Clinical trial results:
A Multicentre, Interventional treatment, Randomised, Double-Blind, Single Group Assignment Placebo Controlled Study to Evaluate the Efficacy and Safety of Two Different Doses of Nefecon in primary IgA nephropathy patients at risk of developing end-stage renal disease

Summary

EudraCT number	2012-001923-11
Trial protocol	FI CZ DE BE SE DK IT GB NL ES
Global end of trial date	25 June 2015

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017
Summary attachment (see zip file)	Study synopsis Nef-202, EudraCT no 2012-001923-11 (Nef-202 study synopsis_23May16.pdf)

Trial information

Trial identification

Sponsor protocol code	Nef-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01738035
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmalink AB
Sponsor organisation address	Wallingatan 26B, Stockholm, Sweden,
Public contact	Project Director (Alex Mercer), Pharmalink AB, 46 84113005, alex.mercer@pharmalink.se
Scientific contact	Project Director (Alex Mercer), Pharmalink AB, 46 84113005, alex.mercer@pharmalink.se

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	25 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2015
Global end of trial reached?	Yes
Global end of trial date	25 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial is to evaluate efficacy and safety of two different doses of Nefecon in the treatment of patients with primary IgA nephropathy (IgAN) at risk of developing end-stage renal disease, under rigorous blood pressure control with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin 2 receptor blocker (ARB).

Protection of trial subjects:

Steroid related adverse reactions were specifically asked for and collected in addition to usual adverse event collection.

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents are retained in accordance with ICH GCP. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures. The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited and no investigational medicinal product (IMP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Pharmalink received copies of these approvals. Safety assessments included several laboratory evaluations (clinical chemistry, haematology, urine analyses) as well as measurements of glomerular filtration rate, vital signs and physical examinations.

Background therapy:

Patients remained on their angiotensin II type I receptor blockade (ARB) and/or angiotensin converting enzyme inhibitor (ACEI) treatment throughout the study treatment phase.

Evidence for comparator:

Placebo-control

Actual start date of recruitment	11 December 2012
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	Netherlands: 5
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Germany: 46

Country: Number of subjects enrolled	Italy: 30
Worldwide total number of subjects	153
EEA total number of subjects	153

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)	150
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started 11 December 2012 and was completed by 26 December 2013.

Pre-assignment

Screening details:

The study included a 6-months run-in period, 9-months treatment period and a 3-months follow-up period. During the run-in period the background anti-hypertensive medication was optimized.

Period 1

Period 1 title	Treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To ensure blinding, placebo capsules without the active ingredient but with the same appearance and route of administration as the active capsules was used. All patients were given the same number of active and/or placebo capsules per day in order to keep the treatment (active or placebo) and dose blinded (16 mg, 8 mg or placebo).

Arms

Are arms mutually exclusive?	Yes
Arm title	Nefecon 8 mg/day

Arm description:

Patients received 8 mg Nefecon 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:

8 mg/day Nefecon® (2 x 4 mg Nefecon capsules + 2 x "placebo" capsules) for 9 months, followed by Placebo (2 x "placebo" capsules) for 2 weeks (titration period).

16 mg/day Nefecon® (4 x 4 mg Nefecon capsules) for 9 months, followed by 8 mg/day Nefecon® (2 x 4 mg capsules) for 2 weeks (titration period).

Arm title	Nefecon 16 mg/day

Arm description:

Patients received 16 mg Nefecon 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:

8 mg/day Nefecon® (2 x 4 mg Nefecon capsules + 2 x "placebo" capsules) for 9 months, followed by Placebo (2 x "placebo" capsules) for 2 weeks (titration period).

16 mg/day Nefecon® (4 x 4 mg Nefecon capsules) for 9 months, followed by 8 mg/day Nefecon® (2 x 4 mg capsules) for 2 weeks (titration period).

Arm title	Placebo

Arm description:

Patients received placebo capsules 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:

4 placebo capsules daily

Number of subjects in period 1	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo
Started	51	51	51
Interim analysis of primary end point	30 [1]	27 [2]	33 [3]
Completed	51	48	50
Not completed	0	3	1
Patient unable to swallow capsules	-	1	-
Protocol deviation	-	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was a planned interim analysis of the primary efficacy end point at 9 months when 90 patients had completed their T5 visit.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was a planned interim analysis of the primary efficacy end point at 9 months when 90 patients had completed their T5 visit.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was a planned interim analysis of the primary efficacy end point at 9 months when 90 patients had completed their T5 visit.

Baseline characteristics

Reporting groups	
Reporting group title	Nefecon 8 mg/day
Reporting group description:	
Patients received 8 mg Nefecon daily for 9 months.	
Reporting group title	Nefecon 16 mg/day
Reporting group description:	
Patients received 16 mg Nefecon daily for 9 months.	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo capsules daily for 9 months.	

Reporting group values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo
Number of subjects	51	51	51
Age categorical			
No additional details			
Units: Subjects			

Age continuous			
No additional information.			
Units: years			
arithmetic mean	40.6	37.3	39.5
full range (min-max)	20 to 82	18 to 64	18 to 73
Gender categorical			
Units: Subjects			
Female	14	15	15
Male	37	36	36

Reporting group values	Total		
Number of subjects	153		
Age categorical			
No additional details			
Units: Subjects			

Age continuous			
No additional information.			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	44		
Male	109		

End points

End points reporting groups

Reporting group title	Nefecon 8 mg/day
Reporting group description:	
Patients received 8 mg Nefecon daily for 9 months.	
Reporting group title	Nefecon 16 mg/day
Reporting group description:	
Patients received 16 mg Nefecon daily for 9 months.	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo capsules daily for 9 months.	
Subject analysis set title	Safety set Nefecon 8 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set consists of all patients who took at least one dose of the study medication.	
Subject analysis set title	Safety set Nefecon 16 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set consists of all patients who took at least one dose of the study medication.	
Subject analysis set title	Safety set Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set consists of all patients who took at least one dose of the study medication.	
Subject analysis set title	Full analysis set Nefecon 8 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for efficacy analysis is defined as all randomised patients who took at least one dose of the study medication and with at least one post dose efficacy measurements.	
Subject analysis set title	Full analysis set Nefecon 16 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for efficacy analysis is defined as all randomised patients who took at least one dose of the study medication and with at least one post dose efficacy measurements.	
Subject analysis set title	Full analysis set Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS for efficacy analysis is defined as all randomised patients who took at least one dose of the study medication and with at least one post dose efficacy measurements.	
Subject analysis set title	Per protocol analysis Nefecon 8 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of the FAS and consists of patients who 1) have completed the 9 month treatment, 2) have sufficiently complied with the protocol and 3) have been compliant.	
Subject analysis set title	Per protocol analysis 16 mg
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of the FAS and consists of patients who 1) have completed the 9 month treatment, 2) have sufficiently complied with the protocol and 3) have been compliant.	
Subject analysis set title	Per protocol analysis Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of the FAS and consists of patients who 1) have completed the 9 month treatment, 2) have sufficiently complied with the protocol and 3) have been compliant.

Primary: Mean reduction in UPCR

End point title	Mean reduction in UPCR

End point description:

The mean reduction in UPCR at 9 months compared to baseline UPCR values.

End point type	Primary

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	33	
Units: g/g				
least squares mean (confidence interval 95%)	0.785 (0.638 to 0.965)	0.727 (0.585 to 0.903)	1.028 (0.841 to 1.256)	

Statistical analyses

Statistical analysis title	Comparison of UPCR change from baseline
Comparison groups	Nefecon 8 mg/day v Nefecon 16 mg/day v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0158 [1]
Method	Mixed models analysis

Notes:

[1] - Interim analysis

Secondary: Mean change in urine protein, UACR and urine albumin (urine protein)

End point title	Mean change in urine protein, UACR and urine albumin (urine protein)

End point description:

Mean change in urine protein from baseline at Month 9

End point type	Secondary

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.804 (0.657 to 0.983)	0.7 (0.567 to 0.865)	1.011 (0.833 to 1.226)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (UPCR)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (UPCR)

End point description:

Mean change in UPCR from 9 to 12 months

End point type	Secondary

End point timeframe:

From 9 to 12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	32	44	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.959 (0.812 to 1.132)	0.915 (0.767 to 1.091)	1.045 (0.894 to 1.222)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum creatinine, CKD-EPI eGFR, MDRD eGFR and creatinine clearance (serum creatinine)

End point title	Mean change in serum creatinine, CKD-EPI eGFR, MDRD eGFR and creatinine clearance (serum creatinine)

End point description:

Mean change in serum creatinine from baseline at 9 months.

End point type	Secondary

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: milligram(s)/dL				
least squares mean (confidence interval 95%)	0.989 (0.943 to 1.037)	0.981 (0.933 to 1.032)	1.072 (1.023 to 1.123)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in urine protein, UACR and urine albumin (UACR)

End point title	Mean change in urine protein, UACR and urine albumin (UACR)
End point description:	
Mean change in UACR from baseline at Month 9	
End point type	Secondary
End point timeframe:	
9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.864 (0.705 to 1.059)	0.715 (0.573 to 0.892)	1.057 (0.865 to 1.291)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in urine protein, UACR and urine albumin (urine albumin)

End point title	Mean change in urine protein, UACR and urine albumin (urine albumin)
End point description:	
Mean change in urine albumin from baseline at Month 9	
End point type	Secondary
End point timeframe:	
9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.815 (0.656 to 1.013)	0.67 (0.531 to 0.846)	1.022 (0.828 to 1.261)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (urine protein)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (urine protein)
End point description:	
Mean change in urine protein from 9 to 12 months	
End point type	Secondary
End point timeframe:	
From 9 to 12 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	32	43	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.98 (0.817 to 1.177)	0.862 (0.711 to 1.046)	1.018 (0.858 to 1.209)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (UACR)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (UACR)
End point description:	
Mean change in UACR from 9 to 12 months	
End point type	Secondary

End point timeframe:

From 9 to 12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	32	44	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.914 (0.758 to 1.101)	0.867 (0.712 to 1.057)	1.037 (0.87 to 1.235)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (urine albumin)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin from 9 to 12 months (urine albumin)

End point description:

Mean change in urine albumin from 9 to 12 months

End point type	Secondary

End point timeframe:

From 9 to 12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	32	43	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.934 (0.763 to 1.144)	0.819 (0.66 to 1.015)	1.021 (0.844 to 1.235)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (CKD EPI)

End point title	Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (CKD EPI)

End point description:

Mean change in chronic kidney disease epidemiology collaboration equation (CKD EPI) estimated GFR (eGFR) from baseline at 9 months.

End point type	Secondary
End point timeframe: 9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.991 (0.934 to 1.052)	1.006 (0.946 to 1.07)	0.902 (0.85 to 0.956)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (MDRD)

End point title	Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (MDRD)
End point description: Mean change in MDRD eGFR from baseline at 9 months	
End point type	Secondary
End point timeframe: 9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.995 (0.937 to 1.056)	1.022 (0.96 to 1.088)	0.906 (0.854 to 0.961)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (creatinine clearance)

End point title	Mean change in serum creatinine, CKD EPI eGFR, MDRD eGFR and creatinine clearance (creatinine clearance)

End point description:	
Mean change in creatinine clearance from baseline at month 9	
End point type	Secondary
End point timeframe:	
9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: millilitre(s)/min/1.73*m2				
least squares mean (confidence interval 95%)	0.952 (0.851 to 1.065)	0.985 (0.877 to 1.107)	0.906 (0.813 to 1.01)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UPCR (≥30%)

End point title	Defined reduction in UPCR (≥30%)
End point description:	
Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline	
End point type	Other pre-specified
End point timeframe:	
9 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: number of patients	14	16	12	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 1)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 1)
End point description:	
Mean change in UPCR, urine protein, UACR and urine albumin from baseline at 1, 3, 6, 10.5 and 12	

months

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	48	49	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.946 (0.831 to 1.077)	1.045 (0.918 to 1.189)	1.046 (0.918 to 1.192)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in CDK-EPI at 1 month

End point title	Mean change in CDK-EPI at 1 month

End point description:

Mean change in CKD-EPI eGFR from baseline at 1, 3, 6, 10.5, and 12 months

End point type	Other pre-specified

End point timeframe:

1 month

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	47	48	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.964 (0.917 to 1.014)	0.989 (0.941 to 1.04)	0.959 (0.912 to 1.008)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in cystatin C-based eGFR

End point title	Mean change in cystatin C-based eGFR

End point description:

Mean change in cystatin C-based eGFR CKD-EPI from baseline at Month 9

End point type	Other pre-specified

End point timeframe:
9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.941 (0.869 to 1.019)	0.93 (0.856 to 1.01)	0.925 (0.857 to 0.999)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of patients with microhaematuria at 9 months

End point title	Proportion of patients with microhaematuria at 9 months

End point description:
Proportion of patients with microhaematuria at Month 9

End point type	Other pre-specified

End point timeframe:
Month 9

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	33	43	
Units: patients with haematuria	32	21	37	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of patients with microhaematuria at 12 months

End point title	Proportion of patients with microhaematuria at 12 months

End point description:

End point type	Other pre-specified

End point timeframe:
Month 12

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	41	
Units: patients with haematuria	27	24	34	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in EPI-CDK at 3 months

End point title	Mean change in EPI-CDK at 3 months

End point description:

End point type	Other pre-specified

End point timeframe:

3 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	42	50	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.974 (0.924 to 1.026)	0.988 (0.937 to 1.042)	0.93 (0.884 to 0.979)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in CDK-EPI at 6 months

End point title	Mean change in CDK-EPI at 6 months

End point description:

End point type	Other pre-specified

End point timeframe:

6 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	37	46	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.994 (0.93 to 1.063)	0.968 (0.903 to 1.039)	0.917 (0.859 to 0.979)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in CDK-EPI at 10.5 months

End point title	Mean change in CDK-EPI at 10.5 months

End point description:

End point type	Other pre-specified

End point timeframe:

10.5 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	42	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.933 (0.878 to 0.992)	0.991 (0.93 to 1.056)	0.891 (0.839 to 0.946)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in CDK-EPI at 12 months

End point title	Mean change in CDK-EPI at 12 months

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	34	46	
Units: millilitre(s)/min/1.73m2				
least squares mean (confidence interval 95%)	0.92 (0.857 to 0.988)	0.993 (0.921 to 1.069)	0.891 (0.832 to 0.954)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UPCR (≥40%)

End point title	Defined reduction in UPCR (≥40%)

End point description:

Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: number of patients	9	10	8	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UPCR (≥50%)

End point title	Defined reduction in UPCR (≥50%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: number of patients	6	8	5	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine protein (≥30%)

End point title	Defined reduction in urine protein (≥30%)

End point description:

Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: number of patients	16	15	12	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine protein (≥40%)

End point title	Defined reduction in urine protein (≥40%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: patients	13	11	9	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine protein (≥50%)

End point title	Defined reduction in urine protein (≥50%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	44	
Units: patients	7	10	8	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UACR (≥30%)

End point title	Defined reduction in UACR (≥30%)

End point description:

Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	14	16	12	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UACR (≥40%)

End point title	Defined reduction in UACR (≥40%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	13	15	7	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in UACR (≥50%)

End point title	Defined reduction in UACR (≥50%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	6	10	5	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine albumin (≥30%)

End point title	Defined reduction in urine albumin (≥30%)

End point description:

Achieving defined reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR and urine albumin at Month 9 compared to baseline

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	16	17	13	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine albumin (≥40%)

End point title	Defined reduction in urine albumin (≥40%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	11	16	9	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Defined reduction in urine albumin (≥50%)

End point title	Defined reduction in urine albumin (≥50%)

End point description:

End point type	Other pre-specified

End point timeframe:

9 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	34	44	
Units: patients	9	10	7	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 3)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 3)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	42	50	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.874 (0.744 to 1.027)	0.868 (0.735 to 1.025)	1.023 (0.872 to 1.2)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 6)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 6)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	38	46	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.815 (0.692 to 0.959)	0.966 (0.814 to 1.147)	1.074 (0.913 to 1.262)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 10.5)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 10.5)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	33	43	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.737 (0.608 to 0.893)	0.646 (0.525 to 0.795)	0.995 (0.826 to 1.199)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 12)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UPCR, Month 12)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	32	46	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.774 (0.656 to 0.914)	0.68 (0.568 to 0.815)	1.005 (0.857 to 1.178)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 1)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 1)

End point description:

Mean change in UPCR, urine protein, UACR and urine albumin from baseline at 1, 3, 6, 10.5 and 12 months

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	47	49	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.917 (0.784 to 1.072)	0.967 (0.828 to 1.128)	1.017 (0.871 to 1.188)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 3)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 3)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	42	50	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.817 (0.68 to 0.981)	0.81 (0.672 to 0.977)	0.999 (0.835 to 1.195)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 6)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 6)

End point description:

End point type	Other pre-specified
End point timeframe: 12 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	38	46	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.804 (0.666 to 0.97)	0.925 (0.761 to 1.125)	1.021 (0.85 to 1.227)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 10.5)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 10.5)
End point description:	

End point type	Other pre-specified
End point timeframe: 12 months	

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	33	43	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.602 (0.464 to 0.78)	0.585 (0.442 to 0.774)	0.896 (0.697 to 1.15)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 12)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine protein, Month 12)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	32	45	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.738 (0.618 to 0.882)	0.599 (0.495 to 0.724)	0.967 (0.815 to 1.147)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 1)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 1)

End point description:

Mean change in UPCR, urine protein, UACR and urine albumin from baseline at 1, 3, 6, 10.5 and 12 months

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	48	49	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.988 (0.864 to 1.129)	1.031 (0.9 to 1.18)	1.008 (0.879 to 1.156)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 3)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 3)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	41	50	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.888 (0.747 to 1.055)	0.834 (0.694 to 1.002)	1.011 (0.85 to 1.202)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 6)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 6)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	38	46	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.828 (0.695 to 0.987)	0.952 (0.787 to 1.151)	1.072 (0.899 to 1.279)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin

(UACR, Month 10.5)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 10.5)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	33	43	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.709 (0.567 to 0.886)	0.556 (0.435 to 0.71)	0.991 (0.798 to 1.232)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 12)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (UACR, Month 12)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	32	46	
Units: gram(s)/gram				
least squares mean (confidence interval 95%)	0.723 (0.6 to 0.871)	0.624 (0.508 to 0.768)	1.003 (0.838 to 1.202)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 1)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 1)

End point description:

Mean change in UPCR, urine protein, UACR and urine albumin from baseline at 1, 3, 6, 10.5 and 12 months

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	47	49	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.955 (0.81 to 1.125)	0.949 (0.806 to 1.118)	0.973 (0.827 to 1.146)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 3)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 3)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	41	50	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.827 (0.678 to 1.01)	0.771 (0.626 to 0.948)	0.98 (0.806 to 1.191)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 6)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 6)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	38	46	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.815 (0.664 to 1)	0.905 (0.731 to 1.121)	1.012 (0.829 to 1.236)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 10.5)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 10.5)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	33	43	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.574 (0.43 to 0.766)	0.502 (0.367 to 0.686)	0.885 (0.671 to 1.169)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 12)

End point title	Mean change in UPCR, urine protein, UACR and urine albumin (urine albumin, Month 12)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	32	45	
Units: gram(s)				
least squares mean (confidence interval 95%)	0.685 (0.559 to 0.838)	0.544 (0.437 to 0.678)	0.956 (0.788 to 1.161)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the informed consent to the completion of the clinical trial (including the second follow up visit) or premature patient discontinuation from the trial.

Adverse event reporting additional description:

An ongoing AE is followed up if patient is withdrawn. The reporting period for SAEs ends at the final follow-up visit 12 months after the first administration of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0E

Reporting groups

Reporting group title	Nefecon 8 mg/day

Reporting group description:

Patients received 8 mg Nefecon daily for 9 months.

Reporting group title	Nefecon 16 mg/day

Reporting group description:

Patients received 16 mg Nefecon daily for 9 months.

Reporting group title	Placebo

Reporting group description:

Patients received placebo capsules daily for 9 months.

Serious adverse events	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	7 / 49 (14.29%)	3 / 50 (6.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			

subjects affected / exposed	0 / 51 (0.00%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Nefecon 8 mg/day	Nefecon 16 mg/day	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 51 (94.12%)	43 / 49 (87.76%)	42 / 50 (84.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 51 (5.88%)	5 / 49 (10.20%)	1 / 50 (2.00%)
occurrences (all)	3	5	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 51 (3.92%)	6 / 49 (12.24%)	2 / 50 (4.00%)
occurrences (all)	3	9	3
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	2 / 49 (4.08%)	3 / 50 (6.00%)
occurrences (all)	2	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 51 (3.92%)	4 / 49 (8.16%)	1 / 50 (2.00%)
occurrences (all)	2	5	1
Oropharyngeal pain			
subjects affected / exposed	3 / 51 (5.88%)	1 / 49 (2.04%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Insomnia			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 51 (11.76%)	8 / 49 (16.33%)	2 / 50 (4.00%)
occurrences (all)	6	9	2
Mood swings			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 51 (5.88%)	5 / 49 (10.20%)	2 / 50 (4.00%)
occurrences (all)	3	5	2
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 51 (3.92%)	3 / 49 (6.12%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Investigations			

Glycosylated haemoglobin increased			
subjects affected / exposed	3 / 51 (5.88%)	4 / 49 (8.16%)	0 / 50 (0.00%)
occurrences (all)	5	4	0
Weight increased			
subjects affected / exposed	2 / 51 (3.92%)	4 / 49 (8.16%)	0 / 50 (0.00%)
occurrences (all)	2	4	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 51 (5.88%)	3 / 49 (6.12%)	3 / 50 (6.00%)
occurrences (all)	4	3	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)	6 / 49 (12.24%)	3 / 50 (6.00%)
occurrences (all)	3	6	4
Blood and lymphatic system disorders			
Increased tendency to bruise			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 51 (5.88%)	3 / 49 (6.12%)	0 / 50 (0.00%)
occurrences (all)	4	3	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences (all)	4	0	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	2 / 51 (3.92%)	7 / 49 (14.29%)	4 / 50 (8.00%)
occurrences (all)	2	9	5
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)	5 / 49 (10.20%)	7 / 50 (14.00%)
occurrences (all)	1	5	9
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 51 (1.96%)	4 / 49 (8.16%)	1 / 50 (2.00%)
occurrences (all)	1	7	1
Abdominal pain			
subjects affected / exposed	4 / 51 (7.84%)	3 / 49 (6.12%)	1 / 50 (2.00%)
occurrences (all)	4	4	1

Nausea			
subjects affected / exposed	4 / 51 (7.84%)	3 / 49 (6.12%)	1 / 50 (2.00%)
occurrences (all)	4	5	1
Vomiting			
subjects affected / exposed	2 / 51 (3.92%)	3 / 49 (6.12%)	2 / 50 (4.00%)
occurrences (all)	2	3	2
Dry mouth			
subjects affected / exposed	1 / 51 (1.96%)	3 / 49 (6.12%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Constipation			
subjects affected / exposed	0 / 51 (0.00%)	3 / 49 (6.12%)	0 / 50 (0.00%)
occurrences (all)	0	4	0
Abdominal distension			
subjects affected / exposed	0 / 51 (0.00%)	0 / 49 (0.00%)	4 / 50 (8.00%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
Acne			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 51 (15.69%)	9 / 49 (18.37%)	3 / 50 (6.00%)
occurrences (all)	9	10	3
Hirsutism			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 51 (5.88%)	5 / 49 (10.20%)	1 / 50 (2.00%)
occurrences (all)	3	5	1
Pruritus			
subjects affected / exposed	2 / 51 (3.92%)	5 / 49 (10.20%)	0 / 50 (0.00%)
occurrences (all)	2	6	0
Alopecia			
subjects affected / exposed	4 / 51 (7.84%)	4 / 49 (8.16%)	2 / 50 (4.00%)
occurrences (all)	5	4	2
Lipohypertrophy			
subjects affected / exposed	2 / 51 (3.92%)	4 / 49 (8.16%)	0 / 50 (0.00%)
occurrences (all)	2	4	0
Skin striae			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 51 (3.92%)	4 / 49 (8.16%)	0 / 50 (0.00%)
occurrences (all)	2	4	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	5 / 51 (9.80%)	8 / 49 (16.33%)	3 / 50 (6.00%)
occurrences (all)	5	8	3
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	8 / 51 (15.69%)	9 / 49 (18.37%)	2 / 50 (4.00%)
occurrences (all)	8	14	2
Back pain			
subjects affected / exposed	6 / 51 (11.76%)	3 / 49 (6.12%)	1 / 50 (2.00%)
occurrences (all)	8	3	1
Muscle spasms			
subjects affected / exposed	5 / 51 (9.80%)	2 / 49 (4.08%)	2 / 50 (4.00%)
occurrences (all)	5	2	3
Arthralgia			
subjects affected / exposed	2 / 51 (3.92%)	3 / 49 (6.12%)	2 / 50 (4.00%)
occurrences (all)	5	5	3
Myalgia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 49 (6.12%)	2 / 50 (4.00%)
occurrences (all)	0	3	2
Pain in extremity			
subjects affected / exposed	3 / 51 (5.88%)	2 / 49 (4.08%)	2 / 50 (4.00%)
occurrences (all)	3	2	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 51 (15.69%)	10 / 49 (20.41%)	10 / 50 (20.00%)
occurrences (all)	16	16	14
Upper respiratory tract infection			
subjects affected / exposed	2 / 51 (3.92%)	3 / 49 (6.12%)	3 / 50 (6.00%)
occurrences (all)	3	3	3
Influenza			
subjects affected / exposed	3 / 51 (5.88%)	3 / 49 (6.12%)	1 / 50 (2.00%)
occurrences (all)	4	3	1
Bronchitis			

subjects affected / exposed	4 / 51 (7.84%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences (all)	4	0	1
Pharyngitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	1
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 49 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2013	To implement a series of measures to improve patient recruitment without compromising the scientific value of the study, the protocol was amended as follows: • The exclusion criterion for patients previously treated with a course of immunosuppressive agents or systemic steroids for IgAN was removed • Number of site visits was reduced • The alternative of using measured GFR to determine a patient's eligibility for the study was added if the Investigator believed that an eGFR calculation would not be likely to reflect a given patient's actual level of renal function. • Minor protocol inconsistencies were corrected
03 March 2014	The protocol was amended to: • Enable all patients enrolled in the 6-month run-in phase of the study to enter the treatment phase, provided they were eligible for randomisation, they continued to consent and that sufficient study drug was available. Study drug kits were available for a maximum of 160 patients • Perform an interim analysis on the primary endpoint and selected secondary and tertiary endpoints once 90 patients had completed the 9 month treatment phase of the study. This interim analysis provided early data on whether NEFECON treatment resulted in a clinical benefit compared with placebo, thereby establishing the potential risk/benefit for the remaining patients in the study and addressing the validity of continuing the study • Introduce statistical methodology to provide more reliable analyses. The primary endpoint, log change from baseline in UPCR values at 9 months, was planned to be assessed by analysis of covariance. Mixed model repeated measures (MMRM) was considered to provide more reliable analyses
06 November 2014	The protocol was amended as follows: • The statistical analysis of mean change in UPCR, urine protein, UACR, urine albumin and CKD-EPI eGFR from baseline to post treatment time-points (1, 3, 6, 9, 10.5 and 12 months) was achieved using a single MMRM analysis for each of these variables • The proportion of patients with microhaematuria at 9 and 12 months were assessed using a single generalised linear mixed model taking into account all data collected post randomisation with treatment effects estimated for the 9 and 12 month time points of interest • Mean change in serum creatinine, MDRD eGFR, cystatin C-based eGFR and creatinine clearance levels from baseline to 9 months as well as specified reductions (≥30%, ≥40%, ≥50%) in UPCR, urine protein, UACR, and urine albumin at 9 months compared with baseline were also evaluated using similar methodology In addition, a subgroup analysis was planned for the primary endpoint, as described in the SAP (Appendix 16.1.9) and in Section 9.7.1.6. Region was based on country but for a few small countries, there was a need to combine into larger geographical regions. All tests were one sided at the 2.5% significance level. These changes were made before the first formal interim analysis. No changes were made to the planned conduct of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported