NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Canakinumab

Trial Indication(s)

Pulmonary sarcoidosis

Protocol Number

CACZ885X2205

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: December 2016 (Actual)
Primary Completion Date: March 2019 (Actual)
Study Completion Date: March 2019 (Actual)

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a 32- week, subject- and investigator blinded, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the clinical efficacy of ACZ885 administered subcutaneously (s.c.) every 4 weeks for a total of 24 weeks. Approximately 38 patients were planned to be randomized to receive either ACZ885 or placebo in a 1:1 ratio. On Days 1, 29, 57, 85, 113 and 141 patients were administered s.c. dosing with ACZ885 at 300 mg or corresponding placebo treatment. A window of ± 5 days was allowed for the treatment visits, but the interval between two doses was to be at least 21 days. All patients returned to the study center for safety and pharmacokinetic (PK) checks on an every 4-week
basis at which time they received either study treatments depending on treatment arm. Additionally, patients underwent clinical assessments that included pulmonary function tests with lung volumes, DLco, 6MWT, and clinical outcome assessments.

Definition: Multicenter, multinational, double blind, placebo-controlled, parallel group, efficacy

Centers

8 centers in 3 countries: Germany(3), Netherlands(2), United States(3)

Objectives:

Primary objective: To compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted forced vital capacity (FVC) at Week 24.

Secondary objectives:

- To determine the effect of ACZ885 on decreasing the maximum standardized uptake value in nodules (nodular uptake regions) after 12 weeks of treatment compared to the placebo.
- To determine the effect of ACZ885 versus the placebo on other parameters of pulmonary function testing, (i.e., absolute FVC, forced expiratory volume in 1 second FEV1), FEV1/FVC, forced expiratory volume in 3 seconds (FEV3), forced expiratory flow 25%-75% (FEF25-75), FEV3/FVC, forced expiratory volume in 6 seconds (FEV6), total lung capacity (TLC), residual volume (RV), RV/TLC, diffusing capacity for carbon monoxide (DLco) and post-bronchodilator FEV1/reversibility) in patients with sarcoidosis at 24 weeks compared to baseline.
- To determine the effect of ACZ885 versus placebo on a high resolution computed tomography (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.
- To determine the effect of ACZ885 versus placebo on a 6-minute walk test (6MWT) distance of patients with sarcoidosis at 12 and 14 weeks compared to baseline.
- To determine the effect of ACZ885 on additional [F- 18]FDG-PET outcomes (i.e., SUVmean, SUVpeak and volume of the lesions) after 12 weeks of treatment compared to placebo.
- To assess the safety and tolerability of ACZ885 in patients with sarcoidosis as measured by adverse events (AEs)

Test Product (s), Dose(s), and Mode(s) of Administration

Subcutaneous injection of ACZ885 (canakinumab) 300 mg or matching placebo

Statistical Methods

The analysis of efficacy variables was based on the pharmacodynamics analysis set.

For the primary endpoint, descriptive statistics of both the raw and change in percent predicted FVC was provided by treatment and visit/time. Summary statistics included arithmetic mean, SD, CV (arithmetic), median, minimum and maximum. The posterior probability that ACZ885 was better than placebo in terms of change from baseline in percent predicted FVC at 24 weeks was derived. If it was at least 90%, it was considered a sign of efficacy of ACZ885 in increasing FVC after 24 weeks of treatment in this patient population.

Subgroup analysis was performed on the primary endpoint by PET positivity in lung parenchyma (yes/no) prior to randomization.

Sensitivity analysis was performed on the primary endpoint adding PET positivity in lung parenchyma (yes/no) prior to randomization as a factor.

For PET and HRCT scan parameters, pulmonary functional parameters (% predicted FVC, FEV1, FEF25-75, FEV1/FVC, FEV3, FEV3/FVC, FEV6, TLC, RV, RV/TLC, DLco, and post-bronchodilator FEV1/reversibility) and 6MWT outcomes, descriptive statistics were provided by treatment and visit/time for all continuous variables. Summary statistics included arithmetic mean, SD, CV (arithmetic), median, minimum and maximum. Graphical methods were employed to show mean (SE) figures for raw or derived value (such as change from baseline or percent change from baseline) for each endpoint.

Incidences of patients with complete response (CR), partial response (PR), stable disease and progressive disease (PD) were summarized by treatment group over time, patients who discontinued for lack of efficacy were treated as a separate category in this summary.

Correlation between changes from initial [F-18]FDG-PET scan in SUVmax and changes from baseline in FVC, FEV1, PROs, 6MWT distance was assessed with scatterplot grids.

All safety evaluations were performed on the safety analysis set. The number and percentage of subjects with treatment emergent AEs were summarized by treatment group, primary system organ class and preferred term. Descriptive summary statistics were provided for laboratory evaluations, vital sign measurements and ECG variables by visit and treatment group. PK concentrations were listed and were summarized by visit and treatment group. Immunogenicity data was only listed.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
-Male and female subjects ages 18 to 80 years of age (both inclusive)
-Pulmonary sarcoidosis disease duration of ≥1 year
-Clinically active disease demonstrated either by a biopsy (any organ) or by bronchoalevolar lavage (lymphocytosis >15%, CD4+/CD8+ ration>3.5, CD103+/CD4+/CD4+ ratio <0.2). Patients must also have all of the following criteria:
a. MMRC dyspnea scale ≥1
b. Threshold FVC 50 - 90% of predicted
c. Evidence of parenchymal lung involvement by HRCT at screening or by historical radiological evidence (e.g. CT, MRI or x-ray)

Key Exclusion Criteria:
-Treated pulmonary hypertension

-Previous exposure to concomitant treatment according to the following criteria:
a. Prednisone >15 mg/day or changes in prednisone dose in the 8 weeks prior to screening
b. More than one immune-modulator (i.e., methotrexate, azathioprine, leflunomide, hydroxychloroquine) or changes in their dosing levels within 12 weeks of randomization.
c. Mycophenolate use within 12 weeks of randomization
-Prior treatment with any biologic drug targeting the immune system within 180 days of randomization or history of any previous use of rituximab
-History of bleeding disorder
-Forced vital capacity (FVC) <50% of predicted
-Extra-pulmonary sarcoidosis as primary treatment indication (e.g., involving brain, heart, eye and renal disease with significant hypercalcemia)
-Any conditions or significant medical problems which in the opinion of the investigator immune-compromise the patient and/or places the patient at unacceptable risk for immunomodulatory therapy, such as:
a. Absolute neutrophil count (ANC) <LLN (1,500/µl)
b. Thrombocytopenia CTCAE v4.03 Grade 1: Platelets <LLN (75.0 x 10exp9/L)
c. Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
d. Presence of human immunodeficiency virus (HIV) infection, hepatitis B or hepatitis C infections based on screening lab results
e. Presence of active or latent tuberculosis (Tb). If historical Tb result is available, Tb status needs to be confirmed pre-randomization as determined by screening laboratory measurements.
f. Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome
-Live vaccinations within 3 months prior to the start of the trial
-Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
-Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception defined in the protocol for the study.

Participant Flow Table

Overall Study

	ACZ885	Placebo	Total
Arm/Group Description	ACZ885 (300 mg s.c. once	Placebo (s.c. once monthly for 6 months)	

	monthly for 6 months)		
Started	20	20	40
Completed	18	15	33
Not Completed	2	5	7
Subject / Guardian decision	1	3	4
New Therapy for study indication	1	0	1
Lack of Efficacy	0	1	1
Adverse Event	0	1	1

Baseline Characteristics

	ACZ885	**Placebo**	**Total**
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)	
Number of Participants [units: participants]	20	20	40
Age Continuous (units: years) Mean ± Standard Deviation			
	51.9±8.45	48.1±9.94	50.0±9.30

Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	8	4	12
Male	12	16	28
Race/Ethnicity, Customized[1] (units: participants) Count of Participants (Not Applicable)			
Black or African American	2	1	3
White	18	16	34
Asian	0	2	2
Other	0	1	1

[1] Race

Summary of Efficacy

Primary Outcome Result(s)

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

(Time Frame: Baseline, Week 24)

	ACZ885	**Placebo**
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20

Change between baseline and week 24 in pulmonary function as measured by spirometry (units: Percent Predicted Forced Vital Capacity) Mean ± Standard Deviation		
raw mean week 24	-1.90 ± 3.91	0.52 ± 3.37

Secondary Outcome Result(s)

Change between baseline and week 12 in pulmonary tissue inflammation (lung parenchyma) as measured by SUVmax[F-18]FDG-PET/CT

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change between baseline and week 12 in pulmonary tissue inflammation (lung parenchyma) as measured by SUVmax[F-18]FDG-PET/CT (units: percentage (Mean % Change In SUVmax)) Mean ± Standard Deviation		

raw mean week 12	-4.48 ± 37.45	4.07 ± 26.61

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

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change between baseline and week 12 in nodular uptake regions as measured by SUVmax[F-18]FDG-PET/CT (units: percentage (Mean % Change In SUVmax)) Mean ± Standard Deviation		
raw mean week 12	-7.70 ± 35.77	1.03 ± 41.10

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

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)

Number of Participants Analyzed [units: participants]	20	20
Change between baseline and week 12 in in the extrathoracic Region as measured by SUVmax[F-18]FDG-PET/CT (units: percentage (Mean % Change In SUVmax)) Mean ± Standard Deviation		
raw mean week 12	-21.4 ± 13.15	1.76 ± 39.60

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

(Time Frame: Baseline, week 24)

	ACZ885	**Placebo**
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change from baseline in other parameters of pulmonary function testing (FEV 1, 3, 6 seconds and predicted) (units: Liter/second) Median (90% Confidence Interval)		
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)

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

(Time Frame: Baseline, Week 24)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change from baseline in High Resolution Computed Tomography (HRCT) scoring (units: score on a scale) Least Squares Mean ± Standard Error		
Parameter (unit): Mean of Consolidation	0.11 ± 0.21	0.00 ± 0.24
Parameter (unit): Mean of Fibrosis	0.14 ± 0.20	-0.26 ± 0.22
Parameter (unit): Mean of Ground Glass Opacities	0.12 ± 0.39	-0.21 ± 0.43
Parameter (unit): Mean of Linear Opacities	-0.08 ± 0.04	-0.00 ± 0.05
Parameter (unit): Mean of Nodule	0.55 ± 0.57	-0.46 ± 0.63

Parameter (unit): Mean of Total Sarcoidosis Score	0.47 ± 1.04	-0.79 ± 1.14

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

(Time Frame: Baseline, Week 12, and Week 24)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change from baseline distance walked as assessed by the 6-minute walk test (units: meter) 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

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

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)

Number of Participants Analyzed [units: participants]	20	20
Change from baseline of additional [F-18]FDG-PET outcomes (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

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

(Time Frame: Baseline, week 24)

	ACZ885	**Placebo**
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
Change from baseline in other parameters of pulmonary function testing : Diffusion Capacity of Lung for CO (units: mL/min/mmHg) Mean ± Standard Deviation		
	-0.85 ± 1.740	-1.05 ± 1.978

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)

(Time Frame: Baseline, week 24)

	ACZ885	Placebo
Arm/Group Description	ACZ885 (300 mg s.c. once monthly for 6 months)	Placebo (s.c. once monthly for 6 months)
Number of Participants Analyzed [units: participants]	20	20
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) (units: percentage) Mean ± Standard Deviation		
% Predicted DLco	-2.68 ± 5.082	-2.71 ± 5.028
% FEV1/FVC	0.19 ± 3.549	0.73 ± 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

Summary of Safety

Safety Results

All-Cause Mortality

	ACZ885 300 mg N = 20	Placebo N = 20
Arm/Group Description	ACZ885 300 mg	Placebo (s.c. once monthly for 6 months)
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	40 months
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment

	ACZ885 300 mg N = 20	Placebo N = 20

Arm/Group Description	ACZ885 300 mg	Placebo (s.c. once monthly for 6 months)
Total participants affected	3 (15.00%)	4 (20.00%)
Cardiac disorders		
Atrial fibrillation	1 (5.00%)	0 (0.00%)
Coronary artery disease	1 (5.00%)	0 (0.00%)
Gastrointestinal disorders		
Large intestine polyp	0 (0.00%)	1 (5.00%)
Infections and infestations		
Appendicitis	0 (0.00%)	1 (5.00%)
Influenza	1 (5.00%)	0 (0.00%)
Peritonitis	0 (0.00%)	1 (5.00%)
Investigations		
Atypical mycobacterium test positive	0 (0.00%)	1 (5.00%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	0 (0.00%)	1 (5.00%)

Other Adverse Events by System Organ Class

Time Frame 40 months

Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	ACZ885 300 mg N = 20	**Placebo N = 20**
Arm/Group Description	ACZ885 300 mg	Placebo (s.c. once monthly for 6 months)
Total participants affected	15 (75.00%)	14 (70.00%)
Ear and labyrinth disorders		
Ear pain	2 (10.00%)	0 (0.00%)
Gastrointestinal disorders		
Diarrhoea	2 (10.00%)	2 (10.00%)
Nausea	2 (10.00%)	1 (5.00%)
Vomiting	2 (10.00%)	1 (5.00%)
General disorders and administration site conditions		
Fatigue	6 (30.00%)	5 (25.00%)
Infections and infestations		
Influenza	0 (0.00%)	2 (10.00%)
Nasopharyngitis	5 (25.00%)	6 (30.00%)

Pulpitis dental	0 (0.00%)	2 (10.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (5.00%)	2 (10.00%)
Muscle spasms	2 (10.00%)	0 (0.00%)
Myalgia	2 (10.00%)	0 (0.00%)
Nervous system disorders		
Dizziness	3 (15.00%)	0 (0.00%)
Headache	4 (20.00%)	2 (10.00%)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (10.00%)	1 (5.00%)
Dyspnoea	3 (15.00%)	0 (0.00%)
Dyspnoea exertional	0 (0.00%)	2 (10.00%)

Other Relevant Findings

None

Conclusion:

- No positive effect was detected in the study primary outcome of percent-predicted FVC (forced vital capacity) at Week 24 in ACZ885 group when compared to the placebo group.
- Signs of anti-inflammatory responses within sarcoidosis disease tissues were noted in the ACZ885 group at Week 12 by decreases in FDG-PET SUVmax (maximum standardized uptake value) when compared to the placebo group. These results were not statistically significant.

- Patients in the ACZ885 group performed better in the 6-minute walk test (6MWT) when compared to the placebo group. However, these results need confirmation in a larger patient population.
- Slight reduction in air trapping was observed in the ACZ885 group when compared to the placebo group. The results were not statistically significant.
- ACZ885 300 mg subcutaneous was safe and well tolerated in patients with pulmonary sarcoidosis. The safety profile of ACZ885 (canakinumab) in this study was consistent with the known safety profile of canakinumab and showed no new or unexpected safety signals.

Date of Clinical Trial Report

Definition: 21-Jan-2020