Clinical trial results:
A subject and investigator blinded, randomized, placebo-controlled, repeat-dose, multicenter study to investigate efficacy, safety, and tolerability of CMK389 in patients with chronic pulmonary sarcoidosis

Summary

EudraCT number	2018-000381-11
Trial protocol	DE GB DK CZ PL
Global end of trial date	12 December 2023

Results information

Result version number	v1 (current)
This version publication date	25 September 2024
First version publication date	25 September 2024

Trial information

Trial identification

Sponsor protocol code	CCMK389X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04064242
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, 41 613241111, novartis.email@novartis.com
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, 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	12 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess the efficacy of CMK389 in participants with chronic pulmonary sarcoidosis.

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:

Participants were required to be on either Methotrexate or Azathioprine (no dose requirement) and on 5-15mg/day of prednisone for at least 6 months prior to screening. Methotrexate/Azathioprine was discontinued in the Run-In period and prednisone was titrated during the trial. Hydroxychloroquine was allowed but not required during the trial.

Evidence for comparator: -

Actual start date of recruitment	23 September 2020
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: 17
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	62
EEA total number of subjects	47

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)	59
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 22 investigative sites in 6 countries.

Pre-assignment

Screening details:

After obtaining signed informed consent, a screening epoch of 28 days was used to assess subject eligibility.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CMK389 10 mg/kg i.v.

Arm description:

CMK389 10 mg/kg i.v. every 4 weeks for a total of 4 doses

Arm type	Experimental
Investigational medicinal product name	CMK389
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CMK389 10 mg/kg i.v. every 4 weeks for a total of 4 doses

Arm title	Placebo i.v.

Arm description:

Placebo i.v. every 4 weeks for a total of 4 doses

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo i.v. every 4 weeks for a total of 4 doses

Number of subjects in period 1	CMK389 10 mg/kg i.v.	Placebo i.v.
Started	31	31
Completed	31	31

Baseline characteristics

Reporting groups	
Reporting group title	CMK389 10 mg/kg i.v.
Reporting group description:	
CMK389 10 mg/kg i.v. every 4 weeks for a total of 4 doses	
Reporting group title	Placebo i.v.
Reporting group description:	
Placebo i.v. every 4 weeks for a total of 4 doses	

Reporting group values	CMK389 10 mg/kg i.v.	Placebo i.v.	Total
Number of subjects	31	31	62
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)	29	30	59
From 65-84 years	2	1	3
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.5	50.7	
standard deviation	± 8.69	± 9.36	-
Sex: Female, Male Units: participants			
Female	7	13	20
Male	24	18	42
Race/Ethnicity, Customized Units: Subjects			
Black Or African American	3	2	5
Unknown	0	1	1
White	28	28	56

End points

End points reporting groups	
Reporting group title	CMK389 10 mg/kg i.v.
Reporting group description:	
CMK389 10 mg/kg i.v. every 4 weeks for a total of 4 doses	
Reporting group title	Placebo i.v.
Reporting group description:	
Placebo i.v. every 4 weeks for a total of 4 doses	

Primary: Change in percent predicted FVC from baseline to 16 weeks of treatment	
End point title	Change in percent predicted FVC from baseline to 16 weeks of treatment
End point description:	
To assess the effect of CMK389 compared to placebo after 16 weeks of treatment on spirometry (Forced Vital Capacity). Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. Percent predicted FVC is the percentage of the age, height and gender adjusted predicted value.	
End point type	Primary
End point timeframe:	
Baseline, Week 16	

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	27		
Units: Percent predicted				
arithmetic mean (standard deviation)	-0.48 (± 1.17)	1.02 (± 1.13)		

Statistical analyses

Statistical analysis title	Percent predicted FVC
Comparison groups	CMK389 10 mg/kg i.v. v Placebo i.v.
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1804
Method	Bayesian analysis
Parameter estimate	Posterior estimate treatment difference
Point estimate	-1.49
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.56
upper limit	0.6

Variability estimate	Standard deviation
Dispersion value	1.62

Secondary: Number of participants who had an increase in steroid usage from baseline to 16 weeks of treatment

End point title	Number of participants who had an increase in steroid usage from baseline to 16 weeks of treatment

End point description:

The Clinical Status Evaluation (CSE) served as a safety evaluation and served to establish the patient's clinical status (Clinical Status Determination [CSD]). CSE was performed prior to the titration of steroids, and the CSD guided selection of the next dose of steroids. Participants with CSD of "improved" or "stable" decreased steroid dose by 1 step on the dosing scale. Participants with CSD of "deteriorating" were ineligible to continue the study (if found during the run-in epoch or at study Day 1); or they increased steroid dose by 1 step (if found during the treatment epoch).

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: participants	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who deteriorate from baseline to 16 weeks of treatment

End point title	Number of participants who deteriorate from baseline to 16 weeks of treatment

End point description:

Composite index of pulmonary physiology (CIPP) and exercise capacity: a participant who deteriorated from baseline to each visit was defined as a patient with:
relative reduction if FVC ≥ 10%, or
relative reduction if FEV1 ≥ 10%, or
relative reduction of DLCO ≥ 15%, or
relative reduction of 6MWD ≥ 50 m.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: participants	9	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in [18F]-FDG-PET/CT (SUVmax and SUVmean) from baseline to 16 weeks of treatment

End point title	Percent change in [18F]-FDG-PET/CT (SUVmax and SUVmean) from baseline to 16 weeks of treatment

End point description:

[18F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) maximum standardized uptake value and mean standardized uptake value (SUVmax and SUVmean) imaging was used to assess potential anti-inflammatory effects by CMK389 on the sarcoidosis process. All participants underwent whole-body head to mid-thigh [18F]FDG-PET/CT imaging state-of-the-art, 3D PET/CT scanners with a reconstructed resolution of ≤5 mm. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: percent change from Baseline				
least squares mean (standard error)				
Lung Parenchyma SUVmax (n=12,18)	-29.23 (± 31.128)	26.78 (± 24.461)		
Lymph Nodes SUVmax (n=11,9)	-23.40 (± 9.083)	-16.48 (± 9.759)		
Extrathoracic SUVmax (n=4,13)	-12.89 (± 14.361)	-19.07 (± 6.908)		
Lung Parenchyma SUVmean (n=12,18)	-34.06 (± 28.626)	20.74 (± 22.443)		
Lymph Nodes SUVmean (n=11,9)	-30.83 (± 8.157)	-22.75 (± 9.101)		
Extrathoracic SUVmean (n=4,13)	-11.23 (± 13.020)	-23.99 (± 6.440)		

Statistical analyses

No statistical analyses for this end point

Secondary: The observed serum concentration following CMK389 administration at end of infusion

End point title	The observed serum concentration following CMK389 administration at end of infusion[1]

End point description:

Pharmacokinetic parameters were directly derived from the PK concentration data using non-compartmental analysis. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Secondary

End point timeframe:

Post 1 hour: Day 1, Day 29, Day 57, Day 85

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to CMK389 arm.

End point values	CMK389 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: ng/mL				
median (full range (min-max))				
Day 1 (n=30)	453000 (236000 to 1230000)			
Day 29 (n=31)	533000 (58100 to 2460000)			
Day 57 (n=29)	571000 (77600 to 3070000)			
Day 85 (n=28)	541000 (78300 to 893000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose trough concentration (Ctrough) of CMK389

End point title	Pre-dose trough concentration (Ctrough) of CMK389[2]

End point description:

Pharmacokinetic parameters were directly derived from the PK concentration data using non-compartmental analysis. Ctrough is the observed plasma concentration that is just prior to the beginning of a dosing interval. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

End point type	Secondary

End point timeframe:

Pre-dose: Day 1, Day 29, Day 57, Day 85

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to CMK389 arm.

End point values	CMK389 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: ng/mL				
median (full range (min-max))				
Day 1 (n=15)	0.00 (0.00 to 619000)			
Day 29 (n=31)	83500 (43300 to 176000)			
Day 57 (n=30)	105000 (41700 to 182000)			
Day 85 (n=30)	125000 (27900 to 444000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FEV1 from baseline to 16 weeks of treatment

End point title	Change in FEV1 from baseline to 16 weeks of treatment

End point description:

FEV1 (forced expiratory volume in one second) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. The least-squares means for change from baseline in FEV1 to assess the effect of CMK389 compared to placebo after 16 weeks were obtained from a mixed effects model for repeated measures (MMRM). A positive change from baseline in pre-dose FEV1 is considered a favourable outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	27		
Units: liters (L)				
least squares mean (standard error)	-0.03 (± 0.033)	0.00 (± 0.032)		

Statistical analyses

Statistical analysis title	FEV1
Comparison groups	CMK389 10 mg/kg i.v. v Placebo i.v.

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.783
Method	Mixed effects Model for Repeated Measure
Parameter estimate	Median difference (net)
Point estimate	-0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.09
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.045

Secondary: Change in diffusion capacity of the lung for carbon monoxide (DLCO) from baseline to 16 weeks of treatment

End point title	Change in diffusion capacity of the lung for carbon monoxide (DLCO) from baseline to 16 weeks of treatment

End point description:

DLCO is a measurement to assess the lungs' ability to transfer gas from inspired air to the bloodstream. The least squares means for change from baseline in DLCO to assess the effect of CMK389 compared to placebo after 16 weeks were obtained from a mixed effects model for repeated measures (MMRM). A positive change from baseline in DLCO is considered a favourable outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	25		
Units: mL/min/mmHg				
least squares mean (standard error)	-0.58 (± 0.493)	-0.40 (± 0.448)		

Statistical analyses

Statistical analysis title	DLCO
Comparison groups	CMK389 10 mg/kg i.v. v Placebo i.v.

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.608
Method	Mixed effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.18
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.05
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	0.664

Secondary: Change in 6-minute walk distance (6MWD) from baseline to 16 weeks of treatment

End point title	Change in 6-minute walk distance (6MWD) from baseline to 16 weeks of treatment

End point description:

The 6MWD test is self-paced, with standardized instructions and encouragement being given as participants walk as far as possible over 6 minutes through a flat corridor. The final distance is recorded in meters. The least squares means for change from baseline in 6MWD to assess the effect of CMK389 compared to placebo after 16 weeks were obtained from a mixed effects model for repeated measures (MMRM). A positive change from baseline in 6MWD is considered a favourable outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	CMK389 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: meters				
least squares mean (standard error)	11.21 (± 9.470)	10.50 (± 9.223)		

Statistical analyses

Statistical analysis title	6MWD
Comparison groups	CMK389 10 mg/kg i.v. v Placebo i.v.

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.479
Method	Mixed effects Model for Repeated Measure
Parameter estimate	Median difference (net)
Point estimate	0.71
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-16.35
upper limit	17.76
Variability estimate	Standard error of the mean
Dispersion value	13.126

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus follow up period, up to a maximum duration of approximately 197 days..

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	CMK389

Reporting group description:

CMK389

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Total

Reporting group description:

Total

Serious adverse events	CMK389	Placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CMK389	Placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 31 (67.74%)	19 / 31 (61.29%)	40 / 62 (64.52%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	2	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	2 / 62 (3.23%)
occurrences (all)	0	2	2
Lipase increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	2	0	2
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	2 / 62 (3.23%)
occurrences (all)	0	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	3 / 62 (4.84%)
occurrences (all)	2	1	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	4 / 62 (6.45%)
occurrences (all)	3	2	5
Headache			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	6 / 62 (9.68%)
occurrences (all)	2	4	6
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	4 / 62 (6.45%)
occurrences (all)	3	1	4
Fatigue			
subjects affected / exposed	4 / 31 (12.90%)	4 / 31 (12.90%)	8 / 62 (12.90%)
occurrences (all)	4	6	10
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	4 / 62 (6.45%)
occurrences (all)	3	1	4
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	3 / 62 (4.84%)
occurrences (all)	1	2	3
Respiratory, thoracic and mediastinal disorders			
Pulmonary sarcoidosis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	3 / 62 (4.84%)
occurrences (all)	2	1	3
Cough			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	6 / 62 (9.68%)
occurrences (all)	2	4	6
Dyspnoea			
subjects affected / exposed	4 / 31 (12.90%)	3 / 31 (9.68%)	7 / 62 (11.29%)
occurrences (all)	4	4	8
Skin and subcutaneous tissue disorders			
Cutaneous sarcoidosis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	2 / 62 (3.23%)
occurrences (all)	2	0	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	2 / 62 (3.23%)
occurrences (all)	0	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 31 (12.90%)	4 / 31 (12.90%)	8 / 62 (12.90%)
occurrences (all)	5	4	9
Back pain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	4 / 62 (6.45%)
occurrences (all)	3	1	4
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	3 / 62 (4.84%)
occurrences (all)	1	2	3
Infections and infestations			

COVID-19			
subjects affected / exposed	3 / 31 (9.68%)	4 / 31 (12.90%)	7 / 62 (11.29%)
occurrences (all)	3	4	7
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	4 / 62 (6.45%)
occurrences (all)	3	2	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 31 (12.90%)	2 / 31 (6.45%)	6 / 62 (9.68%)
occurrences (all)	4	2	6
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	4 / 62 (6.45%)
occurrences (all)	1	3	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2019	The purpose of this amendment was to make operational changes to the visit design to reduce patient and site burden as well as to clarify the procedure in case of premature discontinuation.
17 September 2019	The purpose of this amendment was to make changes to the inclusion criteria and is based on feedback from sites regarding feasibility. The update Inclusion criteria #7 is expected to improve the recruitment rate since lower doses of prednisone (or equivalent) are more common in clinical practice. Now, in the absence of higher prednisone doses, Inclusion criteria #8 has been added as a marker of clinically significant disease
11 December 2019	The purpose of this amendment was to answer to comments from the U.S. Food and Drug Administration (FDA) to add clarifying statements to the exclusion criteria, specify a more objective grading scale for the reporting of Adverse Events, and add instructions for monitoring an adverse event of special interest (hypersensitivity reactions).
17 April 2020	The purpose of this amendment was to answer to comments received from the Paul-Ehrlich-Institut (PEI) in Germany.
20 July 2020	The purpose of this amendment was to answer to comments received from the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom
01 April 2021	The main purpose of this amendment was to revise the inclusion/ exclusion criteria to allow for facilitated recruitment in line with the study rational, and clarify trial conduct. Age and BMI limits are expanded. Inclusion criteria #6 has been clarified to be in line with the study rationale and to include patients with <15% extent of fibrosis instead of <15% reticulation. Pregnancy follow up was re-assessed based on predicted time for IL-18 levels to return within the normal range in healthy volunteers and reduced to 8 weeks after EOS (i.e., 24 weeks after last study treatment). Rescreening is now permitted. The restriction period for administration of live/attenuated vaccines prior to CMK389 treatment is reduced from 3 months to 1 month. The immune response of the vaccine would already be very high and it is therefore expected to have a low risk of any negative impact on either the efficacy or safety profile of the vaccine.

11 August 2021	The main purpose of this amendment was to include Patient Reported Outcomes (PROs) assessments and update the list of eligibility criteria. PROs are added to the protocol to collect more information about health-related quality of life and health status in interstitial lung diseases. These are important parameters of disease activity and prognosis. Both disease symptoms and treatment side effects can impact patients' quality of life.
23 June 2022	The main purpose of this amendment was to revise the inclusion/exclusion criteria to allow for facilitated recruitment in line with the study rationale.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported