Clinical trial results:
A Multi-Dose, Double-Blind, Double-Dummy, Active Control, Randomized Clinical (Phase II) Study of Two Dosing Regimens of Finafloxacin for the Treatment of cUTI and/or Acute Pyelonephritis Requiring Hospitalisation

Summary

EudraCT number	2011-006041-14
Trial protocol	PL
Global end of trial date	15 June 2014

Results information

Result version number	v1 (current)
This version publication date	05 January 2017
First version publication date	05 January 2017

Trial information

Trial identification

Sponsor protocol code	FINA-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01928433
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MerLion Pharmaceuticals GmbH
Sponsor organisation address	Robert-Roessle-Str. 10, Berlin, Germany, 13125
Public contact	Head of Regulatory Affairs, MerLion Pharmaceuticals GmbH, lueckermann@merlionpharma.de
Scientific contact	Head of Regulatory Affairs, MerLion Pharmaceuticals GmbH, lueckermann@merlionpharma.de

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	30 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2014
Global end of trial reached?	Yes
Global end of trial date	15 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the microbiological and clinical outcome of treatment with finafloxacin for 5 days versus finafloxacin for 10 days versus ciprofloxacin for 10 days

Protection of trial subjects:

Stringent ECG monitoring, patients will be excluded in case of any significant ECG abnormalities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 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	Poland: 192
Country: Number of subjects enrolled	Germany: 33
Worldwide total number of subjects	225
EEA total number of subjects	225

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)	144
From 65 to 84 years	75
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 08 December 2012
Last patient completed: 15 June 2014
Countries: Germany and Poland

Pre-assignment

Screening details:

After signing the informed consent patient received screening no. If these patients are eligible to continue the study, based on the inclusion and exclusion criteria they will be assigned to one of the three treatment groups (Finafloxacin for 5 days, Finafloxacin for 10 days or Ciprofloxacin for 10 days) in a ratio of 1:1:1.

Period 1

Period 1 title	Overall Trial (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:

Blinding was conducted using the double-blind, double-dummy technique.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I -Finafloxacin 5 days

Arm description:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 5 days. For blinding the patients received additional 5 days oral placebo treatment.

Arm type	Experimental
Investigational medicinal product name	Finafloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) infused over 60 mins [i.v. pump] for at least 3 days.

Investigational medicinal product name	Finafloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Finafloxacin 800 mg oral (as four 200 mg film-coated tablets) o.d. (outpatient).

Arm title	Group II -Finafloxacin 10 days

Arm description:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 10 days.

Arm type	Experimental

Investigational medicinal product name	Finafloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) infused over 60 mins [i.v. pump] for at least 3 days.

Investigational medicinal product name	Finafloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Finafloxacin 800 mg oral (as four 200 mg film-coated tablets) o.d. (outpatient).

Arm title	Group III - Ciprofloxacin 10 days

Arm description:

Ciprofloxacin 400 mg i.v. two times daily (b.i.d.) for at least 3 days (in-patient) followed by ciprofloxacin 500 mg oral (as two 250 mg capsules each) (b.i.d.) two times daily (outpatient); total treatment period of 10 days.

Arm type	Active comparator
Investigational medicinal product name	Ciprofloxacin hydrogen sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Ciprofloxacin 400 mg i.v. two times daily (b.i.d.) infused over approximately 60 mins (i.v. pump).

Investigational medicinal product name	Ciprofloxacin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ciprofloxacin 500 mg oral (as two 250 mg capsules each) (b.i.d.) two times daily (outpatient).

Number of subjects in period 1	Group I - Finafloxacin 5 days	Group II - Finafloxacin 10 days	Group III - Ciprofloxacin 10 days
Started	76	75	74
Completed	56	54	46
Not completed	20	21	28
Consent withdrawn by subject	-	4	-
Adverse event, non-fatal	5	2	5
Other	3	3	4
Lost to follow-up	-	2	3
Negative screeening urine culture	7	6	10
Lack of efficacy	5	4	4

Protocol deviation	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Group I -Finafloxacin 5 days
Reporting group description:	
Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 5 days. For blinding the patients received additional 5 days oral placebo treatment.	
Reporting group title	Group II -Finafloxacin 10 days
Reporting group description:	
Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 10 days.	
Reporting group title	Group III - Ciprofloxacin 10 days
Reporting group description:	
Ciprofloxacin 400 mg i.v. two times daily (b.i.d.) for at least 3 days (in-patient) followed by ciprofloxacin 500 mg oral (as two 250 mg capsules each) (b.i.d.) two times daily (outpatient); total treatment period of 10 days.	

Reporting group values	Group I - Finafloxacin 5 days	Group II - Finafloxacin 10 days	Group III - Ciprofloxacin 10 days
Number of subjects	76	75	74
Age categorical 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)	52	43	49
From 65-84 years	20	31	24
85 years and over	4	1	1
Age continuous Units: years			
arithmetic mean	54.6	58	51.1
standard deviation	± 19.63	± 19.28	± 20.82
Gender categorical Units: Subjects			
Female	64	62	59
Male	12	13	15

Reporting group values	Total		
Number of subjects	225		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	144		
From 65-84 years	75		
85 years and over	6		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	185		
Male	40		

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who provided written consent to participate and were randomized into the study.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who met the definition of ITT population and who received at least one dose of study medication during the trial.

Subject analysis set title	micro-ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects who met the definition for the ITT population and who had a positive baseline bacterial pathogen on culture of urine that causes UTI against which the investigational drug had antibacterial activity.

Reporting group values	ITT	Safety Set	micro-ITT
Number of subjects	225	223	193
Age categorical			
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)	144	143	123
From 65-84 years	75	74	65
85 years and over	6	6	5
Age continuous			
Units: years			
arithmetic mean	54.6	54.6	54.9

standard deviation	± 20.03	± 20.08	± 19.99

Gender categorical Units: Subjects			
Female	185	183	157
Male	40	40	36

End points

End points reporting groups

Reporting group title	Group I -Finafloxacin 5 days

Reporting group description:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 5 days. For blinding the patients received additional 5 days oral placebo treatment.

Reporting group title	Group II -Finafloxacin 10 days

Reporting group description:

Finafloxacin 800 mg intravenous (i.v.) once daily (o.d.) (infused over 60 mins [i.v. pump]) for at least 3 days (in-patient) followed by finafloxacin 800 mg tablets (as four 200 mg tablets) o.d. (outpatient): total treatment period of 10 days.

Reporting group title	Group III - Ciprofloxacin 10 days

Reporting group description:

Ciprofloxacin 400 mg i.v. two times daily (b.i.d.) for at least 3 days (in-patient) followed by ciprofloxacin 500 mg oral (as two 250 mg capsules each) (b.i.d.) two times daily (outpatient); total treatment period of 10 days.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who provided written consent to participate and were randomized into the study.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who met the definition of ITT population and who received at least one dose of study medication during the trial.

Subject analysis set title	micro-ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects who met the definition for the ITT population and who had a positive baseline bacterial pathogen on culture of urine that causes UTI against which the investigational drug had antibacterial activity.

Primary: Efficacy - Combined Endpoint at Test of Cure

End point title	Efficacy - Combined Endpoint at Test of Cure[1]

End point description:

The primary endpoint of this study was the clinical and microbiological response of patients with cUTI or pyelonephritis to treatment with finafloxacin for 5 days versus finafloxacin for 10 days versus ciprofloxacin for 10 days as a reference comparator at the Test of Cure (ToC) visit (Day 17) in the micro-ITT population.

End point type	Primary

End point timeframe:

Day 17 (+/-2) after treatment start.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was not powered to perform formal inferential statistical analyses.

End point values	Group I - Finafloxacin 5 days	Group II - Finafloxacin 10 days	Group III - Ciprofloxacin 10 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	68	61	
Units: percent				
number (not applicable)	70.3	67.6	57.4	

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy - Clinical Success at Test of Cure

End point title	Efficacy - Clinical Success at Test of Cure[2]

End point description:

The clinical response of patients with cUTI or pyelonephritis to treatment with finafloxacin for 5 days versus finafloxacin for 10 days versus ciprofloxacin for 10 days as a reference comparator at the Test of Cure (ToC) visit (Day 17) in the micro-ITT population.

End point type	Primary

End point timeframe:

Treatment start to day 17 (+/- 2)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was not powered to perform formal inferential statistical analyses.

End point values	Group I - Finafloxacin 5 days	Group II - Finafloxacin 10 days	Group III - Ciprofloxacin 10 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	68	61	
Units: percent				
number (not applicable)	79.7	83.8	72.1	

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy - Microbiological Success at Test of Cure

End point title	Efficacy - Microbiological Success at Test of Cure[3]

End point description:

The microbiological response of patients with cUTI or pyelonephritis to treatment with finafloxacin for 5 days versus finafloxacin for 10 days versus ciprofloxacin for 10 days as a reference comparator at the Test of Cure (ToC) visit (Day 17) in the micro-ITT population.

End point type	Primary

End point timeframe:

Treatment start to day 17 (+/- 2)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was not powered to perform formal inferential statistical analyses.

End point values	Group I - Finafloxacin 5 days	Group II - Finafloxacin 10 days	Group III - Ciprofloxacin 10 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	68	61	
Units: percent				
number (not applicable)	71.9	70.6	59	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timepoint of written informed consent to End of Study Visit (Day 24).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Safety set (2%)
Reporting group description: -	
Reporting group title	Finafloxacin
Reporting group description: -	
Reporting group title	Ciprofloxacin
Reporting group description: -	

Serious adverse events	Safety set (2%)	Finafloxacin	Ciprofloxacin
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 223 (3.59%)	7 / 151 (4.64%)	1 / 72 (1.39%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian adenoma			
subjects affected / exposed	1 / 223 (0.45%)	1 / 151 (0.66%)	0 / 72 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 223 (0.90%)	2 / 151 (1.32%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 151 (0.66%)	0 / 72 (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
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	1 / 223 (0.45%)	1 / 151 (0.66%)	0 / 72 (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
Renal and urinary disorders			
Obstructive uropathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 151 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyonephrosis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 151 (0.66%)	0 / 72 (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
Clostridium difficile infection			
subjects affected / exposed	2 / 223 (0.90%)	2 / 151 (1.32%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	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	Safety set (2%)	Finafloxacin	Ciprofloxacin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 223 (26.01%)	55 / 151 (36.42%)	39 / 72 (54.17%)
Investigations			
Blood pressure increased			
subjects affected / exposed	6 / 223 (2.69%)	4 / 151 (2.65%)	2 / 72 (2.78%)
occurrences (all)	8	5	3
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 223 (6.73%)	9 / 151 (5.96%)	6 / 72 (8.33%)
occurrences (all)	19	10	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 223 (5.83%)	8 / 151 (5.30%)	5 / 72 (6.94%)
occurrences (all)	16	11	5
Nausea			

subjects affected / exposed	7 / 223 (3.14%)	6 / 151 (3.97%)	1 / 72 (1.39%)
occurrences (all)	7	6	1
Abdominal pain			
subjects affected / exposed	6 / 223 (2.69%)	3 / 151 (1.99%)	3 / 72 (4.17%)
occurrences (all)	6	3	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 223 (2.69%)	5 / 151 (3.31%)	1 / 72 (1.39%)
occurrences (all)	7	6	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	5 / 223 (2.24%)	3 / 151 (1.99%)	2 / 72 (2.78%)
occurrences (all)	5	3	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2013	Update of the SmPC for Ciprofloxacin and new Informed Consent was submitted.
25 April 2014	Implementation of an administrative analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported