Clinical trial results:
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

Summary

EudraCT number	2017-003230-93
Trial protocol	HU DE
Global end of trial date	29 June 2023

Results information

Result version number	v2 (current)
This version publication date	17 November 2024
First version publication date	30 June 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CCFZ533X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03610516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	China: 15
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Tunisia: 2
Country: Number of subjects enrolled	Türkiye: 1
Worldwide total number of subjects	57
EEA total number of subjects	3

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)	57
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 21 investigative sites in 10 countries.

Pre-assignment

Screening details:

There was a screening period within 29 days to assess participants eligibility.

Period 1

Period 1 title	Treatment Epoch (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	CFZ533 10 mg/kg i.v.

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	CFZ533
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Placebo i.v.

Arm description:

Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141

Arm type	Placebo
Investigational medicinal product name	CFZ533
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. dose on Day 1, 15, 29, 57, 85, 113, and 141

Number of subjects in period 1	CFZ533 10 mg/kg i.v.	Placebo i.v.
Started	39	18
Completed	21	10
Not completed	18	8
Physician decision	8	5

Consent withdrawn by subject	3	1
Protocol Deviation	1	-
Death	1	-
Adverse event	3	1
No longer requires treatment	1	-
Non-Compliance with study treatment	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CFZ533 10 mg/kg i.v.
Reporting group description:	
CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	
Reporting group title	Placebo i.v.
Reporting group description:	
Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	

Reporting group values	CFZ533 10 mg/kg i.v.	Placebo i.v.	Total
Number of subjects	39	18	57
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)	39	18	57
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	34.1	36.4	
standard deviation	± 9.20	± 9.15	-
Sex: Female, Male Units: participants			
Female	30	17	47
Male	9	1	10
Race/Ethnicity, Customized Units: Subjects			
White	16	7	23
Asian	23	11	34

End points

End points reporting groups

Reporting group title	CFZ533 10 mg/kg i.v.
Reporting group description:	
CFZ533 10 mg/kg i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	
Reporting group title	Placebo i.v.
Reporting group description:	
Placebo i.v. dose on Day 1, 15, 29, 57, 85, 113, and 141	

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

End point title	Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)[1]
End point 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.	
End point type	Primary
End point timeframe:	
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.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: only analyzed descriptively.

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	18		
Units: participants				
Adverse Events	33	18		
Serious Adverse Events	6	3		
AEs leading to discontinuation of study treatment	3	1		
SAEs leading to discontinuation of study treatment	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Ratio to Baseline in Urinary protein creatinine ratio (UPCR)

End point title	Ratio to Baseline in Urinary protein creatinine ratio (UPCR)

End point 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.

End point type	Primary

End point timeframe:

Baseline, Day 169

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	10		
Units: ratio to baseline in UPCR				
geometric mean (confidence interval 95%)	0.369 (0.234 to 0.582)	0.637 (0.338 to 1.202)		

Statistical analyses

Statistical analysis title	Ratio to Baseline in UPCR
Comparison groups	CFZ533 10 mg/kg i.v. v Placebo i.v.
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0788 [2]
Method	Repeated measures Mixed Model
Parameter estimate	Ratio of geometric means CFZ533/placebo
Point estimate	0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.267
upper limit	1.256

Notes:

[2] - one-sided p-value

Secondary: Ratio to baseline for urine protein creatinine ratio (UPCR)

End point title	Ratio to baseline for urine protein creatinine ratio (UPCR)

End point 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.

End point type	Secondary

End point timeframe:

Day 197, Day 225, Day 253, Day 281, Day 309, Day 337 (End of Study)

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	16		
Units: ratio to baseline in UPCR				
arithmetic mean (standard deviation)				
Day 197 (n=35,16)	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)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of CFZ533[3]

End point 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.

End point type	Secondary

End point timeframe:

Day 141: pre dose and 1 hour post dose

Notes:

[3] - 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: PK Endpoint not analyzed for participants on placebo

End point values	CFZ533 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: day*ug/mL				
arithmetic mean (standard deviation)	7250 (± 1800)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose trough concentration (Ctrough) of CFZ533

End point title	Pre-dose trough concentration (Ctrough) of CFZ533[4]

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, 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.

End point type	Secondary

End point timeframe:

Pre-dose at: Day 1, Day 15, Day 29, Day 57, Day 85, Day 113 and Day 141

Notes:

[4] - 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: PK Endpoint not analyzed for participants on placebo

End point values	CFZ533 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ug/mL				
arithmetic 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)			

Statistical analyses

No statistical analyses for this end point

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

End point title	The observed maximum plasma concentration following CFZ533 administration at steady state (Cmax,ss)[5]

End point 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].

End point type	Secondary

End point timeframe:

Day 141: pre dose and 1 hour post dose

Notes:

[5] - 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: PK Endpoint not analyzed for participants on placebo

End point values	CFZ533 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ug/mL				
arithmetic mean (standard deviation)	263 (± 81.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total soluble CD40 plasma concentrations

End point title	Total soluble CD40 plasma concentrations[6]

End point 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.

End point type	Secondary

End point timeframe:

Day 1, Day 15, Day 29, Day 57, Day 113, Day 169, Day 225, Day 281, Day 337 (End of Study)

Notes:

[6] - 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: Endpoint not analyzed for participants on placebo

End point values	CFZ533 10 mg/kg i.v.			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: ng/mL				
arithmetic 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)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-CFZ533 antibodies

End point title	Number of participants with anti-CFZ533 antibodies

End point 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.

End point type	Secondary

End point timeframe:

Day 1, Day 15, Day 29, Day 57, Day 113, Day 169, Day 225, Day 281, Day 337 (End of study)

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	16		
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		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematuria casts- Urine white blood cell casts

End point title	Hematuria casts- Urine white blood cell casts

End point 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. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary

End point timeframe:

Baseline, Day 1 (Pre dose), and Day 309

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	18		
Units: number of casts per low power field				
arithmetic mean (standard deviation)				
Baseline (n=1,0)	2 (± 999)	999 (± 999)		
Day 1 (n=1,0)	2 (± 999)	999 (± 999)		
Day 309 (n=1,0)	4 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hematuria casts- Casts granular

End point title	Hematuria casts- Casts granular

End point 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. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary

End point timeframe:

Day 1 (Pre dose), Day 15 (Pre dose), Day 29 (Pre dose), Day 253, and Day 337 (end of study)

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	18		
Units: number of casts per low power field				
arithmetic mean (standard deviation)				

Day 1 (n=1,0)	3 (± 999)	999 (± 999)		
Day 15 (n=2,0)	2.5 (± 0.71)	999 (± 999)		
Day 29 (n=0,2)	999 (± 999)	3 (± 1.41)		
Day 253 (n=1,0)	14.0 (± 999)	999 (± 999)		
Day 337 (End of Study) (n=2,0)	5 (± 2.83)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in urine hyaline casts

End point title	Change from baseline in urine hyaline casts

End point 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. Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary

End point timeframe:

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)

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	18		
Units: number of casts per low power field				
arithmetic mean (standard deviation)				
Day 1 (n=0,0)	999 (± 999)	999 (± 999)		
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 (± 999)		
Day 113 (n=0,3)	999 (± 999)	18.0 (± 28.58)		
Day 141 (n=0,2)	999 (± 999)	-4.5 (± 6.36)		
Day 169 (n=1,1)	0.0 (± 999)	0.0 (± 999)		
Day 197 (n=3,3)	-1.0 (± 2.65)	2.7 (± 9.02)		
Day 225 (n=1,1)	2.0 (± 999)	0.0 (± 999)		
Day 253 (n=0,2)	999 (± 999)	-0.5 (± 4.95)		
Day 281 (n=1,2)	0.0 (± 999)	-1.5 (± 4.95)		
Day 309 (n=3,1)	1.7 (± 1.15)	-4.0 (± 999)		
Day 337 (EOS) (n=0,2)	999 (± 999)	0.5 (± 0.71)		

Statistical analyses

No statistical analyses for this end point

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

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

End point 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.

End point type	Secondary

End point timeframe:

Baseline, up to Day 169

End point values	CFZ533 10 mg/kg i.v.	Placebo i.v.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	18		
Units: participants	13	4		

Statistical analyses

No statistical analyses for this end point

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 49 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	CCFZ533 10mg/kg

Reporting group description:

CCFZ533 10mg/kg

Reporting group title	All patients

Reporting group description:

All patients

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	CCFZ533 10mg/kg	All patients	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 39 (15.38%)	9 / 57 (15.79%)	3 / 18 (16.67%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	1	1	0
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal behaviour			

subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Systemic lupus erythematosus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CCFZ533 10mg/kg	All patients	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 39 (82.05%)	50 / 57 (87.72%)	18 / 18 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Accelerated hypertension			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 39 (2.56%)	3 / 57 (5.26%)	2 / 18 (11.11%)
occurrences (all)	1	3	2
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Menstrual disorder			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Productive cough			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Nasal congestion			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	4	4	0
Blood immunoglobulin G decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Blood immunoglobulin M decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Blood pressure increased			

subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Lymphocyte count decreased			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Neutrophil count increased			
subjects affected / exposed	3 / 39 (7.69%)	3 / 57 (5.26%)	0 / 18 (0.00%)
occurrences (all)	8	8	0
Protein urine present			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Red blood cell sedimentation rate increased			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Systemic lupus erythematosus disease activity index abnormal			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
White blood cell count decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Limb injury			

subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Skin wound			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Tooth fracture			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Upper limb fracture			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 39 (2.56%)	3 / 57 (5.26%)	2 / 18 (11.11%)
occurrences (all)	1	3	2
Occipital neuralgia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Anaemia			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Leukocytosis			
subjects affected / exposed	3 / 39 (7.69%)	3 / 57 (5.26%)	0 / 18 (0.00%)
occurrences (all)	6	6	0
Leukopenia			
subjects affected / exposed	2 / 39 (5.13%)	3 / 57 (5.26%)	1 / 18 (5.56%)
occurrences (all)	3	4	1
Thrombocytopenia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Eye disorders			
Eyelid bleeding			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Corneal erosion			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Keratitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Visual acuity reduced			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Aphthous ulcer			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Flatulence			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Oesophagitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Mouth ulceration			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Gingival swelling			

subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Gingival pain			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Gastritis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Cholelithiasis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Cholecystitis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Butterfly rash			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Alopecia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Acne			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	2 / 39 (5.13%)	3 / 57 (5.26%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Rash			

subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Pruritus			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Ecchymosis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Urticaria			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Dermatitis contact			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Haematuria			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Acute kidney injury			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	3	4	1
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Bursitis			

subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Periarthritis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Tendonitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
COVID-19			
subjects affected / exposed	5 / 39 (12.82%)	8 / 57 (14.04%)	3 / 18 (16.67%)
occurrences (all)	5	8	3
Gastroenteritis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Fungal skin infection			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Folliculitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Cytomegalovirus infection			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1

Conjunctivitis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Gastrointestinal infection			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Herpes zoster			
subjects affected / exposed	3 / 39 (7.69%)	4 / 57 (7.02%)	1 / 18 (5.56%)
occurrences (all)	3	4	1
Influenza			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 39 (10.26%)	4 / 57 (7.02%)	0 / 18 (0.00%)
occurrences (all)	7	7	0
Peri-implantitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Pneumonia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pulpitis dental			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Pyuria			
subjects affected / exposed	0 / 39 (0.00%)	1 / 57 (1.75%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Soft tissue infection			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

Vulvovaginal candidiasis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)	5 / 57 (8.77%)	3 / 18 (16.67%)
occurrences (all)	3	7	4
Upper respiratory tract infection			
subjects affected / exposed	7 / 39 (17.95%)	9 / 57 (15.79%)	2 / 18 (11.11%)
occurrences (all)	9	12	3
Tuberculosis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Tonsillitis			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Tinea cruris			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Herpes simplex			
subjects affected / exposed	0 / 39 (0.00%)	2 / 57 (3.51%)	2 / 18 (11.11%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Decreased appetite			
subjects affected / exposed	2 / 39 (5.13%)	2 / 57 (3.51%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Hyperlipidaemia			
subjects affected / exposed	1 / 39 (2.56%)	2 / 57 (3.51%)	1 / 18 (5.56%)
occurrences (all)	2	3	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hypoproteinaemia			

subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Diabetes mellitus			
subjects affected / exposed	1 / 39 (2.56%)	1 / 57 (1.75%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2018	The key purpose of this amendment was to: i) To address the comments received from Health Authorities in response to the Sponsors clinical trial application (CTA) submission. ii) To adapt the protocol to allow enrollment of patients with a histologic diagnosis of class III/IV lupus nephritis within 5 years (instead of 2 years). iii) To correct inconsistencies, errors or typos and to improve clarity.
22 May 2019	The key purposes of this amendment was: i) To adjust hepatitis B screening and monitoring procedures in accordance with the current international guidelines, including the guidance of the American Association for the Study of Liver Diseases (Terrault et al 2018) and the European Association For The Study Of The Liver (EASL 2017). ii) To add the collection and assessment of a first morning void urine sample on visit days when urine collection is foreseen in the assessment schedule and to use the urine protein creatinine ratio (UPCR) from this sample as the UPCR for the primary endpoint. iii) To update relevant sections as per the latest version of the IB. iv) To address the comment received in response to the Sponsor's clinical trial application (CTA) submission from Health Authority in Tunisia with regards to Section 9.7 Pregnancy reporting. v) To incorporate the local Protocol Amendment 1
09 July 2020	The key purpose of this amendment is to mitigate the risk of human cytomegalovirus (CMV) infection. In addition, guidance related to COVID19 as well as clarifications in the protocol are also proposed.
26 July 2021	The key purpose of this amendment was to introduce updated guidance to investigators regarding vaccinations against SARS-CoV-2 during the study, previously communicated via Letter to investigators. Further, we introduced changes regarding inclusion/exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported