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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not Applicable

Trial Indication(s)

Atopic dermatitis

Protocol Number

CCMK389B12201

Protocol Title

A randomized, subject and investigator blinded, placebo-controlled multicenter study to assess the efficacy and safety of CMK389 in patients with moderate to severe atopic dermatitis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: April 20, 2021 (Actual)
Primary Completion Date: July 14, 2022 (Actual)
Study Completion Date: December 13, 2022 (Actual)

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Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a randomized, placebo-controlled, parallel-group, non-confirmatory, investigator and participant blinded study in adult participants with moderate to severe atopic dermatitis. The study consisted of up to 4 weeks screening period to assess participants eligibility, the baseline visit, 4-weekly administrations of CMK389 within the first 12 weeks of the 16-week treatment period, and an approximately 12 weeks follow up period which finished with the end of study visit (EoS). Baseline visit was omitted when the screening visit and Day 1 visit (first study drug administration) were not more than 9 days apart. In that case, the assessments performed at Screening constituted baseline visit assessments.

Women of child-bearing potential (WoCBP) were followed up for 6 months at monthly intervals after the last dose of CMK389 to ensure that they continued to use highly effective contraception. Home urinary pregnancy tests were included during and at the end of this period.

Centers

18 centers in 6 countries: Germany(7), Poland(3), Hungary(2), Czech Republic(2), Spain(1), France(3)

Objectives:

- The primary objective of the trial was to assess the efficacy of CMK389 in participants with moderate to severe atopic dermatitis.

- The secondary objective of the trial was to assess the safety and tolerability of CMK389 in participants with atopic dermatitis.

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

Participants received monthly intravenously (i.v.) doses of CMK389 10 mg/kg or placebo or monthly subcutaneous (s.c.) doses of CMK389 300 mg or placebo.

Statistical Methods

The primary aim of the study was to assess efficacy of CMK389 in participants with moderate to severe atopic dermatitis. This was evaluated by assessing the IGA response at week 16.

Assessing safety and tolerability of CMK389 in participants with atopic dermatitis was the secondary objective of the study. All information obtained on adverse events was displayed by treatment group (CMK389 10 mg/kg i.v., Placebo i.v., CMK389 300 mg s.c., Placebo s.c., and Pooled placebo) and participant. The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) was summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Adult male or female participants with chronic atopic dermatitis, aged 18 to 65 years, present for at least 1 year before screening.

- Participants with Moderate to severe AD defined by IGA score of ≥ 3 (on a scale of 0 to 4, in which 3 is moderate and 4 is severe) at Baseline, EASI score of ≥ 12 at Baseline and Pruritus (NRS) of at least ≥ 3 at Baseline

- Participants who are candidates for a systemic therapy, defined as e.g. inadequate response to treatment with topical medications, or for whom topical treatments are otherwise medically inadvisable (e.g. because of important side effects or safety risks, patients with large affected body surface areas) as assessed by the investigator.

- Participants must have a body mass index (BMI) at screening within the range of 18 to ≤35 kg/m2.

Exclusion Criteria:

- Any skin disease that, in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity.

- Participants taking prohibited medication not completing the wash out period

- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.

- Any active, recent or recurrent systemic or localized infection at screening or prior to first treatment which in the opinion of the investigator immunocompromises the participant and/or places the participant at unacceptable risk for immunomodulatory therapy, such as:
  - Any acute bacterial, fungal, or viral skin/mucosal infection that has not resolved within 2 weeks prior to first treatment or within 12 months in case of eczema herpeticum.
  - Clinically infected AD within 4 weeks prior to first treatment.
  - Any other infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to first treatment.
  - Tuberculosis (TB), Human Immunodeficiency Virus (HIV), Hepatitis B, Hepatitis C

- Any other current or past clinically significant medical condition, including psychiatric condition, which in the Investigator's opinion may interfere with safety of the participant, study objectives or adherence to the protocol.

- Participants with confirmed abnormal absolute neutrophil count (ANC) of <1.5 x 10^9/L or with thrombocytopenia of < 75.0 x 10^9/L at screening and baseline

- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

- History of hypersensitivity to any component of the study drug product, or to drugs of similar chemical classes.

- History of severe or serious allergy or hypersensitivity reactions, such as anaphylactic shock, asthma, or uncontrolled urticaria.

- Pregnant or nursing (lactating) women.

Participant Flow Table

Overall Study

	CMK389 10mg/kg i.v.	CMK389 300mg s.c.	Placebo i.v.	Placebo s.c.	Total
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	
Started	38	17	8	8	71
Safety Analysis set	34	17	8	8	67
Completed	30	17	8	6	61
Not Completed	8	0	0	2	10
Adverse Event	0	0	0	1	1
Lost to Follow-up	1	0	0	0	1
Subject/Guardian decision	3	0	0	1	4
Randomized but not treated	4	0	0	0	4

Baseline Characteristics

	CMK389 10mg/kg i.v.	CMK389 300mg s.c.	Placebo i.v.	Placebo s.c.	Total
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	
Number of Participants [units: participants]	34	17	8	8	67
Baseline Analysis Population Description	Safety analysis set defined as all participants who received any study drug.				

Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation					
	33.7±9.86	34.1±11.35	35.3±8.86	31.9±8.53	33.8±9.83
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants					
Female	8	9	3	2	22
Male	26	8	5	6	45
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants					
Asian	0	1	0	0	1
White	34	16	8	8	66

Primary Outcome Result(s)

Number of participants with Investigator Global assessment (IGA) response

Description	The Investigator Global assessment (IGA) scale used was vIGA-AD™ (Validated Investigator Global Assessment scale for Atopic Dermatitis). The IGA rating scale was used to determine the severity of atopic dermatitis and clinical response to treatment. It reflected a participant's overall disease severity for the whole body based on a 5-point scale. The 5-point scale included: clear, almost clear, mild, moderate, and severe disease. IGA response is defined as clear or almost clear and at least a 2 point-reduction from baseline at week 16.
Time Frame	Baseline, Week 16
Analysis Population Description	The safety analysis set included all participants who received any study drug.

	CMK389 10mg/kg i.v.	CMK389 300mg s.c.	Placebo i.v.	Placebo s.c.	Pooled Placebo
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	Pooled Placebo monthly i.v. and s.c. dose
Number of Participants Analyzed [units: participants]	34	17	8	8	16
Number of participants with Investigator Global assessment (IGA) response (units: participants)	**Count of Participants**	**Count of Participants**	**Count of Participants**	**Count of Participants**	**Count of Participants**
Week 16	5 (14.71%)	2 (11.76%)	0 (%)	0 (%)	0 (%)

Secondary Outcome Result(s)

Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

Description	Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs led to study treatment discontinuation, SAEs and SAEs led to study treatment discontinuation.
Time Frame	AEs were reported from first dose until the end of the 12 weeks follow up period, up to a max. duration of approx. 197 days. For women of child-bearing potential, pregnancies were reported (if occurred) for up to approx. 268 days after first dose.
Analysis Population Description	The safety analysis set included all participants who received any study drug.

	CMK389 10mg/kg i.v.	CMK389 300mg s.c.	Placebo i.v.	Placebo s.c.
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose

Number of Participants Analyzed [units: participants]	34	17	8	8
Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) (units: participants)	**Count of Participants**	**Count of Participants**	**Count of Participants**	**Count of Participants**
Adverse Events	25 (73.53%)	11 (64.71%)	5 (62.5%)	8 (100%)
Serious Adverse Events	1 (2.94%)	1 (5.88%)	0 (%)	0 (%)
AEs leading to discontinuation of study treatment	0 (%)	0 (%)	0 (%)	0 (%)
SAEs leading to discontinuation of study treatment	0 (%)	0 (%)	0 (%)	0 (%)

Safety Results

Time Frame	AEs were reported from first dose until the end of the 12 weeks follow up period, up to a max. duration of approx. 197 days. For women of child-bearing potential, pregnancies were reported (if occurred) for up to approx. 268 days after first dose.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

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All-Cause Mortality

	CMK389 10 mg/kg i.v. N = 34	CMK389 300 mg s.c. N = 17	Placebo i.v. N = 8	Placebo s.c. N = 8	Pooled Placebo N = 16	Total N = 67
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	Pooled Placebo monthly i.v. and s.c. dose	Total
Total Number Affected	0	0	0	0	0	0
Total Number At Risk	34	17	8	8	16	67

Serious Adverse Events

	CMK389 10 mg/kg i.v. N = 34	CMK389 300 mg s.c. N = 17	Placebo i.v. N = 8	Placebo s.c. N = 8	Pooled Placebo N = 16	Total N = 67
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	Pooled Placebo monthly i.v. and s.c. dose	Total
Total # Affected by any Serious Adverse Event	1	1	0	0	0	2
Total # at Risk by any Serious Adverse Event	34	17	8	8	16	67
Reproductive system and breast disorders						
Heavy menstrual bleeding	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Skin and subcutaneous tissue disorders						
Dermatitis atopic	1 (2.94%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)

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Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	CMK389 10 mg/kg i.v. N = 34	**CMK389 300 mg s.c. N = 17**	**Placebo i.v. N = 8**	**Placebo s.c. N = 8**	**Pooled Placebo N = 16**	**Total N = 67**
Arm/Group Description	CMK389 10 mg/kg monthly i.v. dose	CMK389 300mg monthly s.c. dose	Placebo monthly i.v. dose	Placebo monthly s.c. dose	Pooled Placebo monthly i.v. and s.c. dose	Total
Total # Affected by any Other Adverse Event	20	11	5	8	13	44
Total # at Risk by any Other Adverse Event	34	17	8	8	16	67
Blood and lymphatic system disorders						
Anaemia	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Cardiac disorders						
Sinus bradycardia	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
Ear and labyrinth disorders						
Vertigo	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Eye disorders						
Eyelid oedema	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)

Visual impairment	0 (0.00%)	1 (5.88%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	2 (2.99%)
Gastrointestinal disorders						
Diarrhoea	3 (8.82%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (7.46%)
Nausea	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
General disorders and administration site conditions						
Fatigue	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
Injection site reaction	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Infections and infestations						
Asymptomatic bacteriuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Bacteriuria	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
COVID-19	10 (29.41%)	5 (29.41%)	3 (37.50%)	1 (12.50%)	4 (25.00%)	19 (28.36%)
Nasopharyngitis	7 (20.59%)	4 (23.53%)	1 (12.50%)	1 (12.50%)	2 (12.50%)	13 (19.40%)
Otitis externa	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Rhinitis	1 (2.94%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)
Upper respiratory tract infection	1 (2.94%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)
Investigations						
Alanine aminotransferase increased	2 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)
Aspartate aminotransferase increased	2 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)
Blood creatine increased	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Blood creatine phosphokinase increased	2 (5.88%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	3 (4.48%)
Blood ketone body increased	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)

Glucose urine	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Urinary sediment present	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
Urine analysis abnormal	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
Metabolism and nutrition disorders						
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Hyperlipidaemia	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Musculoskeletal and connective tissue disorders						
Arthralgia	2 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)
Bursitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Muscle tightness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Uterine leiomyoma	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Nervous system disorders						
Dizziness	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Headache	3 (8.82%)	1 (5.88%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	5 (7.46%)
Migraine	0 (0.00%)	0 (0.00%)	2 (25.00%)	0 (0.00%)	2 (12.50%)	2 (2.99%)
Renal and urinary disorders						
Hypertonic bladder	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Reproductive system and breast disorders						
Menstruation irregular	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)

Respiratory, thoracic and mediastinal disorders						
Dysphonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (6.25%)	1 (1.49%)
Oropharyngeal pain	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Rhinitis allergic	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)	1 (6.25%)	1 (1.49%)
Skin and subcutaneous tissue disorders						
Dermatitis atopic	2 (5.88%)	2 (11.76%)	0 (0.00%)	4 (50.00%)	4 (25.00%)	8 (11.94%)
Psoriasis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.49%)
Vascular disorders						
Hypertension	0 (0.00%)	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.99%)

Conclusion:

- Only participants on CMK389 10 mg/kg i.v. (14.71%) and CMK389 300 mg s.c. (11.76%) obtained an IGA response compared with pooled placebo (0%).
- Treatment with CMK389 was well tolerated with a favorable safety profile.

Date of Clinical Trial Report

22-September-2023