Clinical trial results:
A Randomized, Double-Blind, Placebo Controlled Study to Evaluate Efficacy and Safety of Nefecon in Patients with Primary IgA Nephropathy at Risk of Progressing to End-Stage Renal Disease (NefIgArd).

Summary

EudraCT number	2017-004902-16
Trial protocol	CZ SE BE FI ES GB PL IT
Global end of trial date	19 June 2023

Results information

Result version number	v1 (current)
This version publication date	03 July 2024
First version publication date	03 July 2024

Trial information

Trial identification

Sponsor protocol code	Nef-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03643965
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Calliditas Therapeutics AB
Sponsor organisation address	Kungsbron 1, Stockholm, Sweden, 111 22
Public contact	Clinical Operations, Calliditas Therapeutics AB, kristin.onnestam@calliditas.com
Scientific contact	Clinical Operations, Calliditas Therapeutics AB, kristin.onnestam@calliditas.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	08 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A:
The primary objective of Part A is to assess the effect of Nefecon 16 mg treatment on urine protein to creatinine ratio (UPCR) over 9 months compared to placebo.
Part B:
The primary objective of Part B is to assess the effect of the Nefecon 16 mg treatment given in Part A on clinical consequences of any proteinuria reduction as measured by estimated glomerular filtration rate (eGFR) recorded over 2 years compared to placebo.

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB) was established to review and discuss the available study data as patients were randomized and followed throughout the study. The DSMB also acted as an expert, independent advisory to study conduct. The DSMB met periodically throughout the course of the study to review unblinded safety data.

Background therapy:

Optimized renin angiotensin system (RAS) inhibitor therapy

Evidence for comparator: -

Actual start date of recruitment	28 May 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	Poland: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Czechia: 31
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belarus: 7

Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	China: 33
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 20
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Türkiye: 21
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	364
EEA total number of subjects	150

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)	353
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Global multi-center study. Randomized.

Pre-assignment

Screening details:

Screening period up to 35 days prior to enrollment

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Nefecon 16 mg

Arm description:

Nefecon 16 mg once daily for 9 months.

Arm type	Experimental
Investigational medicinal product name	Nefecon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

16 mg (4 capsules) once daily by mouth

Arm title	Placebo

Arm description:

Placebo once daily for 9 months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo (4 capsules) once daily for 9 months.

Number of subjects in period 1	Nefecon 16 mg	Placebo
Started	182	182
Completed	175	174
Not completed	7	8
All	7	8

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Part B was an observation period without treatment. Blinding to treatment in Part A applied.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nefecon 16 mg

Arm description:

No treatment in Part B but observation following Part A treatment.

Arm type	Experimental
Investigational medicinal product name	Nefecon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

16 mg (4 capsules) once daily by mouth

Arm title	Placebo

Arm description:

No treatment in Part B but observation following Part A treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo (4 capsules) once daily for 9 months.

Number of subjects in period 2	Nefecon 16 mg	Placebo
Started	175	174
Completed	161	165
Not completed	14	9
All	14	9

Baseline characteristics

Reporting groups	
Reporting group title	Nefecon 16 mg
Reporting group description: Nefecon 16 mg once daily for 9 months.	
Reporting group title	Placebo
Reporting group description: Placebo once daily for 9 months	

Reporting group values	Nefecon 16 mg	Placebo	Total
Number of subjects	182	182	364
Age categorical Units: Subjects			
Adults (18-64 years)	174	179	353
From 65-84 years	8	3	11
Age continuous Units: years			
arithmetic mean	43.8	41.6	
standard deviation	± 10.78	± 10.65	-
Gender categorical Units: Subjects			
Female	65	59	124
Male	117	123	240
Baseline UPCR Units: g/gram			
geometric mean	1.300	1.264	
inter-quartile range (Q1-Q3)	0.902 to 1.764	0.877 to 1.752	-
Baseline eGFR Units: ml/min/1.73m2			
geometric mean	56.006	55.565	
inter-quartile range (Q1-Q3)	45.497 to 70.972	45.957 to 67.735	-

End points

End points reporting groups	
Reporting group title	Nefecon 16 mg
Reporting group description: Nefecon 16 mg once daily for 9 months.	
Reporting group title	Placebo
Reporting group description: Placebo once daily for 9 months	
Reporting group title	Nefecon 16 mg
Reporting group description: No treatment in Part B but observation following Part A treatment.	
Reporting group title	Placebo
Reporting group description: No treatment in Part B but observation following Part A treatment.	

Primary: Part A: Ratio of UPCR at 9 Months Compared to Baseline	
End point title	Part A: Ratio of UPCR at 9 Months Compared to Baseline
End point description:	
End point type	Primary
End point timeframe: 9 months	

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: g/gram				
least squares mean (confidence interval 96%)	0.69 (0.61 to 0.79)	0.95 (0.83 to 1.08)		

Statistical analyses

Statistical analysis title	Part A: Ratio of UPCR at 9 Months Compared to Base
Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0003
Method	MMRM model
Parameter estimate	Ratio of geometric LS means
Point estimate	0.73

Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	0.61
upper limit	0.88

Notes:

[1] - Ratio of UPCR at 9 months compared to baseline for Nefecon compared to Placebo

Primary: Part B: Time-weighted Average of eGFR

End point title	Part B: Time-weighted Average of eGFR

End point description:

End point type	Primary

End point timeframe:

Up to 2 years

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	0.96 (0.93 to 0.98)	0.87 (0.84 to 0.89)		

Statistical analyses

Statistical analysis title	Time-weighted average of eGFR, Nefecon vs Placebo
Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	robust regression
Parameter estimate	Ratio of geometric LS means
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.15

Notes:

[2] - Time-weighted average of eGFR

Secondary: Part A: Ratio of eGFR at 9 Months

End point title	Part A: Ratio of eGFR at 9 Months

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	1.00 (0.96 to 1.03)	0.93 (0.90 to 0.96)		

Statistical analyses

Statistical analysis title	Ratio of eGFR at 9 months Nefecon vs Placebo
Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0014
Method	robust regression
Parameter estimate	Ratio of geometric LS means
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.13

Notes:

[3] - Ratio of eGFR at 9 months comparison of Nefecon to Placebo

Secondary: Part A: Ratio of eGFR at 12 Months

End point title	Part A: Ratio of eGFR at 12 Months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	0.97 (0.93 to 1.01)	0.91 (0.88 to 0.95)		

Statistical analyses

Statistical analysis title	Ratio of eGFR at 12 months Nefecon vs Placebo
Comparison groups	Placebo v Nefecon 16 mg
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0106
Method	robust regression
Parameter estimate	Ratio of geometric LS means
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.13

Notes:

[4] - Ratio of eGFR at 12 months comparison of Nefecon to Placebo

Secondary: Part A: Ratio of UACR at 9 Months

End point title	Part A: Ratio of UACR at 9 Months

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: g/gram				
least squares mean (confidence interval 95%)	0.64 (0.55 to 0.75)	0.93 (0.80 to 1.09)		

Statistical analyses

Statistical analysis title	Ratio of UACR at 9 months Nefecon vs Placebo
Comparison groups	Placebo v Nefecon 16 mg
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0005
Method	MMRM model
Parameter estimate	Ratio of geometric LS means
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.86

Notes:

[5] - Ratio of UACR at 9 months comparison of Nefecon to Placebo

Secondary: Part B: Time to 30% Reduction in eGFR

End point title	Part B: Time to 30% Reduction in eGFR
End point description:	
End point type	Secondary
End point timeframe:	
Up to 2 years	

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: Participants	21	39		

Statistical analyses

Statistical analysis title	Time to 30% reduction in eGFR Nefecon vs Placebo
Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0028
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.75

Notes:

[6] - Time to 30% reduction in eGFR comparison Nefecon to Placebo.
Cox proportional hazards model with individual patient censoring weighting.

Secondary: Part B: Time to Receiving Rescue Medication.

End point title	Part B: Time to Receiving Rescue Medication.

End point description:

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: Participants	15	20		

Statistical analyses

Statistical analysis title	Time to receiving rescue medication comparison

Statistical analysis description:

Time to receiving rescue medication comparison Nefecon to Placebo

Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.2647
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.33

Notes:

[7] - Time to receiving rescue medication comparison Nefecon to Placebo

Secondary: Part B: Ratio of UPCR Compared to Baseline Averaged Over Time Points Between 12 and 24 Months

End point title	Part B: Ratio of UPCR Compared to Baseline Averaged Over

	Time Points Between 12 and 24 Months

End point description:

End point type	Secondary

End point timeframe:

12 to 24 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	173		
Units: g/gram				
least squares mean (confidence interval 95%)	0.60 (0.54 to 0.66)	1.01 (0.91 to 1.12)		

Statistical analyses

Statistical analysis title	Ratio of UPCR compared to baseline

Statistical analysis description:

Ratio of UPCR compared to baseline averaged over time points between 12 and 24 months, comparison Nefecon vs Placebo

Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	MMRM model
Parameter estimate	Ratio of geometric LS means
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.68

Notes:

[8] - Ratio of UPCR compared to baseline averaged over time points between 12 and 24 months, comparison Nefecon vs Placebo

Secondary: Part B: Ratio of UACR Compared to Baseline Averaged Over Time Points Between 12 and 24 Months

End point title	Part B: Ratio of UACR Compared to Baseline Averaged Over Time Points Between 12 and 24 Months

End point description:

End point type	Secondary

End point timeframe:

12 to 24 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	173		
Units: g/gram				
least squares mean (confidence interval 95%)	0.52 (0.46 to 0.58)	0.96 (0.86 to 1.08)		

Statistical analyses

Statistical analysis title	Ratio of UACR compared to baseline
Statistical analysis description:	
Ratio of UACR compared to baseline averaged over time points between 12 and 24 months, Nefecon vs Placebo	
Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001
Method	MMRM model
Parameter estimate	Ratio of geometric LS means
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.63

Notes:

[9] - Ratio of UACR compared to baseline averaged over time points between 12 and 24 months, Nefecon vs Placebo

Secondary: Part B: Ratio of eGFR Compared to Baseline Averaged Over Time Points Between 12 and 24 Months

End point title	Part B: Ratio of eGFR Compared to Baseline Averaged Over Time Points Between 12 and 24 Months
End point description:	
End point type	Secondary
End point timeframe:	
12 to 24 months	

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	166		
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	0.93 (0.90 to 0.96)	0.84 (0.81 to 0.86)		

Statistical analyses

Statistical analysis title	Ratio of eGFR compared to baseline

Statistical analysis description:

Ratio of eGFR compared to baseline averaged over time points between 12 and 24 months, comparison Nefecon vs Placebo

Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	robust regression
Parameter estimate	Ratio of geometric LS means
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.16

Notes:

[10] - Ratio of eGFR compared to baseline averaged over time points between 12 and 24 months, comparison Nefecon vs Placebo

Secondary: Part B: Proportion of Patients Without Microhematuria

End point title	Part B: Proportion of Patients Without Microhematuria

End point description:

End point type	Secondary

End point timeframe:

12 to 24 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: Participants	94	59		

Statistical analyses

Statistical analysis title	Proportion of patients without microhematuria

Statistical analysis description:

Proportion of patients without microhematuria, comparison Nefecon vs Placebo

Comparison groups	Nefecon 16 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	4.1

Notes:

[11] - Proportion of patients without microhematuria, comparison Nefecon vs Placebo

Secondary: Part B: Short Form 36 (SF-36) Quality of Life Assessment at 9 months

End point title	Part B: Short Form 36 (SF-36) Quality of Life Assessment at 9 months

End point description:

End point type	Secondary

End point timeframe:

9 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: score				
arithmetic mean (standard deviation)				
Bodily Pain	54.353 (± 9.0306)	54.659 (± 9.2387)		
General Health	47.058 (± 9.6373)	48.014 (± 10.0120)		
Mental Component Summary	49.564 (± 9.2834)	49.760 (± 8.8974)		
Mental Health	50.226 (± 8.9539)	50.099 (± 8.8483)		
Physical Component Summary	52.257 (± 7.2188)	53.732 (± 6.5876)		
Physical Functioning	52.722 (± 6.7370)	54.276 (± 5.2243)		
Role Emotional	49.574 (± 9.4322)	50.393 (± 8.3001)		
Role Physical	51.028 (± 8.0207)	52.693 (± 6.6600)		
Social Function	50.941 (± 8.3606)	51.707 (± 7.9259)		

Vitality	51.826 (± 10.0909)	53.490 (± 9.3987)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Short Form 36 (SF-36) Quality of Life Assessment at 24 months

End point title	Part B: Short Form 36 (SF-36) Quality of Life Assessment at 24 months

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Nefecon 16 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	164		
Units: score				
arithmetic mean (standard deviation)				
Bodily Pain	53.385 (± 9.6352)	53.208 (± 9.9811)		
General Health	47.038 (± 9.3450)	47.214 (± 9.9564)		
Mental Component Summary	51.246 (± 8.1362)	49.743 (± 10.2184)		
Mental Health	51.691 (± 8.2104)	50.294 (± 10.0007)		
Physical Component Summary	51.443 (± 7.5200)	51.993 (± 7.1783)		
Physical Functioning	52.665 (± 7.6364)	53.059 (± 6.9006)		
Role Emotional	50.322 (± 8.4690)	49.333 (± 10.0789)		
Role Physical	50.948 (± 7.8921)	50.722 (± 8.8255)		
Social Functioning	51.949 (± 7.9677)	51.471 (± 8.9304)		
Vitality	53.291 (± 8.8558)	52.364 (± 10.0023)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from time of first dose of study treatment until 2 yrs after first dose (end of study). SAEs from ICF.
Treatment Emergent AEs were those that occurred after the first dose of study drug until 14 days after the last dose.

Adverse event reporting additional description:

Treatment emergent AEs and SAEs are reported below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Nefecon 16 mg

Reporting group description:

Nefecon 16 mg once daily for 9 months.

Reporting group title	Placebo

Reporting group description:

Placebo once daily for 9 months

Serious adverse events	Nefecon 16 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 182 (9.89%)	11 / 182 (6.04%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 182 (1.10%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			

subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 182 (1.10%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow oedema			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis haemorrhagic			

subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 182 (0.55%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 182 (1.10%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Campylobacter colitis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection	Additional description: Treatment emergent		
subjects affected / exposed	2 / 182 (1.10%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 182 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 182 (1.10%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nefecon 16 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 182 (59.34%)	69 / 182 (37.91%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 182 (11.54%)	6 / 182 (3.30%)	
occurrences (all)	24	6	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	28 / 182 (15.38%)	7 / 182 (3.85%)	
occurrences (all)	33	8	

Fatigue			
subjects affected / exposed	10 / 182 (5.49%)	7 / 182 (3.85%)	
occurrences (all)	10	8	
Headache			
subjects affected / exposed	19 / 182 (10.44%)	14 / 182 (7.69%)	
occurrences (all)	26	16	
Weight increased			
subjects affected / exposed	10 / 182 (5.49%)	5 / 182 (2.75%)	
occurrences (all)	10	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 182 (4.95%)	10 / 182 (5.49%)	
occurrences (all)	9	11	
Dyspepsia			
subjects affected / exposed	13 / 182 (7.14%)	4 / 182 (2.20%)	
occurrences (all)	18	4	
Nausea			
subjects affected / exposed	8 / 182 (4.40%)	12 / 182 (6.59%)	
occurrences (all)	8	12	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	20 / 182 (10.99%)	2 / 182 (1.10%)	
occurrences (all)	21	2	
Rash			
subjects affected / exposed	10 / 182 (5.49%)	7 / 182 (3.85%)	
occurrences (all)	13	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 182 (5.49%)	7 / 182 (3.85%)	
occurrences (all)	10	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 182 (6.59%)	4 / 182 (2.20%)	
occurrences (all)	12	5	
Muscle spasms			

subjects affected / exposed	22 / 182 (12.09%)	7 / 182 (3.85%)	
occurrences (all)	27	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 182 (9.34%)	19 / 182 (10.44%)	
occurrences (all)	18	25	
Upper respiratory tract infection			
subjects affected / exposed	10 / 182 (5.49%)	10 / 182 (5.49%)	
occurrences (all)	12	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2018	Updated exclusion criteria Biopsy limit changed from 5 years to 10 years GCS treatment before randomization changed from 2 years to 1 year Schedule of procedures related to exploratory sampling changed SAE reporting period starts from signature of ICF Quality control requirements clarified
02 January 2019	2 consecutive measurements of proteinuria required The lower limit of the eGFR value was reduced from 45 to 35 mL/min per 1.73 m2 Schedule of event at study visits was updated Clarified that AESIs would be followed until 2 years after the first dose of study drug
19 December 2019	Updated exclusion criteria Primary endpoint Part B eGFR was time-weighted average of AUC over 24 months Secondary objectives to assess Nefecon treatment effects with Part A China included 360 patients to be randomized Part B duration changed to 12 months Updated exclusion criteria AESI's specified
28 April 2020	Covid-19 - study treatment up to 10 m possible Covid-19 - study procedures – last visit ((V11 Part A) to site changed to by phone
14 January 2021	Consistency with SAP v 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported