Clinical trial results:
Evaluation of the efficacy and safety of prulifloxacin vs levofloxacin in the treatment of Chronic Bacterial Prostatitis

Summary

EudraCT number	2014-003757-33
Trial protocol	IT GR
Global end of trial date	19 May 2020

Results information

Result version number	v1 (current)
This version publication date	04 June 2021
First version publication date	04 June 2021

Trial information

Trial identification

Sponsor protocol code	027IC13250

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03201796
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Angelini Pharma S.p.A
Sponsor organisation address	Viale Amelia, 70, Rome, Italy, 00181
Public contact	Global Medical Department - Clinical Operations alessandro.ruggieri@angelinipharma.com, Angelini Pharma S.p.A. Viale Amelia, 70 00181 Rome (Italy), +39
Scientific contact	Global Medical Department - Clinical Operations alessandro.ruggieri@angelinipharma.com, Angelini Pharma S.p.A Viale Amelia, 70 00181 Rome (Italy), +39 0691045309

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	19 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2020
Global end of trial reached?	Yes
Global end of trial date	19 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study was to assess the efficacy and safety of Prulifloxacin in comparison to Levofloxacin in the treatment of patients affected by Chronic Bacterial Prostatitis (CBP).

Protection of trial subjects:

No specific measures are provided. In case of ineffective treatment the pattient discontinue study and the Investigator can administer alternative drugs.

Background therapy:

Not applicable

Evidence for comparator:

Levofloxacin 500 mg tablets has been selected as treatment comparator because it represents the drug of choice authorized for the treatment of Chronic Bacterial Prostatitis (CBP). Consequently, the dosage regimen administered to the patients is consistent with that reported in the relevant SPC.

Actual start date of recruitment	02 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	44

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 168 patients accepted to participate and entered the study after having signed the Informed Consent Form. Forty-four (44) of them (26,2%) met inclusion/exclusion criteria and have been randomized and treated with at least one dose of Prulifloxacin or Levofloxacin.

Pre-assignment

Screening details:

Visit 0 (Screening, 7-10 days before Visit 1): patient’s information, written informed consent, demographic data, medical history, physical examination, vital signs, BMI, digital rectal examination, ECG, prostate sovrapubic ultrasound, NIH-CPSI, I-PSS, IIEF-5, laboratory analysis, urinalysis, Meares&Stamey 4-glass test for microbiological assessmen

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The present study was performed in double blind condition. Consequently, during the study, neither the Investigator nor the patient were aware of the treatment assigned.
In case of medical emergency, the Investigator was able to unblind the treatment code through the blinded labels provided by the Sponsor. The reason for unblinding had to be properly documented and promptly notified to the Sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Prulifloxacin 600 mg

Arm description:

Prulifloxacin (Unidrox®) 600 mg tablet once daily in the evening

Arm type	Experimental
Investigational medicinal product name	Prulifloxacin 600 mg
Investigational medicinal product code	027
Other name	Unidrox®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One Prulifloxacin 600 mg tablet (Unidrox®) once daily for 28 days. Patients have been instructed to orally take the tablet in the evening with a glass of water.

Investigational medicinal product name	Levofloxacin 500 mg
Investigational medicinal product code	
Other name	Levoxacin®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One Levofloxacin 500 mg tablet (Levoxacin®) once daily for 28 days. Patients have been instructed to orally take the tablet in the evening with a glass of water.

Arm title	Levofloxacin 500 mg

Arm description:

Levofloxacin (Levoxacin®) 500 mg tablet once daily in the evening

Arm type	Active comparator
Investigational medicinal product name	Levofloxacin 500 mg
Investigational medicinal product code	
Other name	Levoxacin®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One Levofloxacin 500 mg tablet (Levoxacin®) once daily for 28 days. Patients have been instructed to orally take the tablet in the evening with a glass of water.

Number of subjects in period 1	Prulifloxacin 600 mg	Levofloxacin 500 mg
Started	23	21
Completed	9	10
Not completed	14	11
Consent withdrawn by subject	1	1
Not presenting microbiological success at V3 or V4	-	7
Adverse event, non-fatal	1	-
Requiring an additional antimicrobial therapy	1	-
Other reasons	-	1
Lost to follow-up	3	1
Not presenting microbiologica success at V3 or V4	7	-
other reason	1	-
Poor compliance to the experimental procedures	-	1

Baseline characteristics

Reporting groups

Reporting group title	Prulifloxacin 600 mg

Reporting group description:

Prulifloxacin (Unidrox®) 600 mg tablet once daily in the evening

Reporting group title	Levofloxacin 500 mg

Reporting group description:

Levofloxacin (Levoxacin®) 500 mg tablet once daily in the evening

Reporting group values	Prulifloxacin 600 mg	Levofloxacin 500 mg	Total
Number of subjects	23	21	44
Age categorical			
The demographic characteristics were well-balanced between the two groups at baseline. The age ranged from 21.0 to 50.0, with a mean of about 39 years-old in both groups. All about one subject were Caucasian (white).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	21	44
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	39.43	39.00	
standard deviation	± 10.17	± 7.44	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	23	21	44
Ethnic group			
Units: Subjects			
Black	0	1	1
White	23	20	43

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population (SP) was defined as all randomized patients who took at least one dose of the study medication. Forty-four (44) patients were included in the SP population.

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intention-to-Treat (m-ITT) population was defined as all randomized patients who took at least one dose of the study medication with a bacteriologically confirmed infection by M&S 4-glass test at Visit 0 (Screening) and with a microbiological assessment by M&S 4-glass test at Visit 3 (TOC).
Thirty-eight (38) patients out of 44 in the Safety population, were included in the m-ITT population.
Six (6) patients, random #89, #145, #219, #226, #230, #254, were not included in the m-ITT population because the microbiological assessment by M&S 4-glass test at Visit 3 (TOC) was missing.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population was defined as patients from the m-ITT population with no major protocol violations.
22 out of 38 patients of the m-ITT population, were included in the PP population, 10 (43.5%) in Prulifloxacin and 12 (57.1%) in Levofloxacin group.
All the 16 patients not included in the PP population met the major violation regarding Visit 3 (TOC) scheduled out of 7 days after EOT (±2).

Reporting group values	Safety population	m-ITT population	PP population
Number of subjects	44	38	22
Age categorical			
The demographic characteristics were well-balanced between the two groups at baseline. The age ranged from 21.0 to 50.0, with a mean of about 39 years-old in both groups. All about one subject were Caucasian (white).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	44	38	22
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	39.23	38.82	36.55
standard deviation	± 8.88	± 8.78	± 9.88
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	44	38	22
Ethnic group			
Units: Subjects			
Black	1	1	1
White	43	37	21

End points

End points reporting groups

Reporting group title	Prulifloxacin 600 mg

Reporting group description:

Prulifloxacin (Unidrox®) 600 mg tablet once daily in the evening

Reporting group title	Levofloxacin 500 mg

Reporting group description:

Levofloxacin (Levoxacin®) 500 mg tablet once daily in the evening

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population (SP) was defined as all randomized patients who took at least one dose of the study medication. Forty-four (44) patients were included in the SP population.

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified Intention-to-Treat (m-ITT) population was defined as all randomized patients who took at least one dose of the study medication with a bacteriologically confirmed infection by M&S 4-glass test at Visit 0 (Screening) and with a microbiological assessment by M&S 4-glass test at Visit 3 (TOC). Thirty-eight (38) patients out of 44 in the Safety population, were included in the m-ITT population. Six (6) patients, random #89, #145, #219, #226, #230, #254, were not included in the m-ITT population because the microbiological assessment by M&S 4-glass test at Visit 3 (TOC) was missing.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population was defined as patients from the m-ITT population with no major protocol violations.
22 out of 38 patients of the m-ITT population, were included in the PP population, 10 (43.5%) in Prulifloxacin and 12 (57.1%) in Levofloxacin group.
All the 16 patients not included in the PP population met the major violation regarding Visit 3 (TOC) scheduled out of 7 days after EOT (±2).

Primary: Microbiological Eradication at Visit 3

End point title	Microbiological Eradication at Visit 3

End point description:

The primary endpoint of the study is the microbiological efficacy of Prulifloxacin in comparison to Levofloxacin assessed as eradication at Visit 3.
Primary efficacy endpoint is evaluated by calculating the two-sided 95% confidence interval of the difference in the proportion of microbiological success between Prulifloxacin and Levofloxacin.
The non-inferiority is declared if the lower limit of the 95% Confidence Interval (95% CI) calculated on the m-ITT and PP populations, do not exceed the threshold of -20%.

End point type	Primary

End point timeframe:

Test of Cure (TOC) Visit, 7 days (±2) after End of Treatment (EOT)

End point values	Prulifloxacin 600 mg	Levofloxacin 500 mg	Safety population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: Percentage				
number (not applicable)	70.0	75.0	72.7	

Statistical analyses

Statistical analysis title	95% Confidence Interval
Statistical analysis description:	
Primary efficacy endpoint is evaluated by calculating the two-sided 95% confidence interval of the difference in the proportion of microbiological success between Prulifloxacin and Levofloxacin.	
Comparison groups	Prulifloxacin 600 mg v Levofloxacin 500 mg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	95% CI
Point estimate	-20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.51
upper limit	32.51

Secondary: Microbiological eradication at Visit 4

End point title	Microbiological eradication at Visit 4
End point description:	
Microbiological success at Visit 4 was defined as eradication, while microbiological failure was defined as relapse, superinfection or relapse with superinfection.	
End point type	Secondary
End point timeframe:	
3 months after the EOT ±5 days;	

End point values	Prulifloxacin 600 mg	Levofloxacin 500 mg	PP population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7	9	16	
Units: Percentage				
number (not applicable)	85.7	100	93.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological eradication at Visit 5

End point title	Microbiological eradication at Visit 5

End point description:

Microbiological success at Visit 5 was defined as eradication, while microbiological failure was defined as relapse, superinfection or relapse with superinfection.

End point type	Secondary

End point timeframe:

6 months after the EOT ±5 days

End point values	Prulifloxacin 600 mg	Levofloxacin 500 mg	PP population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	9	15	
Units: Percentage				
number (not applicable)	100	100	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Change of clinical improvement

End point title	Change of clinical improvement

End point description:

Clinical efficacy at Visit 3 was analysed by calculating the two-sided 95% confidence interval of the difference in the proportion of clinical improvement between Prulifloxacin and Levofloxacin.

End point type	Secondary

End point timeframe:

This endpoint was assessed at Visit 3.

End point values	Prulifloxacin 600 mg	Levofloxacin 500 mg	PP population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	12	22	
Units: Percentage				
number (not applicable)	90.0	100.0	95.5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported, between the first drug intake up to the end of six-month follow-up period.

Adverse event reporting additional description:

Overall, 12/23 patients in Prulifloxacin reported 34 AEs, while 8/21 patients in Levofloxacin experienced 9 AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Prulifloxacin 600 mg

Reporting group description:

Twenty-three (23) subjects received at least one dose of Prulifloxacin.

Reporting group title	Levofloxacin 500 mg

Reporting group description:

Twenty-one (21) subjects received at least one dose of Levofloxacin.

Serious adverse events	Prulifloxacin 600 mg	Levofloxacin 500 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Prulifloxacin 600 mg	Levofloxacin 500 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 23 (52.17%)	8 / 21 (38.10%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Blood cholesterol increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Protein total increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Haemorrhoids			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	2 / 23 (8.70%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Photophobia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Gastrointestinal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Painful ejaculation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Perineal pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 21 (0.00%)	
occurrences (all)	2	0	

Scrotal discomfort			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Tracheitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Micturition urgency			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Renal colic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Infections and infestations Oral herpes subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1	 0 / 21 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2015	In Substantial Amendment n.01 , together with the updated protocol version, the new version of the Investigational Medicinal Product Dossier (IMPD version 2/0 of 5May2015) was submitted, updated with the new data relating to the long-term stability of Prulifloxacin batch product after 9 and 12 months (storage conditions at 25°C/60% RH and at 30°C/65% RH). The new data allowed to prolong the shelf life of the investigational product from 6 to 12 months, together with the updated version of the Investigator's Brochure (version no.15 of 26Mar2015).
24 May 2016	Substantial Amendment n.02 included a new version of the IMPD (3.0_26Oct2015, and 4.0 _23Oct2016, that reported new stability data and prolonged the Prulifloxacin batch shelf-life from 12 to 27 months was submitted to AC/ECs. Furthermore, the maximum temperature of storage condition was increased from 25°C to 30°C. The Investigator's Brochure was also updated (version no.16_19May2016), in order to add clinical data regarding the Prulifloxacin dose-adjustement for patient with renal impairment, and safety information related to Clostridium difficile-associated disease, a fluoroquinolone class-effect warning and a few adverse reactions with unknown incidence in the section "Reference Safety Information". The informed consent form was consequently updated.
02 November 2016	Substantial Amendment n.03 (for Italy only) was due to the PI change of Italy site IT-10.
16 November 2016	Substantial Amendment n.04 (for Italy only) was submitted due to the PI change of Italy site IT-05.
11 February 2020	A Substantial Amendment n.09 (for Greece only) was released with the IB version no.20 of 07Feb2020 and ICF version 3/1 of 11Feb2020, updated with safety information since some patients were still in study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The number of patients randomized was not sufficient to reach definitive statistical conclusions for non-inferiority, the rate of microbiological success and improvement of clinical symptoms resulted the same between the two drugs.

Notes: