Clinical trial results:
EFFICACY AND SAFETY OF A SINGLE TRUS-GUIDED INTRAPROSTATIC INJECTION OF NX-1207 IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA:
A PHASE III EUROPEAN CLINICAL STUDY

Summary

EudraCT number	2012-002451-41
Trial protocol	DE PT ES GB IT PL RO
Global end of trial date	25 January 2016

Results information

Result version number	v1 (current)
This version publication date	21 January 2017
First version publication date	21 January 2017

Trial information

Trial identification

Sponsor protocol code	NX1207-IT-CL0414

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02003742
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Recordati S.p.A
Sponsor organisation address	Via Civitali 1, Milan, Italy,
Public contact	Clin. Proj. Leader - Medical Dep., Recordati S.p.A., +39 (0)248787183, miotto.f@recordati.it
Scientific contact	Clin. Proj. Leader - Medical Dep., Recordati S.p.A., +(039) (0)248787183, miotto.f@recordati.it

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 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the core of the study was to demonstrate that a single TRUS-guided intraprostatic injection of NX-1207 provided a long lasting therapeutic improvement of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) in patients not adequately controlled by medical therapy with α-blockers, as assessed by a change from baseline in the International Prostate Symptom Score (IPSS) total score.

Protection of trial subjects:

The study was conducted in EU and in extra-EU countries in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/1995), with Directive 2001/20/EC (for Europe [EU]), and with all local laws and regulations concerning clinical trials.
All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Germany: 68
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	212
EEA total number of subjects	179

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)	162
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators at 47 centres (4 in France, 12 in Germany, 5 in Italy, 5 in Poland, 3 in Portugal, 5 in Romania, 5 in Russia, 5 in Spain, and 3 in the United Kingdom) agreed to participate in this study.

Study initiation date (Fist patient in): 11 November 2013
Study completion date (Last patient last visit): 29 January 2015

Pre-assignment

Screening details:

Men aged 45 years or older with LUTS/BPH not adequately controlled by medical therapy with α-blockers and presence of moderate/severe LUTS (IPSS ≥ 15) at screening and at baseline (after a 4 week with tamsulosin 0.4 mg QD), Prostate Volume ≥ 30 mL and ≤ 70 mL (as assessed by TRUS) and Qmax < 15 mL/sec based on a minimum void of 125 mL.

Pre-assignment period milestones

Number of subjects started	212
Number of subjects completed	196

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 16

Period 1

Period 1 title	Open-label Run-in period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in period

Arm description:

A 4 week run-in period in which all subjects were treated with the most commonly used α-blocker at the current recommended dosage (i.e. tamsulosin 0.4 mg QD).

Arm type	Tamsulosin 0.4 mg
Investigational medicinal product name	Tamsulosin 0.4 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All enrolled subjects received 1 film coated, prolonged release tablets of tamsulosin 0.4 mg to be taken per oral route once daily

Number of subjects in period 1[1]	Run-in period
Started	196
Completed	104
Not completed	92
Consent withdrawn by subject	4
Run-in failure	21
Protocol deviation	67

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 212 patients have been screened and 196 enrolled in the run-in period. 16 patients were excluded prior to run-in period due to selection criteria not met (screening failure).

Period 2

Period 2 title	Single-blind Randomised treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	NX-1207 injection

Arm description:

A single TRUS-guided intraprostatic injection of 2.5 mg of NX-1207 (NX-1207 arm) followed by 1 tablet of tamsulosin placebo to be taken orally QD

Arm type	Experimental
Investigational medicinal product name	NX-1207
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intraprostatic use

Dosage and administration details:

A single TRUS-guided intraprostatic injection of 2.5 mg of NX-1207 (NX-1207 arm) followed by 1 tablet of tamsulosin placebo to be taken orally QD

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of tamsulosin placebo to be taken orally QD

Arm title	Tamsulosin 0.4 mg

Arm description:

TRUS procedure only (comparator arm) followed by 1 film coated, prolonged release tablet of tamsulosin 0.4 mg, to be taken orally QD.

Arm type	Active comparator

Investigational medicinal product name	Tamsulosin hydrochloride 0.4 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Marketed tablets of tamsulosin hydrochloride 0.4 mg (film coated, prolonged release tablet - Omexel® L.P.).

Number of subjects in period 2	NX-1207 injection	Tamsulosin 0.4 mg
Started	49	55
Completed	4	4
Not completed	45	51
Consent withdrawn by subject	2	3
Adverse event, non-fatal	3	-
Drop out due to the early termination of study	38	-
Drop out due to the early termination of study	-	45
Lack of efficacy	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Open-label Run-in period

Reporting group description: -

Reporting group values	Open-label Run-in period	Total	
Number of subjects	196	196	
Age categorical			
Men aged 45 years or older			
Units: Subjects			
Adults (18-64 years)	162	162	
From 65-84 years	34	34	
85 years and over	0	0	
Age continuous			
Units: years			
median	66.5		
full range (min-max)	51 to 85	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	196	196	
Ethnic group			
Units: Subjects			
Caucasian male	196	196	

End points

End points reporting groups

Reporting group title	Run-in period
Reporting group description:	
A 4 week run-in period in which all subjects were treated with the most commonly used α-blocker at the current recommended dosage (i.e. tamsulosin 0.4 mg QD).	
Reporting group title	NX-1207 injection
Reporting group description:	
A single TRUS-guided intraprostatic injection of 2.5 mg of NX-1207 (NX-1207 arm) followed by 1 tablet of tamsulosin placebo to be taken orally QD	
Reporting group title	Tamsulosin 0.4 mg
Reporting group description:	
TRUS procedure only (comparator arm) followed by 1 film coated, prolonged release tablet of tamsulosin 0.4 mg, to be taken orally QD.	

Primary: Change from baseline in IPSS total score

End point title	Change from baseline in IPSS total score
End point description:	
The primary objective of the study was to demonstrate that a single transrectal ultrasound (TRUS)-guided intraprostatic injection of NX-1207 provided a long lasting therapeutic improvement of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) in patients not adequately controlled by medical therapy with α-blockers, as assessed by a change from baseline in the International Prostate Symptom Score (IPSS) total score.	
End point type	Primary
End point timeframe:	
Change from baseline in the International Prostate Symptom Score (IPSS) total score.	

End point values	NX-1207 injection	Tamsulosin 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	54		
Units: IPSS total score				
number (not applicable)	48	54		

Statistical analyses

Statistical analysis title	Descriptive statistics of the variables collected
Statistical analysis description:	
The statistical plan has been revised after the premature study termination.	
Comparison groups	NX-1207 injection v Tamsulosin 0.4 mg

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - Due to the reduced number of patients randomised and completing the study only descriptive statistics on the parameters, as well as on the change from the baseline, were calculated.
No treatment group comparison and any inferential statistical analysis as planned by the protocol has been performed.
The efficacy and safety analisyses were based only the Safety Set. The Safety Set was defined as all patients who took at least one dose-post baseline of study medication.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of AEs was extended from Visit 1 up to the final/early termination visit.
In addition, all SAEs which came to the attention of the investigator within 4 weeks from the end of the study were also to be recorded.

Adverse event reporting additional description:

Specific attention was requested for AEs involving the urinary tract and reproductive system, with special mention to infections, e.g: fever, urinary tract infections, prostatic infections, prostatitis, epididymitis, urethral infections, cystitis, even though these would not qualify as serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Run-in period
Reporting group description: -	
Reporting group title	NX-1207 group
Reporting group description: -	
Reporting group title	Tamsulosin group
Reporting group description: -	

Serious adverse events	Run-in period	NX-1207 group	Tamsulosin group
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 196 (0.51%)	2 / 48 (4.17%)	0 / 54 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Thermal burn	Additional description: The death of patient was caused by thermal burn due to gas explosion. This patient had also experienced pneumonia, pyelonephritis and chronic obstructive pulmonary disease. All SAEs were considered as not related.		
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Sick sinus syndrome	Additional description: The investigator assessed the event as moderate and not related to study drug but to pre-existing condition.		
subjects affected / exposed	1 / 196 (0.51%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease	Additional description: The investigator assessed the events as severe and not related to study drug as it was a known pre-existing condition.		
subjects affected / exposed	1 / 196 (0.51%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia	Additional description: The investigator assessed the event as not related to study drug .		
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Pyelonephritis	Additional description: The investigator assessed the event as moderate and not related to study drug .		
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (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: 0 %

Non-serious adverse events	Run-in period	NX-1207 group	Tamsulosin group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 196 (1.53%)	6 / 48 (12.50%)	7 / 54 (12.96%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 196 (0.00%)	3 / 48 (6.25%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 196 (0.00%)	2 / 48 (4.17%)	0 / 54 (0.00%)
occurrences (all)	0	2	0

Infections and infestations			
Bacteriuria			
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	2 / 54 (3.70%)
occurrences (all)	0	1	2
Cystitis			
subjects affected / exposed	0 / 196 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2013	The aim of the Amendment No. 1 was to modify (on a conservative approach) the storage conditions of the investigational medicinal product under test and the handling and dispensing instruction, in order to better clarify the use of the reconstituted product. This amendment had no significant impact on the scientific value of the clinical trial. All subjects were enrolled in the study only after approval of Amendment No. 1.
25 July 2014	The aim of the Amendment No. 2 was to modify exclusion criteria No. 12: "Poorly controlled diabetes (type 1 or type 2), as determined by HbA1c >6% and/or glycosuria" in "Poorly controlled diabetes (type 1 or type 2), as determined by HbA1c > 7% and/or glycosuria". In order to avoid excluding from study participation patients who have an acceptable glycemic control as per reference scientific guideline and medical practice. This amendment had no significant impact on the safety of the patients or the scientific value of the clinical trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 November 2014	After the news released by the Nymox Pharmaceutical Corporation (originator of NX-1207), announcing that their two double-blind, placebo-controlled, Phase III clinical trials conducted in the US with NX-1207 2.5 mg had failed to meet their primary efficacy endpoint, the clinical trial was prematurely terminated. Since only a minority of patients had completed the 12 month study period, the investigators were asked to proceed to schedule an early termination visit at a suitable date for the patient.	-

Notes:

Limitations and caveats

None reported