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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iscalimab

Trial Indication(s)

Lupus Nephritis

Protocol Number

CCFZ533X2202

Protocol Title

A randomized, placebo-controlled, patient and investigator blinded, study investigating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of CFZ533 in patients with moderately active proliferative lupus nephritis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

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Study Start/End Dates

Study Start Date: September 12, 2018 (Actual)
Primary Completion Date: June 29, 2023 (Actual)
Study Completion Date: June 29, 2023 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was an exploratory, randomized (2:1 active:placebo), subject- and investigator-blind, placebo-controlled, multicenter study evaluating the safety, tolerability, PK, and preliminary efficacy of multiple doses of 10 mg/kg CFZ533 administered IV in lupus nephritis (LN) patients.

The study comprised of two periods. The 24-week treatment period was followed by a 24-week safety follow-up period (starting on Day 169). The duration of the study (including a screening period of up to 4 weeks) for each subject was approximately 53 weeks. The investigational drug or placebo was administered on top of standard of care therapy for LN. The randomization was stratified by Baseline daily dose equivalent of prednisone (≤10 mg, >10 mg). Patients who did not receive corticosteroids at Baseline were included in the ≤10 mg stratum.

Centers

21 centers in 10 countries: Hungary(1), Hong Kong(1), Turkey(1), Taiwan(3), Korea, Republic of(2), Argentina(2), Germany(1), Russia(4), Tunisia(1), China(5)

Objectives:

Primary objectives:

- To evaluate the safety and tolerability of 24 weeks of treatment with multiple intravenous (IV) doses of 10 mg/kg CFZ533 as an add-on therapy of CFZ533 to standard of care in moderately active lupus nephritis (LN) patients

- To assess the effect of CFZ533 on renal proteinuria using urinary protein creatinine ratio (UPCR) in moderately active LN patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo

Secondary objectives:

- To assess the effect of CFZ533 on relevant renal outcomes at different time points

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CFZ533 in LN patients after multiple 10 mg/kg IV doses

- To evaluate the immunogenicity of CFZ533 in LN patients after multiple 10 mg/kg IV doses

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

Subjects were assigned to one of the following two treatment arms in a ratio of 2:1:

- CFZ533 (Iscalimab): multiple doses of 10 mg/kg CFZ533 IV infusion

- Placebo: multiple doses of placebo IV infusion

The dosage form of the supplied drug was a “ready to use” aqueous buffered sterile solution also referred to as CFZ533 Concentrate for infusion (liquid in vial). The solution contained 150 mg/mL CFZ533 and the excipients L-histidine, sucrose, and polysorbate 20, pH 6.0 ± 0.5. The placebo control selected for this study was a solution with matching composition of inactive excipients.

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Statistical Methods

Analysis sets:

For all analysis sets, subjects were analyzed according to the study treatments received.

The safety analysis set included all subjects that received any study drug.

The pharmacokinetic (PK) analysis set included all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement who received any study drug and with no protocol deviations that impact on PK data.

The pharmacodynamic (PD) analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data.

Efficacy: The primary variable was the ratio from baseline in UPCR at Week 25 (Day 169) using first morning void. This ratio was log transformed prior to the analysis. A repeated measures mixed model was fitted with factors for treatment group (CFZ533 or placebo) and visit (e.g., Week 5, 9, 13, etc.). The model also included a factor for the prednisone dose-equivalent at Baseline (≤ 10 mg, >10 mg), which was a stratification factor for the randomization. Log-transformed baseline UPCR was included in the model as a covariate along with the interactions between visit and all of the fixed effects. A normal errors model was assumed with an unstructured covariance matrix to account for the correlation within subjects.

At the day 169 visit, the difference between the CFZ533 and placebo group was estimated (along with its corresponding 95% confidence interval) and then back-transformed to provide an estimate of the ratio between treatment groups.

PD: Total soluble CD40 concentrations in plasma were listed by treatment. Descriptive summary statistics were provided by treatment and visit/sampling time point.

PK: Descriptive summary statistics were provided. CFZ533 plasma concentrations below the lower limit of quantification (LLOQ) were considered as zero for the calculation of PK parameters.

Safety: Descriptive statistics were provided for the safety data.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Men and women with systemic lupus erythematosus (SLE) aged ≥ 18 years and ≤ 75 years at screening, fulfilling at least 4 out of 11 criteria for SLE as defined by the American College of Rheumatology (Tan at al 1982, revised by Hochberg 1997)
- Subjects must have a body mass index (BMI) within the range of 18 - 40 kg/m2 at screening visit
- Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening
- Presence of antinuclear autoantibody (ANA titer ≥ 1:80) at screening
- Morning UPCR ≥ 0.5 at screening visit and baseline visit
- At least one of the following:

a) low complement level (C3 < 0.9 g/L) or (C4 < 0.1 g/L), and/or

b) elevated anti-dsDNA (≥ 30 IU/mL), and/or

c) urine sediment consistent with active proliferative LN such as presence of cellular (granular or red blood cell) casts or hematuria (>5 red blood cells per high power field) if other causes such as menstrual bleeding are excluded

- Patient must have sufficient kidney function as estimated by eGFR > 30mL/min/1.73 m2 at screening and baseline visits (Levey et al 2009)
- Patient must have active disease as defined by proteinuria and additional symptoms as above despite standard of care therapy for LN as considered appropriate by the treating physician (e.g., corticosteroids and/or immunosuppressive or immunomodulatory treatments such as mycophenolate, azathioprine, methotrexate or hydroxychloroquine). For guidance, see published guidelines such

as Bertsias et all 2012 and Hahn et al 2012.

- Women of childbearing potential (defined as all women physiologically capable of becoming pregnant) must use highly effective methods of contraception during dosing and until study completion.

Key Exclusion Criteria:

- Any glomerulonephritis other than WHO Class III or IV lupus nephritis. Patients with proliferative nephritis (Class III or IV) who, in addition, have overlapping histological signs for other glomerulonephritis, e.g., Class V, are eligible at the investigator´s discretion.
- Hypoalbuminemia (serum albumin of less than 2.0 g/dL)
- Patients who have received:

a) oral or i.v. cyclophosphamide within 3 months prior to randomization

b) i.v. corticosteroid bolus (dose > 1 mg/kg) within 3 months prior to randomization

c) rituximab or other B cell depleting agent within 12 months. for patients who received such treatment earlier, B cell count should be within normal ranges prior to randomization

d) belimumab within 6 months prior to randomization

e) any other biologic drug or an investigational drug within one months or five times the half-life, whichever is longer prior to randomization

f) any calcineurin inhibitor (e.g., tacrolimus or cyclosporin A) within 3 months prior to randomization

- Patients who are at significant risk for the thromboembolic events based on the following:

a) history of either thrombosis or 3 or more spontaneous abortions

b) presence of lupus anticoagulant or prolonged activated partial thromboplastin time (aPTT) and no prophylactic treatment with aspirin or anticoagulants as per local standard of care

- Have had signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to randomization

- Live vaccines within 4 weeks of the first study drug infusion

Participant Flow Table

Treatment Epoch

	CFZ533 10 mg/kg i.v.	Placebo i.v.	Total
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	
Started	39	18	57
Completed	21	10	31
Not Completed	18	8	26
Adverse Event	3	1	4
Death	1	0	1
Lack of Efficacy	0	1	1
No longer requires treatment	1	0	1
Non-Compliance with study treatment	1	0	1
Physician Decision	8	5	13
Protocol Deviation	1	0	1
Withdrawal by Subject	3	1	4

Post-Treatment follow-up

	CFZ533 10 mg/kg i.v.	Placebo i.v.	Total

Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	
Started	34	16	50
Completed	32	16	48
Not Completed	2	0	2
Subject/Guardian Decision	1	0	1
Death	1	0	1

Baseline Characteristics

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**	**Total**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	
Number of Participants [units: participants]	39	18	57
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Mean ± Standard Deviation			
	34.1±9.20	36.4±9.15	34.8±9.17
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	30	17	47
Male	9	1	10
Race/Ethnicity, Customized (units: participants)			

Analysis Population Type: Participants
Count of Participants (Not Applicable)

White	16	7	23
Asian	23	11	34

Primary 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	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 49 weeks.
Analysis Population Description	The safety analysis set included all participants who received any study drug.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	39	18
Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) (units: participants)	**Count of Participants**	**Count of Participants**
Adverse Events	33 (84.62%)	18 (100%)
Serious Adverse Events	6 (15.38%)	3 (16.67%)

AEs leading to discontinuation of study treatment	3 (7.69%)	1 (5.56%)
SAEs leading to discontinuation of study treatment	0 (%)	0 (%)

Ratio to Baseline in Urinary protein creatinine ratio (UPCR)

Description	A urine protein creatinine ratio (UPCR) test is a urine test. It measures the levels of protein and creatinine in urine. UPCR was assessed using the first morning void if available at a visit otherwise using the clinic spot sample, and was expressed as protein/creatinine (mg/mmol). High UPCR values can be a sign of kidney disease. An UPCR ratio to baseline <1 indicates improvement from baseline.
Time Frame	Baseline, Day 169
Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with an available value for the outcome measure. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	20	10
Ratio to Baseline in Urinary protein creatinine ratio (UPCR) (units: ratio to baseline in UPCR)	**Geometric Mean** **(95% Confidence Interval)**	**Geometric Mean** **(95% Confidence Interval)**
	0.369 (0.234 to 0.582)	0.637 (0.338 to 1.202)

Statistical Analysis

Groups	CFZ533 10 mg/kg i.v., Placebo i.v.
Type of Statistical Test	Other

Non-Inferiority/Equivalence Test	A repeated measures mixed model was fitted with factors for treatment group (CFZ533 or placebo) and visit.	
P Value	0.0788	one-sided p-value
Method	Other Repeated measures Mixed Model	
Other Ratio of geometric means CFZ533/placebo	0.579	
95 % Confidence Interval 2-Sided	0.267 to 1.256	

Secondary Outcome Result(s)

Ratio to baseline for urine protein creatinine ratio (UPCR)

Description	A urine protein creatinine ratio (UPCR) test is a urine test. It measures the levels of protein and creatinine in urine. UPCR was assessed using the first morning void if available at a visit otherwise using the clinic spot sample, and was expressed as protein/creatinine (mg/mmol). High UPCR values can be a sign of kidney disease. An UPCR ratio to baseline <1 indicates improvement from baseline. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 (End of Study)
Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with an available value for the outcome measure. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	35	16

Ratio to baseline for urine protein creatinine ratio (UPCR) (units: ratio to baseline in UPCR)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**
Day 197	0.532 ± 0.4160	0.985 ± 0.9045
Day 225 (n=32,16)	0.456 ± 0.3876	1.153 ± 1.2178
Day 253 (n=33,14)	0.648 ± 1.3314	0.667 ± 0.3612
Day 281 (n=27,13)	0.526 ± 0.5440	0.701 ± 0.7690
Day 309 (n=26,12)	0.580 ± 0.7175	1.101 ± 1.1337
Day 337 (n=20,10)	0.640 ± 0.7446	0.735 ± 0.5323

Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of CFZ533

Description	Pharmacokinetic parameters were directly derived from the PK concentration data using non-compartmental analysis. AUClast is the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of free CFZ533.
Time Frame	Day 141: pre dose and 1 hour post dose
Analysis Population Description	Participants in the Pharmacokinetic (PK) analysis set with an available value for the outcome measure. The (PK) analysis set included all subjects with at least one available valid PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. The PK analysis set is only applicable to the CFZ533 arm.

	CFZ533 10 mg/kg i.v.
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	11
Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of CFZ533 (units: day*ug/mL)	**Mean** **± Standard Deviation**
	7250 ± 1800

Pre-dose trough concentration (Ctrough) of CFZ533

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, or at the end 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.
Time Frame	Pre-dose at: Day 1, Day 15, Day 29, Day 57, Day 85, Day 113 and Day 141
Analysis Population Description	Participants in the Pharmacokinetic (PK) analysis set with an available value for the outcome measure. The (PK) analysis set included all subjects with at least one available valid PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. The PK analysis set is only applicable to the CFZ533 arm.

	CFZ533 10 mg/kg i.v.
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	33
Pre-dose trough concentration (Ctrough) of CFZ533 (units: ug/mL)	**Mean ± Standard Deviation**
Day 1 (n=33)	0 ± 0
Day 15 (n=14)	49.8 ± 37.0
Day 29 (n=30)	64.1 ± 31.6
Day 57 (n=15)	34.5 ± 21.7
Day 85 (n=25)	33.2 ± 25.0
Day 113 (n=26)	32.7 ± 26.3
Day 141 (n=21)	34.1 ± 26.6

The observed maximum plasma concentration following CFZ533 administration at steady state (Cmax,ss)

Description	Pharmacokinetic parameters were directly derived from the PK concentration data using non-compartmental analysis. Cmax,ss is the observed maximum plasma concentration following CFZ533 administration at steady state [mass/volume].

Time Frame	Day 141: pre dose and 1 hour post dose
Analysis Population Description	Participants in the Pharmacokinetic (PK) analysis set with an available value for the outcome measure. The PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. The PK analysis set is only applicable to the CFZ533 arm.

	CFZ533 10 mg/kg i.v.
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	20
The observed maximum plasma concentration following CFZ533 administration at steady state (Cmax,ss) (units: ug/mL)	**Mean ± Standard Deviation**
	263 ± 81.8

Total soluble CD40 plasma concentrations

Description	Total soluble CD40 concentrations in plasma. An increase in soluble CD40 concentrations is considered a marker for CFZ533 target engagement. This endpoint is only applicable to the CFZ533 arm. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Day 1, Day 15, Day 29, Day 57, Day 113, Day 169, Day 225, Day 281, Day 337 (End of Study)
Analysis Population Description	Participants in the Pharmacodynamics (PD) analysis set who received CFZ533 and had an available value for the outcome measure. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141

Number of Participants Analyzed [units: participants]	30
Total soluble CD40 plasma concentrations (units: ng/mL)	**Mean ± Standard Deviation**
Day 1 (n=30)	0.2723 ± 0.22222
Day 15 (n=16)	78.7375 ± 20.58802
Day 29 (n=28)	90.4286 ± 23.86165
Day 57 (n=14)	127.6214 ± 26.11617
Day 113 (n=24)	109.2672 ± 50.19834
Day 169 (n=7)	158.5714 ± 22.24753
Day 225 (n=16)	8.3406 ± 17.77703
Day 281 (n=15)	0.7981 ± 0.32464
Day 337 (End of Study) (n=13)	0.5331 ± 0.30080

Number of participants with anti-CFZ533 antibodies

Description	To evaluate the immunogenicity of CFZ533 via the quasi-quantitative analysis of anti-CFZ533 antibodies. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Day 1, Day 15, Day 29, Day 57, Day 113, Day 169, Day 225, Day 281, Day 337 (End of study)
Analysis Population Description	Participants in the Pharmacodynamics (PD) analysis set who received CFZ533 and had an available value for the outcome measure. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	33	16
Number of participants with anti-CFZ533 antibodies (units: Participants)		

Day 1-Negative (n=33,13)	32	13
Day 1-Positive (n=33,13)	1	0
Day 15-Negative (n=17,8)	17	8
Day 15-Positive (n=17,8)	0	0
Day 29-Negative (n=33,16)	33	16
Day 29-Positive (n=33,16)	0	0
Day 57-Negative (n=17,8)	17	8
Day 57-Positive (n=17,8)	0	0
Day 113-Negative (n=32,15)	32	15
Day 113-Positive (n=32,15)	0	0
Day 169-Negative (n=14,8)	14	8
Day 169-Positive (n=14,8)	0	0
Day 225-Negative (n=26,13)	25	13
Day 225-Positive (n=26,13)	1	0
Day 281-Negative (n=24,13)	23	13
Day 281-Positive (n=24,13)	1	0
Day 337-Negative (EOS) (n=13,8)	12	8
Day 337-Positive (EOS) (n=13,8)	1	0

Hematuria casts- Urine white blood cell casts

Description	Urine was tested using a dipstick. If the dipstick result was positive for protein, nitrite, leucocytes and/or blood, a microscopic analysis of white blood cells (WBC), red blood cells (RBC) and casts was performed. Hematuria is the presence of blood in the urine. Hematuria casts were assessed by microscopic urinalysis and classified as granular casts and WBC casts. Only in the event of a positive result, these samples were submitted to reflex testing microscopic analysis for counting of casts which resulted in a numeric value related to the number of respective casts presented in the urine. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Baseline, Day 1 (Pre dose), and Day 309

Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with a microscopic urinalysis and an available value for the outcome measure at baseline and the corresponding time point. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	37	18
Hematuria casts- Urine white blood cell casts (units: number of casts per low power field)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Baseline (n=1,0)	2	
Day 1 (n=1,0)	2	
Day 309 (n=1,0)	4	

Hematuria casts- Casts granular

Description	Urine was tested using a dipstick. If the dipstick result was positive for protein, nitrite, leucocytes and/or blood, a microscopic analysis of white blood cells (WBC), red blood cells (RBC) and casts was performed. Hematuria is the presence of blood in the urine. Hematuria casts were assessed by microscopic urinalysis and classified as granular casts and WBC casts. Only in the event of a positive result, these samples were submitted to reflex testing microscopic analysis for counting of casts which resulted in a numeric value related to the number of respective casts presented in the urine. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Day 1 (Pre dose), Day 15 (Pre dose), Day 29 (Pre dose), Day 253, and Day 337 (end of study)
Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with a microscopic urinalysis and an available value for the outcome measure at baseline and the corresponding time point. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**

Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	37	18
Hematuria casts- Casts granular (units: number of casts per low power field)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**
Day 1 (n=1,0)	3	
Day 15 (n=2,0)	2.5 ± 0.71	
Day 29 (n=0,2)		3 ± 1.41
Day 253 (n=1,0)	14.0	
Day 337 (End of Study) (n=2,0)	5 ± 2.83	

Change from baseline in urine hyaline casts

Description	Urine was tested using a dipstick. If the dipstick result was positive for protein, nitrite, leucocytes and/or blood, a microscopic analysis of white blood cells (WBC), red blood cells (RBC) and casts was performed. Urine hyaline casts were assessed by microscopic urinalysis. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.
Time Frame	Baseline, Day 1 (Pre dose), Day 15 (Pre dose), Day 29 (Pre dose), Day 57 (Pre dose), Day 85 (Pre dose), Day 113 (Pre dose), Day 141 (Pre dose), Day 169, Day 197, Day 225, Day 253, Day 281, Day 309 and Day 337 (end of study)
Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with a microscopic urinalysis and an available value for the outcome measure at baseline and the corresponding time point. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data. The participants analyzed are the ones with available value for the outcome measure at baseline and the corresponding time point.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	37	18
Change from baseline in urine hyaline casts (units: number of casts per low power field)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**

Day 1 (n=0,0)		
Day 15 (n=4,3)	8.3 ± 15.88	3.7 ± 3.51
Day 29 (n=4,4)	2.8 ± 4.99	5.0 ± 2.16
Day 57 (n=3,2)	-5.0 ± 3.61	1.0 ± 1.41
Day 85 (n=2,1)	0.5 ± 2.12	-4.0
Day 113 (n=0,3)		18.0 ± 28.58
Day 141 (n=0,2)		-4.5 ± 6.36
Day 169 (n=1,1)	0.0	0.0
Day 197 (n=3,3)	-1.0 ± 2.65	2.7 ± 9.02
Day 225 (n=1,1)	2.0	0.0
Day 253 (n=0,2)		-0.5 ± 4.95
Day 281 (n=1,2)	0.0	-1.5 ± 4.95
Day 309 (n=3,1)	1.7 ± 1.15	-4.0
Day 337 (EOS) (n=0,2)		0.5 ± 0.71

Number of participants who fulfil the criteria for complete renal remission (CRR)

Description	The criteria for CRR were defined as: 1. Urinary protein creatinine ratio (UPCR) ≤ 0.2 mg/mg 2. Estimated glomerular filtration rate (eGFR) ≤ 25% of Baseline 3. Normal urine sediment. If the UPCR from the first morning void sample was not available, then the UPCR from the corresponding spot sample taken at the investigator site was used in the derivation of complete renal remission.
Time Frame	Baseline, up to Day 169
Analysis Population Description	Participants in the pharmacodynamics (PD) analysis set with an available value for the outcome measure. The PD analysis set included all participants with available PD data and no protocol deviations with relevant impact on PD data.

	CFZ533 10 mg/kg i.v.	**Placebo i.v.**

Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141
Number of Participants Analyzed [units: participants]	37	18
Number of participants who fulfil the criteria for complete renal remission (CRR) (units: participants)	**Count of Participants**	**Count of Participants**
Complete Response	13 (35.14%)	4 (22.22%)

Safety Results

Time Frame	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 49 weeks.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	CCFZ533 10mg/kg N = 39	**Placebo i.v. N = 18**	**All patients N = 57**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	All patients
Total Number Affected	2	0	2
Total Number At Risk	39	18	57

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Serious Adverse Events

	CCFZ533 10mg/kg N = 39	Placebo i.v. N = 18	All patients N = 57
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	All patients
Total # Affected by any Serious Adverse Event	6	3	9
Total # at Risk by any Serious Adverse Event	39	18	57
Hepatobiliary disorders			
Cholecystitis	0 (0.00%)	1 (5.56%)	1 (1.75%)
Immune system disorders			
Haemophagocytic lymphohistiocytosis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Infections and infestations			
Bronchitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Cytomegalovirus infection reactivation	1 (2.56%)	0 (0.00%)	1 (1.75%)
Gastroenteritis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Pneumonia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Urinary tract infection	1 (2.56%)	0 (0.00%)	1 (1.75%)
Urosepsis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus	0 (0.00%)	1 (5.56%)	1 (1.75%)

Psychiatric disorders			
Suicidal behaviour	0 (0.00%)	1 (5.56%)	1 (1.75%)
Renal and urinary disorders			
Lupus nephritis	0 (0.00%)	1 (5.56%)	1 (1.75%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 0%

	CCFZ533 10mg/kg N = 39	**Placebo i.v. N = 18**	**All patients N = 57**
Arm/Group Description	CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	All patients
Total # Affected by any Other Adverse Event	32	18	50
Total # at Risk by any Other Adverse Event	39	18	57
Blood and lymphatic system disorders			
Anaemia	2 (5.13%)	0 (0.00%)	2 (3.51%)
Leukocytosis	3 (7.69%)	0 (0.00%)	3 (5.26%)
Leukopenia	2 (5.13%)	1 (5.56%)	3 (5.26%)
Lymphadenitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Thrombocytopenia	1 (2.56%)	0 (0.00%)	1 (1.75%)

Ear and labyrinth disorders			
Vertigo	0 (0.00%)	1 (5.56%)	1 (1.75%)
Eye disorders			
Corneal erosion	0 (0.00%)	1 (5.56%)	1 (1.75%)
Eyelid bleeding	1 (2.56%)	0 (0.00%)	1 (1.75%)
Keratitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Visual acuity reduced	0 (0.00%)	1 (5.56%)	1 (1.75%)
Gastrointestinal disorders			
Abdominal pain upper	1 (2.56%)	0 (0.00%)	1 (1.75%)
Aphthous ulcer	1 (2.56%)	0 (0.00%)	1 (1.75%)
Chronic gastritis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Flatulence	1 (2.56%)	0 (0.00%)	1 (1.75%)
Gastritis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Gingival pain	2 (5.13%)	0 (0.00%)	2 (3.51%)
Gingival swelling	1 (2.56%)	0 (0.00%)	1 (1.75%)
Mouth ulceration	1 (2.56%)	1 (5.56%)	2 (3.51%)
Oesophagitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
General disorders and administration site conditions			
Oedema peripheral	1 (2.56%)	2 (11.11%)	3 (5.26%)
Hepatobiliary disorders			
Cholecystitis	1 (2.56%)	1 (5.56%)	2 (3.51%)
Cholelithiasis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Hepatic function abnormal	2 (5.13%)	0 (0.00%)	2 (3.51%)

Infections and infestations

Bronchitis	1 (2.56%)	1 (5.56%)	2 (3.51%)
Conjunctivitis	1 (2.56%)	1 (5.56%)	2 (3.51%)
COVID-19	5 (12.82%)	3 (16.67%)	8 (14.04%)
Cystitis	0 (0.00%)	1 (5.56%)	1 (1.75%)
Cytomegalovirus infection	1 (2.56%)	0 (0.00%)	1 (1.75%)
Folliculitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Fungal skin infection	1 (2.56%)	0 (0.00%)	1 (1.75%)
Gastroenteritis	2 (5.13%)	0 (0.00%)	2 (3.51%)
Gastrointestinal infection	1 (2.56%)	0 (0.00%)	1 (1.75%)
Herpes simplex	0 (0.00%)	2 (11.11%)	2 (3.51%)
Herpes zoster	3 (7.69%)	1 (5.56%)	4 (7.02%)
Influenza	1 (2.56%)	0 (0.00%)	1 (1.75%)
Nasopharyngitis	4 (10.26%)	0 (0.00%)	4 (7.02%)
Peri-implantitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Pharyngitis	1 (2.56%)	1 (5.56%)	2 (3.51%)
Pneumonia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Pulpitis dental	1 (2.56%)	0 (0.00%)	1 (1.75%)
Pyuria	0 (0.00%)	1 (5.56%)	1 (1.75%)
Respiratory tract infection viral	1 (2.56%)	0 (0.00%)	1 (1.75%)
Soft tissue infection	1 (2.56%)	0 (0.00%)	1 (1.75%)
Tinea cruris	1 (2.56%)	0 (0.00%)	1 (1.75%)
Tonsillitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Tuberculosis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Upper respiratory tract infection	7 (17.95%)	2 (11.11%)	9 (15.79%)

Urinary tract infection	2 (5.13%)	3 (16.67%)	5 (8.77%)
Vulvovaginal candidiasis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Injury, poisoning and procedural complications			
Arthropod bite	0 (0.00%)	1 (5.56%)	1 (1.75%)
Limb injury	1 (2.56%)	0 (0.00%)	1 (1.75%)
Skin wound	1 (2.56%)	0 (0.00%)	1 (1.75%)
Tooth fracture	2 (5.13%)	0 (0.00%)	2 (3.51%)
Upper limb fracture	1 (2.56%)	0 (0.00%)	1 (1.75%)
Investigations			
Blood bicarbonate decreased	0 (0.00%)	1 (5.56%)	1 (1.75%)
Blood creatinine increased	1 (2.56%)	0 (0.00%)	1 (1.75%)
Blood immunoglobulin G decreased	1 (2.56%)	0 (0.00%)	1 (1.75%)
Blood immunoglobulin M decreased	1 (2.56%)	0 (0.00%)	1 (1.75%)
Blood pressure increased	0 (0.00%)	1 (5.56%)	1 (1.75%)
Lymphocyte count decreased	2 (5.13%)	0 (0.00%)	2 (3.51%)
Neutrophil count increased	3 (7.69%)	0 (0.00%)	3 (5.26%)
Protein urine present	0 (0.00%)	1 (5.56%)	1 (1.75%)
Red blood cell sedimentation rate increased	1 (2.56%)	1 (5.56%)	2 (3.51%)
Systemic lupus erythematosus disease activity index abnormal	1 (2.56%)	0 (0.00%)	1 (1.75%)
Urine albumin/creatinine ratio increased	1 (2.56%)	0 (0.00%)	1 (1.75%)
Urine protein/creatinine ratio increased	0 (0.00%)	1 (5.56%)	1 (1.75%)
Weight decreased	1 (2.56%)	0 (0.00%)	1 (1.75%)
White blood cell count decreased	1 (2.56%)	0 (0.00%)	1 (1.75%)
Metabolism and nutrition disorders			

Decreased appetite	2 (5.13%)	0 (0.00%)	2 (3.51%)
Diabetes mellitus	1 (2.56%)	0 (0.00%)	1 (1.75%)
Hypercalcaemia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Hyperlipidaemia	1 (2.56%)	1 (5.56%)	2 (3.51%)
Hypertriglyceridaemia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Hypoproteinaemia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (2.56%)	1 (5.56%)	2 (3.51%)
Back pain	0 (0.00%)	1 (5.56%)	1 (1.75%)
Bursitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Pain in extremity	1 (2.56%)	0 (0.00%)	1 (1.75%)
Periarthritis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Systemic lupus erythematosus	0 (0.00%)	1 (5.56%)	1 (1.75%)
Tendonitis	1 (2.56%)	0 (0.00%)	1 (1.75%)
Nervous system disorders			
Headache	1 (2.56%)	2 (11.11%)	3 (5.26%)
Occipital neuralgia	1 (2.56%)	0 (0.00%)	1 (1.75%)
Psychiatric disorders			
Insomnia	2 (5.13%)	0 (0.00%)	2 (3.51%)
Sleep disorder	1 (2.56%)	0 (0.00%)	1 (1.75%)
Renal and urinary disorders			
Acute kidney injury	1 (2.56%)	0 (0.00%)	1 (1.75%)
Haematuria	0 (0.00%)	1 (5.56%)	1 (1.75%)
Lupus nephritis	1 (2.56%)	0 (0.00%)	1 (1.75%)

Proteinuria	0 (0.00%)	1 (5.56%)	1 (1.75%)
Reproductive system and breast disorders			
Adenomyosis	0 (0.00%)	1 (5.56%)	1 (1.75%)
Menstrual disorder	1 (2.56%)	0 (0.00%)	1 (1.75%)
Respiratory, thoracic and mediastinal disorders			
Cough	2 (5.13%)	0 (0.00%)	2 (3.51%)
Nasal congestion	0 (0.00%)	1 (5.56%)	1 (1.75%)
Oropharyngeal pain	0 (0.00%)	1 (5.56%)	1 (1.75%)
Productive cough	1 (2.56%)	0 (0.00%)	1 (1.75%)
Rhinorrhoea	1 (2.56%)	0 (0.00%)	1 (1.75%)
Skin and subcutaneous tissue disorders			
Acne	1 (2.56%)	0 (0.00%)	1 (1.75%)
Alopecia	0 (0.00%)	1 (5.56%)	1 (1.75%)
Butterfly rash	1 (2.56%)	0 (0.00%)	1 (1.75%)
Dermatitis allergic	2 (5.13%)	0 (0.00%)	2 (3.51%)
Dermatitis contact	1 (2.56%)	0 (0.00%)	1 (1.75%)
Ecchymosis	1 (2.56%)	1 (5.56%)	2 (3.51%)
Pruritus	1 (2.56%)	0 (0.00%)	1 (1.75%)
Rash	1 (2.56%)	1 (5.56%)	2 (3.51%)
Seborrhoeic dermatitis	2 (5.13%)	1 (5.56%)	3 (5.26%)
Urticaria	0 (0.00%)	1 (5.56%)	1 (1.75%)
Vascular disorders			
Accelerated hypertension	0 (0.00%)	1 (5.56%)	1 (1.75%)
Hypertension	2 (5.13%)	0 (0.00%)	2 (3.51%)

Hypotension	0 (0.00%)	1 (5.56%)	1 (1.75%)

Conclusion:

•The primary efficacy endpoint was met as UPCR showed a statistically significant (one sided p value<0.1) relative improvement of 42.1% in the CFZ533 group compared to the placebo group at Week 25. UPCR values were considered missing for the subject assessments after the date of treatment discontinuation.

•More subjects in the CFZ533 group achieved complete (35.1% vs 22.2%) renal response compared to the placebo group.

•CFZ533 was well tolerated, and no unexpected safety signal was observed. A numerical imbalance between active and placebo groups in the rate of opportunistic infections could be explained by the mechanism of action in the context of use in combination with other immunosuppressive treatments.

Date of Clinical Trial Report

11-April-2024