Clinical trial results:
A prospective, randomized, double-blind, placebo controlled clinical trial to assess the effects of long-acting somatostatin (Octreotide LAR) therapy on disease progression in patients with Autosomal Dominant Polycystic Kidney Disease and moderate to severe renal insufficiency

Summary

EudraCT number	2011-000138-12
Trial protocol	IT
Global end of trial date	14 April 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2019
First version publication date	20 June 2019
Summary attachment (see zip file)	Paper (journal.pmed.1002777.pdf) Supplementary 2 (pmed.1002777.s002.doc) Supplementary 6 (pmed.1002777.s006.pdf) Supplementary 7 (pmed.1002777.s007.docx) Supplementary 8 (pmed.1002777.s008.docx) Supplementary 9 (pmed.1002777.s009.docx) Supplementary 10 (pmed.1002777.s010.docx) Supplementary 11 (pmed.1002777.s011.docx) Supplementary 15 (pmed.1002777.s015.pdf)

Trial information

Trial identification

Sponsor protocol code	ALADIN2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01377246
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	V. G. B. Camozzi, 3, Ranica / Bergamo, Italy, 24020
Public contact	Norberto Perico, Centro di Ricerche Cliniche per le Malattie Rare Aldo e Cele Daccò Via G.B. Camozzi Ranica (BG), 0039 03545351, norberto.perico@marionegri.it
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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	05 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2017
Global end of trial reached?	Yes
Global end of trial date	14 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Short-term (1-year): To compare the effect of long acting somatostatin analogue (Octreotide LAR) versus placebo on total kidney volume (TKV) change (delta TKV) as assessed by spiral computed tomography (spiral CT) scan.
Long-term (3-years): To compare the effect of long-acting somatostatin analogue vs. placebo on the rate of GFR decline as assessed by serial measurements of the iohexol plasma clearance.

Protection of trial subjects:

This study was conducted in conformance with Declaration of Helsinki, Good Clinical Practice standards and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research and privacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2011
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	Italy: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	94
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified among patients with ADPKD referred to the outpatient clinics of 4 hospitals in Italy coordinated by the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. Patients were recruited between 20th September, 2011, and March 10, 2014

Pre-assignment

Screening details:

Of 104 assessed patients (who signed the Informed consent form between 20/09/2011 and 10/03/2014), 3 withdrew IC during the screening period and 1 had eGFR < 15 ml/min/1.73 m2. Thus, 100 patients were randomized from 11/10/2011, to 20/03/2014 (51 to octreotide-LAR and 49 to placebo), and followed for a median (IQR) of 36 (24 to 37) until 14/04/2017

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Octreotide LAR

Arm description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Arm type	Experimental
Investigational medicinal product name	Long-Acting Somatostatin (Octreotide LAR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Patients randomized to treatment group will receive intramuscularly Long-Acting Somatostatin (Octreotide LAR) at the dose of 40 mg every 28 days (in two intragluteal 20 mg injections) for three years.

Arm title	0.9% sodium chloride solution

Arm description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Arm type	Experimental

Investigational medicinal product name	0.9% sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Patients randomized to placebo group will receive intramuscularly saline solution at the same volume of study drug every 28 days (in two intragluteal injections) for three years.

Number of subjects in period 1	Octreotide LAR	0.9% sodium chloride solution
Started	51	49
Completed	45	46
Not completed	6	3
Profressed to End stage Renal Disease	-	1
Consent withdrawn by subject	4	2
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Octreotide LAR
Reporting group description:	
Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.	
Reporting group title	0.9% sodium chloride solution
Reporting group description:	
Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.	

Reporting group values	Octreotide LAR	0.9% sodium chloride solution	Total
Number of subjects	51	49	100
Age categorical Units: Subjects			
Adults (18-64 years)	48	46	94
From 65-84 years	3	3	6
Age continuous Units: years			
arithmetic mean	48.7	50	
standard deviation	± 8.9	± 9.3	-
Gender categorical Units: Subjects			
Female	20	23	43
Male	31	26	57
Imagin classification Units: Subjects			
1A	2	1	3
1B	2	6	8
1C	16	13	29
1D	13	13	26
1E	15	14	29
Not evaluable	3	2	5
Height Units: CM			
arithmetic mean	172.3	170.7	
standard deviation	± 9.8	± 10.8	-
Weight			

Units: Kg			
arithmetic mean	77.2	76.4	
standard deviation	± 14.6	± 14.1	-
Systolic blood pressure			
Units: mm Hg			
arithmetic mean	134.9	132.3	
standard deviation	± 15.4	± 13.2	-
Diastolic blood pressure			
Units: mm Hg			
arithmetic mean	81.8	83.1	
standard deviation	± 9.3	± 8.4	-
Total Cholesterol			
Units: mmol/L			
arithmetic mean	5	4.8	
standard deviation	± 1	± 1	-
LDL Choletserol			
Units: mmol/L			
arithmetic mean	3	2.9	
standard deviation	± 0.8	± 0.9	-
Triglycerides			
Units: mmol/L			
arithmetic mean	1.3	1.3	
standard deviation	± 0.7	± 0.6	-
Serum Glucose			
Units: mmol/L			
arithmetic mean	5	4.9	
standard deviation	± 0.6	± 0.7	-
Serum phosphorus			
Units: mmol/L			
arithmetic mean	1.2	1.2	
standard deviation	± 0.2	± 0.2	-
Serum Calcium			
Units: mmol/L			
arithmetic mean	2.3	2.3	
standard deviation	± 0.1	± 0.2	-
Hemoglobin			
Units: g/L			
arithmetic mean	124	121	
standard deviation	± 15	± 12	-
Serum albumin			
Units: g/L			
arithmetic mean	41	41	
standard deviation	± 4	± 4	-
Serum Creatinine			
Units: µmol/L			
arithmetic mean	229.8	238.7	
standard deviation	± 79.6	± 79.6	-
mGFR			
Measured by iohexol plasma clearance			
Units: ml/min/1.73m2			
median	31.5	30.9	
inter-quartile range (Q1-Q3)	25.6 to 36.6	21.6 to 37.4	-

eGFR			
Estimated by the 4-variable equation from Modification of Diet in Renal Disease Study			
Units: ml/min/1.73m2			
median	27.9	25.8	
inter-quartile range (Q1-Q3)	23.5 to 32.2	19.5 to 33.2	-
Urinary proteins			
Units: mg/24h			
median	268	260	
inter-quartile range (Q1-Q3)	135 to 805	130 to 460	-
Urinary albumin			
Units: µg/ml			
median	50.7	28.3	
inter-quartile range (Q1-Q3)	21 to 118.1	12.8 to 96.2	-
UAC			
Units: mg/g			
median	77.3	45.4	
inter-quartile range (Q1-Q3)	35.9 to 225.9	25.5 to 181.9	-
Total Kidney volume (TKV)			
Units: ml			
median	2338	2591	
inter-quartile range (Q1-Q3)	1967 to 3807	1959 to 3835	-
Height adjusted total kidnet volume			
Units: ml/m			
median	1.344	1.528	
inter-quartile range (Q1-Q3)	1.129 to 2.098	1.155 to 2.291	-
osmolality			
Units: mOsm/L			
median	279.2	313.7	
inter-quartile range (Q1-Q3)	217.8 to 365.5	253.8 to 407.6	-
Urine protein			
Units: mg/dl			
median	11.4	9.1	
inter-quartile range (Q1-Q3)	7 to 23.6	6 to 18.6	-
Urine Albumin			
Units: µg/mL			
median	50.7	28.3	
inter-quartile range (Q1-Q3)	21.0 to 118.1	12.8 to 96.2	-
Urine Creatinine			
Units: mg/dL			
median	60.2	59.0	
inter-quartile range (Q1-Q3)	45.0 to 70.4	50.1 to 73.1	-
P/C			
Units: mg/g			
median	0.24	0.15	
inter-quartile range (Q1-Q3)	0.12 to 0.55	0.1 to 0.37	-
A/C			
Units: mg/g			
median	77.3	45.4	
inter-quartile range (Q1-Q3)	35.9 to 225.9	25.5 to 181.9	-

End points

End points reporting groups

Reporting group title	Octreotide LAR

Reporting group description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Reporting group title	0.9% sodium chloride solution

Reporting group description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Primary: Short-term outcome - TKV change

End point title	Short-term outcome - TKV change

End point description:

Total Kidney Volume (TKV) change as assessed by spiral computed tomography scan.
Measurable unit for TKV is ml and for htTKV is ml/m

End point type	Primary

End point timeframe:

Baseline compared to 1-year afte the Treatment period (Octreotide LAR/Placebo)

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	39		
Units: ml and ml/m				
median (inter-quartile range (Q1-Q3))				
TKV	2513.3 (2023.6 to 3923.5)	2935.1 (2197.1 to 4094.4)		
Absolute Change TKV	135.5 (40.4 to 453.1)	257.7 (112.6 to 497.7)		
htTKV	1528.1 (1237.1 to 2281.1)	1769.5 (1258.3 to 2488.3)		
Absolute Change htTKV	80.7 (24.8 to 258.9)	155.3 (66.1 to 286.0)		

Statistical analyses

Statistical analysis title	Primary End Point
Statistical analysis description:	
Difference between changes of TKV and htTKV in Octreotide-LAR and Placebo at 1 year	
Comparison groups	Octreotide LAR v 0.9% sodium chloride solution
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [1]
Method	ANCOVA

Notes:

[1] - TKV changes between treatment and placebo reported a p value of 0.027;
htTKV changes between treatment and placebo reported a p value of 0.020;

Primary: Long-term outcome (3-years) - Rate of GFR decline

End point title	Long-term outcome (3-years) - Rate of GFR decline

End point description:

The primary long-term outcome was the chronic rate of GFR decline from 6 months to study end as assessed by serial measurement of the iohexol plasma clearance

The unit measurement for Total slope 0-3 years and Chronic slope 6 months-3years is ml/min/1.73m2 per year

End point type	Primary

End point timeframe:

At the baseline and every 6 months until the final visit (36 months of study treatment)

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: ml/min/1.73m2				
median (inter-quartile range (Q1-Q3))				
GFR 6 months	27.0 (22.2 to 32.3)	26.3 (20.9 to 34.8)		
GFR 1 year	25.3 (19.4 to 29.9)	24.4 (20.9 to 34.8)		
GFR 2 years	22.5 (17.2 to 26.9)	22.2 (17.9 to 28.5)		
GFR 3 years	19.8 (15.5 to 23.7)	18.1 (14.7 to 26.7)		
Total slope 0-3 years	-4.26 (-6.2 to -3)	-4.19 (-5.5 to -1.7)		
Chronic slope 6 months-3years	-3.76 (-5.1 to -2.4)	-3.97 (-5.9 to -2.0)		

Statistical analyses

Statistical analysis title	Primary End Point
Statistical analysis description:	
Changes in GFR over Octreotide-LAR and placebo	
Comparison groups	Octreotide LAR v 0.9% sodium chloride solution
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.295 [2]
Method	ANCOVA

Notes:

[2] - All differences in GFR changes over 6-12-24-36 months are not significant between treatment and placebo groups.

Secondary: Doubling of serum creatinine or ESRD

End point title	Doubling of serum creatinine or ESRD
End point description:	
Secondary composite endpoint of doubling of serum creatinine or ESRD in pateint treated with octreotide LAR/Placebo	
End point type	Secondary
End point timeframe:	
From Baseline to the study end	

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: Patient				
Doubling serum creatinine or ESRD	6	18		
No Doubling serum creatinine or ESRD	45	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary protein excretion rate

End point title	Urinary protein excretion rate
End point description:	
Urinary protein excretion rate compared to the baseline at 1 year and 3 year after the treatment period	

End point type	Secondary

End point timeframe:

At baseline and every 6 months until the study end

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: mg/24h				
median (inter-quartile range (Q1-Q3))				
Urinary protein excretion rate - 1 year	340 (170 to 920)	340 (130 to 580)		
Urinary protein excretion rate - 3 year	480 (190 to 820)	580 (180 to 968)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blodd pressure control

End point title	Blodd pressure control

End point description:

Blood pressure parameters compared to the baseline at 1 year and 3 year after the treatment period

End point type	Secondary

End point timeframe:

1 year and 3 year after the treatment period

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: mm Hg				
median (standard deviation)				
Systolic - 1 year	133.3 (± 15.1)	130.3 (± 12.2)		
Systolic - 3 year	132.6 (± 13.6)	130.3 (± 6.9)		
Diastolic - 1 year	81.5 (± 9.2)	82.3 (± 6)		
Diastolic - 3 year	82.4 (± 6.1)	82.9 (± 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary osmolality

End point title	Urinary osmolality

End point description:

End point type	Secondary

End point timeframe:

At baseline and 1 year and 3 year after the treatment period

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: mOsm/L				
median (inter-quartile range (Q1-Q3))				
Osmolality - 1 year	289.4 (230.8 to 381.2)	341.0 (245.1 to 396.4)		
Osmolality - 3 year	266.5 (221.3 to 306.4)	317.3 (252.2 to 384.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Morning spot urine sample

End point title	Morning spot urine sample

End point description:

Measurement units
Protein: mg/dl
Albumin: µg/mL
Creatinine: mg/dL
P/C: mg/g
A/C: mg/g

End point type	Secondary

End point timeframe:

1 year and 3 year compared to baseline

End point values	Octreotide LAR	0.9% sodium chloride solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: mg/dl and µg/ml				
median (inter-quartile range (Q1-Q3))				

Protein - 1 year	14.9 (8.4 to 39.3)	16.5 (7.2 to 24)		
Protein - 3 year	18.1 (9 to 28.7)	25.2 (8.7 to 43.8)		
Albumin- 1 year	42.5 (33.3 to 210.5)	57.7 (18.4 to 130.0)		
Albumin- 3 year	74.3 (33.5 to 111.0)	90.0 (53.5 to 150.0)		
Creatinine - 1 year	58.3 (48.4 to 70.4)	55.6 (46.7 to 69.3)		
Creatinine - 3 year	49.3 (41.8 to 59.6)	52.7 (44.0 to 60.0)		
P/C - 1 year	0.26 (0.13 to 0.73)	0.30 (0.15 to 0.44)		
P/C - 3 year	0.40 (0.15 to 0.62)	0.39 (0.24 to 0.81)		
A/C - 1 year	80.0 (51.9 to 364.4)	108.1 (35.0 to 211.0)		
A/C - 3 year	130.6 (54.2 to 286.0)	162.2 (102.8 to 260.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events will be reported during whole study up to 30 days after last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Octreotide LAR

Reporting group description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Reporting group title	0.9% sodium chloride solution

Reporting group description:

Eligible patients will be stratified for the presence (YES or NO) of concomitant clinical conditions that could appreciably affect the rate of renal function loss over time including diabetes mellitus, 24 hour urinary protein excretion >1g, or any other evidence of concomitant renal disease without indication for specific therapy. Within each stratum patients will be randomized on a 1:1 basis to Long-acting Somatostatin (Octreotide LAR) 40 mg (treatment group) or saline solution (placebo group). All study participants including patients, doctors and nurses involved in patient care, and technicians, monitors and statisticians involved in data analyses will be blinded to treatment allocation. The only subject who will not be blinded to treatment allocation will be the research nurse who will prepare the study drug (the active compound or placebo) and will administer it to the patient.

Serious adverse events	Octreotide LAR	0.9% sodium chloride solution	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 51 (23.53%)	11 / 49 (22.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Pancreatic enzyme elevation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
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			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Acute retinal detachment			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Umbilical hernia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pancreatitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary vomiting			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genitourinary prolapse			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	2 / 51 (3.92%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst rupture or infection			
subjects affected / exposed	1 / 51 (1.96%)	3 / 49 (6.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral obstruction due to lithiasis			

subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pyelonephritis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis due to Klebsiella pneumoniae			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Octreotide LAR	0.9% sodium chloride solution	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 51 (90.20%)	45 / 49 (91.84%)	
General disorders and administration site conditions			
Allergic reaction due to study drug			

subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Non-treatment-related allergic reactions			
subjects affected / exposed	3 / 51 (5.88%)	2 / 49 (4.08%)	
occurrences (all)	4	3	
Flu like syndrome			
subjects affected / exposed	6 / 51 (11.76%)	9 / 49 (18.37%)	
occurrences (all)	6	9	
Fever (unspecified)			
subjects affected / exposed	5 / 51 (9.80%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Reproductive system and breast disorders			
Ovarian cyst, follicle rupture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	2	
Endometrial hyperplasia, endometrial polyps			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Bening prostatic hyperplasia			
subjects affected / exposed	1 / 51 (1.96%)	5 / 49 (10.20%)	
occurrences (all)	1	5	
Prostatitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Impotence			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Other urologic events			
subjects affected / exposed	2 / 51 (3.92%)	1 / 49 (2.04%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Pharyngitis, rhinitis, coomon cold, Cough			
subjects affected / exposed	4 / 51 (7.84%)	7 / 49 (14.29%)	
occurrences (all)	10	8	

Acute Bronchitis			
subjects affected / exposed	4 / 51 (7.84%)	5 / 49 (10.20%)	
occurrences (all)	4	5	
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Investigations			
High CPK value			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Rash			
subjects affected / exposed	2 / 51 (3.92%)	2 / 49 (4.08%)	
occurrences (all)	2	2	
Subcutaneous hematoma of the limbs			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Cardiac disorders			
Calf swelling			
subjects affected / exposed	9 / 51 (17.65%)	6 / 49 (12.24%)	
occurrences (all)	12	6	
Hydrosaline retention			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 51 (1.96%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Bilateral pleural effusion			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Aortic calcification			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Claudicatio intermittents			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	

Calf vein thrombosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Left atrial enlargement			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Palpitations			
subjects affected / exposed	3 / 51 (5.88%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Hypotension			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Precordial pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Nervous system disorders			
Depression, Anxiety			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 51 (1.96%)	4 / 49 (8.16%)	
occurrences (all)	1	4	
Dizziness			
subjects affected / exposed	2 / 51 (3.92%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Neuropatic pain			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Tremor			

subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Other nervous system events			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Hyposmia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 51 (21.57%)	23 / 49 (46.94%)	
occurrences (all)	12	24	
Benign cutaneous lymphoid infiltrate			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Eye disorders			
degenerative maculopathy			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Amblyopia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Other ocular, ear, labyrinth, oral, nasal events			
subjects affected / exposed	4 / 51 (7.84%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	15 / 51 (29.41%)	5 / 49 (10.20%)	
occurrences (all)	28	7	
Abdominal pain, bloating			
subjects affected / exposed	12 / 51 (23.53%)	10 / 49 (20.41%)	
occurrences (all)	12	16	

Gastritis, Nausea, Dyspepsia, Vomiting			
subjects affected / exposed	4 / 51 (7.84%)	9 / 49 (18.37%)	
occurrences (all)	4	10	
Biliary sand			
subjects affected / exposed	8 / 51 (15.69%)	0 / 49 (0.00%)	
occurrences (all)	8	0	
Gallbladder polyp			
subjects affected / exposed	2 / 51 (3.92%)	1 / 49 (2.04%)	
occurrences (all)	2	1	
Liver steatosis			
subjects affected / exposed	1 / 51 (1.96%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Hepatic, cyst rupture, hemorrhagic hepatic cyst			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	3	
Flatulence			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Colon diverticulosis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Other gastrointestinal events			
subjects affected / exposed	6 / 51 (11.76%)	3 / 49 (6.12%)	
occurrences (all)	7	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 51 (1.96%)	5 / 49 (10.20%)	
occurrences (all)	2	5	
Dermatitis			
subjects affected / exposed	1 / 51 (1.96%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Folliculitis, forunculosis			

subjects affected / exposed	1 / 51 (1.96%)	1 / 49 (2.04%)	
occurrences (all)	1	1	
Alopecia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	4 / 51 (7.84%)	5 / 49 (10.20%)	
occurrences (all)	5	5	
Renal colic, lithiasis			
subjects affected / exposed	7 / 51 (13.73%)	3 / 49 (6.12%)	
occurrences (all)	10	3	
Hematuria			
subjects affected / exposed	6 / 51 (11.76%)	9 / 49 (18.37%)	
occurrences (all)	11	15	
Urinary tract infection			
subjects affected / exposed	6 / 51 (11.76%)	5 / 49 (10.20%)	
occurrences (all)	10	6	
Renal cyst infection or rupture			
subjects affected / exposed	1 / 51 (1.96%)	6 / 49 (12.24%)	
occurrences (all)	1	8	
Asynptomatic bacteriuria, Dysuria			
subjects affected / exposed	2 / 51 (3.92%)	2 / 49 (4.08%)	
occurrences (all)	3	2	
Cholelithiasis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 49 (2.04%)	
occurrences (all)	3	1	
Endocrine disorders			
Secondary hyperparathyroidism			
subjects affected / exposed	25 / 51 (49.02%)	18 / 49 (36.73%)	
occurrences (all)	25	18	
Musculoskeletal and connective tissue disorders			
Chronic kidney disease-mineral and bone disorder (CKD-MBD)			
subjects affected / exposed	19 / 51 (37.25%)	17 / 49 (34.69%)	
occurrences (all)	20	19	
Back pain, Flank pain			

subjects affected / exposed	8 / 51 (15.69%)	10 / 49 (20.41%)	
occurrences (all)	9	14	
Muscular pain, cramps			
subjects affected / exposed	9 / 51 (17.65%)	9 / 49 (18.37%)	
occurrences (all)	13	13	
Fatigue			
subjects affected / exposed	10 / 51 (19.61%)	8 / 49 (16.33%)	
occurrences (all)	11	10	
Site injection pain, site injection nodule			
subjects affected / exposed	7 / 51 (13.73%)	3 / 49 (6.12%)	
occurrences (all)	16	6	
Osteoarthritis			
subjects affected / exposed	2 / 51 (3.92%)	3 / 49 (6.12%)	
occurrences (all)	2	3	
Fracture, trauma, tendonitis, tendon tear			
subjects affected / exposed	2 / 51 (3.92%)	6 / 49 (12.24%)	
occurrences (all)	2	6	
Discal hernia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Other musculoskeletal events			
subjects affected / exposed	1 / 51 (1.96%)	2 / 49 (4.08%)	
occurrences (all)	2	2	
Infections and infestations			
Septic Arthritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Vaginitis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Otitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Onychomycosis			

subjects affected / exposed	0 / 51 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	23 / 51 (45.10%)	17 / 49 (34.69%)	
occurrences (all)	23	17	
Hyperuricemia			
subjects affected / exposed	16 / 51 (31.37%)	9 / 49 (18.37%)	
occurrences (all)	16	9	
Dyslipidemia			
subjects affected / exposed	10 / 51 (19.61%)	5 / 49 (10.20%)	
occurrences (all)	10	5	
Hyperkalaemia			
subjects affected / exposed	3 / 51 (5.88%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Hypokalaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 49 (2.04%)	
occurrences (all)	0	1	
Hyponatremia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 49 (0.00%)	
occurrences (all)	1	0	
Hyperhomocysteinaemia			
subjects affected / exposed	3 / 51 (5.88%)	4 / 49 (8.16%)	
occurrences (all)	3	4	
Pancytopenia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
Other metabolic, endocrine, hematological events			

subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 5	2 / 49 (4.08%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2013	The amendment concerned the increase in the size of the originally calculated patient sample and the administration of the SF36 and SF-HLQ questionnaires to patients. Specifically, the sample size was recalculated, maintaining the initial considerations relating to end points and patient follow-up unchanged, but increasing the incidence of drop-outs from 15% to 30%. It was therefore estimated that the inclusion of 98 patients (49 per group) could guarantee the study to maintain a statistical power of more than 80%. The amendment did not change either the criteria for inclusion of the study, nor the general philosophy and main objective of the project .

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30951521