 20 patients ACZ885

PD Analysis set : 20 patients CAZ885 and 20 patients placebo

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind <sup>[1]</sup>
Roles blinded	Subject, Investigator

Blinding implementation details:

Roles Blinded : Subjects and Investigators

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ACZ885

Arm description:

ACZ885 (300 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.

Arm type	Experimental
Investigational medicinal product name	ACZ5885
Investigational medicinal product code	
Other name	canakinumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

vials of 150mg/mL

administration :

Doses of 300 mg ACZ885 s.c. every four weeks

<b>Arm title</b>	Placebo
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Arm description:

Placebo (0 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

vials of 150mg/mL

administration :

Doses of placebo to match the 300 mg ACZ885 s.c. every four weeks

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Investigator and subjects were blinded

<b>Number of subjects in period 1</b>	ACZ885	Placebo
Started	20	20
Completed	18	15
Not completed	2	5
Adverse event, non-fatal	-	1
Subject / Guardian decision	1	3
New Therapy for study indication	1	-
Lack of efficacy	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	ACZ885
Reporting group description: ACZ885 (300 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.	
Reporting group title	Placebo
Reporting group description: Placebo (0 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.	

Reporting group values	ACZ885	Placebo	Total
Number of subjects	20	20	40
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)	20	19	39
From 65-84 years	0	1	1
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	51.9	48.1	-
standard deviation	± 8.45	± 9.94	-
Sex: Female, Male			
Units: participants			
Female	8	4	12
Male	12	16	28
Race/Ethnicity, Customized			
Race			
Units: Subjects			
Black or African American	2	1	3
White	18	16	34
Asian	0	2	2
Other	0	1	1

## End points

### End points reporting groups

Reporting group title	ACZ885
Reporting group description: ACZ885 (300 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.	
Reporting group title	Placebo
Reporting group description: Placebo (0 mg/2 mL) will be administered subcutaneously to assigned study subjects once monthly for 6 months.	

### Primary: Change between baseline and week 24 in pulmonary function as measured by spirometry

End point title	Change between baseline and week 24 in pulmonary function as measured by spirometry <sup>[1]</sup>
End point description: To compare the effect of ACZ885 versus placebo in the change between baseline and week 24 in pulmonary function as measured by spirometry (Predicted Forced Vital Capacity).	
End point type	Primary
End point timeframe: Baseline, Week 24	

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 were provided

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Percent Predicted Forced Vital Capacity				
arithmetic mean (standard deviation)	-1.90 (± 3.91)	0.52 (± 3.37)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change between baseline and week 12 in pulmonary tissue inflammation as measured by SUVmax [F-18]FDG-PET/CT

End point title	Change between baseline and week 12 in pulmonary tissue inflammation as measured by SUVmax [F-18]FDG-PET/CT
End point description: To determine the effect of ACZ885 on the change of pulmonary tissue inflammation (lung parenchyma) as measured by SUVmax [F-18]FDG-PET/CT from baseline after 12 weeks of treatment compared to placebo.	
End point type	Secondary
End point timeframe: Baseline, Week 12	

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Percent of Change in [F-18]FDG-PET				
arithmetic mean (standard deviation)	-4.48 (± 37.45)	4.07 (± 26.61)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change between baseline and week 12 in nodular uptake regions as measured by SUVmax[F-18]FDG-PET/CT

End point title	Change between baseline and week 12 in nodular uptake regions as measured by SUVmax[F-18]FDG-PET/CT
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End point description:

To determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) [F-18]FDG-PET in nodules (nodular uptake regions) after 12 weeks of treatment, compared to placebo.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: percentage (Mean % Change In SUVmax)				
arithmetic mean (standard deviation)	-7.70 (± 35.77)	1.03 (± 41.10)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change between baseline and week 12 in in the extrathoracic Region as measured by SUVmax[F-18]FDG-PET/CT

End point title	Change between baseline and week 12 in in the extrathoracic Region as measured by SUVmax[F-18]FDG-PET/CT
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End point description:

To determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) [F-18]FDG-PET in in the extrathoracic Region after 12 weeks of treatment, compared to placebo.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: percentage (Mean % Change In SUVmax)				
arithmetic mean (standard deviation)	-21.4 (± 13.15)	1.76 (± 39.60)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in other parameters of pulmonary function testing (FEV 1, 3, 6 seconds and predicted)

End point title	Change from baseline in other parameters of pulmonary function testing (FEV 1, 3, 6 seconds and predicted)
End point description:	To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing in patients with sarcoidosis at 24 weeks compared to baseline. Forced Expiratory Volume (FEV) in 1, 3, 6 seconds, predicted and forced expiratory flow 25-75%. Results expressed in change from baseline
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Liter/second				
median (full range (min-max))				
FEV in 1 Second	-0.06 (-0.12 to 0.01)	0.05 (-0.202 to 0.12)		
FEV in 3 seconds	-0.08 (-0.15 to 0.01)	0.04 (-0.04 to 0.11)		
FEV in 6 seconds	-0.08 (-0.15 to 0.01)	0.04 (-0.03 to 0.11)		
Predicted FEV	-1.20 (-2.87 to 0.48)	0.89 (-0.87 to 2.66)		
Forced Expiratory Flow 25-75%	-0.0 (-1.0 to 0.8)	0.1 (-0.1 to 0.6)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in High Resolution Computed Tomography (HRCT) scoring

End point title	Change from baseline in High Resolution Computed Tomography (HRCT) scoring
End point description:	To determine the effect of ACZ885 versus placebo on HRCT of patients with sarcoidosis at 24 weeks compared to initial HRCT scan as measured by side-by-side comparison by blinded reviewers and HRCT scoring.
End point type	Secondary
End point timeframe:	Baseline, Week 24

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: score on a scale				
least squares mean (standard error)				
Parameter (unit): Mean of Consolidation	0.11 ( $\pm$ 0.21)	0.00 ( $\pm$ 0.24)		
Parameter (unit): Mean of Fibrosis	0.14 ( $\pm$ 0.20)	-0.26 ( $\pm$ 0.22)		
Parameter (unit): Mean of Ground Glass Opacities	0.12 ( $\pm$ 0.39)	-0.21 ( $\pm$ 0.43)		
Parameter (unit): Mean of Linear Opacities	-0.08 ( $\pm$ 0.04)	-0.00 ( $\pm$ 0.05)		
Parameter (unit): Mean of Nodule	0.55 ( $\pm$ 0.57)	-0.46 ( $\pm$ 0.63)		
Parameter (unit): Mean of Total Sarcoidosis Score	0.47 ( $\pm$ 1.04)	-0.79 ( $\pm$ 1.14)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline distance walked as assessed by the 6-minute walk test

End point title	Change from baseline distance walked as assessed by the 6-minute walk test
End point description:	To determine the effect of ACZ885 versus placebo on the 6-minute walk test distance of patients with sarcoidosis at 12 and 24 weeks compared to baseline
End point type	Secondary
End point timeframe:	Baseline, Week 12, and Week 24

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: meter				
arithmetic mean (standard deviation)				
Baseline	453.65 (± 98.643)	502.36 (± 79.368)		
Week 12	471.57 (± 85.623)	510.39 (± 99.555)		
Week 24	479.40 (± 95.212)	511.74 (± 104.359)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline of additional [F-18]FDG-PET outcomes

End point title	Change from baseline of additional [F-18]FDG-PET outcomes
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End point description:

To determine the effect of ACZ885 on additional [F-18]FDG-PET outcomes after 12 weeks of treatment compared to placebo. SUVmean: Mean standard uptake value for activity in the focal region volume  
SUVpeak: Mean standardized uptake value of a sphere (a diameter of approximately 1.2cm – to produce a 1-cm<sup>3</sup>-volume spherical Region of Interest (ROI) that has the highest average SUV with the lesion volume

End point type	Secondary
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End point timeframe:

Baseline, Week 12

<b>End point values</b>	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 <sup>[2]</sup>	20 <sup>[3]</sup>		
Units: percentage of Change In SUVmean				
least squares mean (standard error)				
SUV mean lymph nodes	-12.1 (± 8.09)	-4.77 (± 8.35)		
SUV mean lung parenchyma	-6.39 (± 9.00)	-3.87 (± 9.30)		
SUV mean extra thoracic Region	-9.75 (± 15.23)	-15.2 (± 11.39)		

Notes:

[2] - lymph nodes n =17  
lung parenchyma n =16  
extra thoracic Region n =4  
[3] - lymph nodes n =16  
lung parenchyma n=15  
extra thoracic Region n=7

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change from baseline in other parameters of pulmonary function testing : Diffusion Capacity of Lung for CO**

End point title	Change from baseline in other parameters of pulmonary function testing : Diffusion Capacity of Lung for CO
End point description:	To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing in patients with sarcoidosis at 24 weeks compared to baseline.
End point type	Secondary
End point timeframe:	Baseline, week 24

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mL/min/mmHg				
arithmetic mean (standard deviation)	-0.85 ( $\pm$ 1.740)	-1.05 ( $\pm$ 1.978)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from baseline in other parameters of pulmonary function testing : Percent Predicted DLco, FEV1/FVC, FEV3/FVC, percent Predicted forced expiratory flow (FEF) 25-75, RV/TLC (Residual Volume /Total Lung Capacity)**

End point title	Change from baseline in other parameters of pulmonary function testing : Percent Predicted DLco, FEV1/FVC, FEV3/FVC, percent Predicted forced expiratory flow (FEF) 25-75, RV/TLC (Residual Volume /Total Lung Capacity)
End point description:	To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing in patients with sarcoidosis at 24 weeks compared to baseline. Percent Predicted DLco (Diffusion Capacity of Lung for CO), FEV1/FVC, FEV3/FVC (forced expiratory volume in 1 or 3 seconds /forced vital capacity), percent Predicted FEF25-75, RV/TLC
End point type	Secondary
End point timeframe:	Baseline, week 24

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: percentage				
arithmetic mean (standard deviation)				
% Predicted DLco	-2.68 ( $\pm$ 5.082)	-2.71 ( $\pm$ 5.028)		
% FEV1/FVC	0.19 ( $\pm$ 3.549)	0.73 ( $\pm$ 2.221)		

% FEV3/FVC	-0.05 (± 2.617)	0.21 (± 1.612)		
%Predicted FEF25-75	-0.94 (± 11.375)	3.22 (± 5.485)		
% RV/TLC (Residual Volume /Total Lung Capacity)	0.63 (± 3.106)	0.23 (± 3.243)		

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

40 months

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	ACZ885 300 mg
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Reporting group description:

ACZ885 300 mg

Reporting group title	Placebo
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Reporting group description:

Placebo

<b>Serious adverse events</b>	ACZ885 300 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	4 / 20 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Large intestine polyp subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	ACZ885 300 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 20 (75.00%)	14 / 20 (70.00%)	
Nervous system disorders			
Dizziness subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Headache subjects affected / exposed	4 / 20 (20.00%)	2 / 20 (10.00%)	
occurrences (all)	4	2	

General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 20 (30.00%) 6	5 / 20 (25.00%) 6	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2  2 / 20 (10.00%) 2  2 / 20 (10.00%) 2	2 / 20 (10.00%) 2  1 / 20 (5.00%) 1  1 / 20 (5.00%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)  Dyspnoea exertional subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2  3 / 20 (15.00%) 3  0 / 20 (0.00%) 0	1 / 20 (5.00%) 1  0 / 20 (0.00%) 0  2 / 20 (10.00%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Muscle spasms subjects affected / exposed occurrences (all)  Myalgia	1 / 20 (5.00%) 2  2 / 20 (10.00%) 2  2 / 20 (10.00%) 2	2 / 20 (10.00%) 2  0 / 20 (0.00%) 0  0	

subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 20 (0.00%) 0	
Infections and infestations			
Influenza			
subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 20 (10.00%) 2	
Nasopharyngitis			
subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 7	6 / 20 (30.00%) 9	
Pulpitis dental			
subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 20 (10.00%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2017	This amendment was prepared to modify the inclusion and exclusion criteria to better recruit the relevant patient population for the study and to address operational challenges

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported