Clinical trial results:
A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Levofloxacin in Complicated Urinary Tract Infections

Summary

EudraCT number	2013-004556-38
Trial protocol	HU DE IT EE CZ LV GR BG PL
Global end of trial date	01 March 2016

Results information

Result version number	v1 (current)
This version publication date	22 November 2018
First version publication date	22 November 2018

Trial information

Trial identification

Sponsor protocol code	TP-434-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01978938
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tetraphase Pharmaceuticals, Inc.
Sponsor organisation address	480 Arsenal Street, Suite 110, Watertown, United States, 02472
Public contact	Chief Medical Officer, Tetraphase Pharmaceuticals, Inc., 1 617-715-3600, medinfo@tphase.com
Scientific contact	Chief Medical Officer, Tetraphase Pharmaceuticals, Inc., 1 617-715-3600, medinfo@tphase.com

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	01 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2015
Global end of trial reached?	Yes
Global end of trial date	01 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that eravacycline is non-inferior to levofloxacin in responder outcome (clinical and microbiological response versus failure) at the post-treatment (PT) visit (defined as 6 to 8 days after the completion of therapy).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2014
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: 46
Country: Number of subjects enrolled	Bulgaria: 76
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Estonia: 39
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Latvia: 77
Country: Number of subjects enrolled	Georgia: 46
Country: Number of subjects enrolled	Moldova, Republic of: 23
Country: Number of subjects enrolled	Romania: 125
Country: Number of subjects enrolled	Ukraine: 189
Country: Number of subjects enrolled	Russian Federation: 112
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	South Africa: 34

Worldwide total number of subjects	908
EEA total number of subjects	457

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)	592
From 65 to 84 years	311
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants with a diagnosis of complicated urinary tract infection (cUTI), including participants with acute pyelonephritis, were recruited into this study.

Pre-assignment

Screening details:

Screening and baseline assessments were performed after informed consent was obtained and within 36 hours prior to enrollment.

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, Carer, Assessor

Blinding implementation details:

The Sponsor designee designated a randomisation administrator who maintained the randomisation codes to ensure that the blind was properly maintained and that only designated personnel who required knowledge of treatment assignments were unblinded. The study blind codes were broken after the statistical analysis plan was finalized and the database was locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Eravacycline

Arm description:

Eravacycline was administered intravenously (IV) at a dose of 1.5 milligrams per kilogram (mg/kg) of body weight every 24 hours (q24h). At minimum, the first 3 doses were administered IV. After an IV-to-oral (PO) transition, provided adequate clinical improvement, participants were administered 200 mg PO twice a day (BID) for a total therapy of 7 dosing cycles.

Arm type	Experimental
Investigational medicinal product name	Eravacycline IV
Investigational medicinal product code	
Other name	TP-434
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each participant received 7 dose cycles of the study drug. At a minimum, the first 3 doses were administered IV. During each 24-hour dosing cycle on IV administration days, participants received 1 infusion over 60 minutes.

Investigational medicinal product name	Eravacycline PO
Investigational medicinal product code	
Other name	TP-434
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After an IV-to-PO transition, provided adequate clinical improvement, participants received PO doses (200 mg) administered BID (approximately 12 hours apart).

Arm title	Levofloxacin

Arm description:

Levofloxacin (750 mg) was administered IV q24h. At minimum, the first 3 doses were administered IV. After an IV-to-PO transition, provided adequate clinical improvement, participants were administered 750 mg PO once a day (QD) for a total therapy of 7 dosing cycles.

Arm type	Active comparator
Investigational medicinal product name	Levofloxacin IV
Investigational medicinal product code	
Other name	Levaquin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each participant received 7 dose cycles of study drug. At a minimum, the first 3 doses were administered IV. Levofloxacin (750 mg) was administered over a 60-minute infusion q24h.

Investigational medicinal product name	Levofloxacin PO
Investigational medicinal product code	
Other name	Levaquin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After an IV-to-PO transition, provided adequate clinical improvement, participants received a PO dose (750 mg) administered QD for 1 dose and a PO placebo dose for the second dose of the day (approximately 12 hours apart) to maintain treatment group blind.

Number of subjects in period 1	Eravacycline	Levofloxacin
Started	455	453
Received at least 1 dose of study drug	454	451
Completed	432	439
Not completed	23	14
Consent withdrawn by subject	8	4
Did not meet inclusion criteria	-	1
Adverse event, non-fatal	2	1
Previously scheduled procedure	-	1
Lost to follow-up	12	6
Noncompliance	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Eravacycline
Reporting group description:	
Eravacycline was administered intravenously (IV) at a dose of 1.5 milligrams per kilogram (mg/kg) of body weight every 24 hours (q24h). At minimum, the first 3 doses were administered IV. After an IV-to-oral (PO) transition, provided adequate clinical improvement, participants were administered 200 mg PO twice a day (BID) for a total therapy of 7 dosing cycles.	
Reporting group title	Levofloxacin
Reporting group description:	
Levofloxacin (750 mg) was administered IV q24h. At minimum, the first 3 doses were administered IV. After an IV-to-PO transition, provided adequate clinical improvement, participants were administered 750 mg PO once a day (QD) for a total therapy of 7 dosing cycles.	

Reporting group values	Eravacycline	Levofloxacin	Total
Number of subjects	455	453	908
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)	291	301	592
From 65-84 years	161	150	311
85 years and over	3	2	5
Age continuous Units: years			
arithmetic mean	53.7	51.7	
standard deviation	± 18.82	± 19.81	-
Gender categorical Units: Subjects			
Female	291	302	593
Male	164	151	315
Race Units: Subjects			
White	434	433	867
Black or African American	14	14	28
Asian	3	1	4
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	4	5	9
Ethnicity Units: Subjects			
Hispanic or Latino	15	18	33
Not Hispanic or Latino	440	435	875

End points

End points reporting groups

Reporting group title	Eravacycline

Reporting group description:

Eravacycline was administered intravenously (IV) at a dose of 1.5 milligrams per kilogram (mg/kg) of body weight every 24 hours (q24h). At minimum, the first 3 doses were administered IV. After an IV-to-oral (PO) transition, provided adequate clinical improvement, participants were administered 200 mg PO twice a day (BID) for a total therapy of 7 dosing cycles.

Reporting group title	Levofloxacin

Reporting group description:

Levofloxacin (750 mg) was administered IV q24h. At minimum, the first 3 doses were administered IV. After an IV-to-PO transition, provided adequate clinical improvement, participants were administered 750 mg PO once a day (QD) for a total therapy of 7 dosing cycles.

Subject analysis set title	Intent-To-Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of all randomised participants regardless of whether or not the participant received study drug. A participant was considered randomised when the Investigator or Investigator's designee received the interactive web-based response system-generated randomisation number.

Subject analysis set title	Microbiological ITT (micro-ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The micro-ITT population consisted of all participants in the ITT population who had at least 1 baseline bacterial pathogen from a urine or blood culture that caused a urinary tract infection against which eravacycline had expected antibacterial activity.

Subject analysis set title	Microbiological Modified ITT (micro-MITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The micro-MITT population consisted of all participants in the micro-ITT population who received at least 1 dose of study drug.

Subject analysis set title	Microbiologically Evaluable (ME)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The ME population consisted of all participants in the micro-ITT and clinically evaluable populations who had a suitable urine specimen and an interpretable urine culture.

Primary: Participants In The Micro-MITT Population With A Microbiologic Response

End point title	Participants In The Micro-MITT Population With A Microbiologic Response

End point description:

This outcome measure (Food and Drug Administration [FDA] and European Medicines Agency [EMA]) compared the microbiological responses of eravacycline to levofloxacin for both treatment groups in the micro-MITT population. Responses were success, failure, or indeterminate/missing. Success was considered a reduction of the baseline pathogen(s) to <10^4 colony-forming units/milliliter (CFU/mL). Failure required blood cultures at or beyond end of therapy (EOT) to be positive for baseline pathogen(s), or urine culture to grow ≥10^4 CFU/mL of the baseline pathogen(s). Indeterminate/missing indicated no interpretable culture data available.

End point type	Primary

End point timeframe:

PT Visit

End point values	Eravacycline	Levofloxacin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	302		
Units: Participants				
Success	194	213		
Failure	85	78		
Indeterminate/missing	18	11		

Statistical analyses

Statistical analysis title	micro-MITT Population and Microbiological Response

Statistical analysis description:

For the EMA, a 10% non-inferiority (NI) margin was used to determine success and the primary efficacy analysis was based on the micro-MITT population (co-primary efficacy outcome). The primary efficacy outcome was microbiological success at the PT visit in the micro-MITT population.

Since the lower limit of the 99% confidence interval (CI) did not exceed the established NI margin, NI of eravacycline to levofloxacin in the micro-MITT population was not declared.

Comparison groups	Eravacycline v Levofloxacin
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment Difference
Point estimate	-5.2
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-14.6
upper limit	4.8

Notes:

[1] - To test the null hypothesis, an adjusted 2-sided 99% CI (using the Miettinen-Nurminen method) for the observed difference in microbiological success rates (eravacycline treatment group minus levofloxacin treatment group) was calculated for the micro-MITT population. If the lower limit of the 99% CI for the difference in microbiological success rates in the micro-MITT population exceeded –10%, then the null hypothesis was rejected and the NI of eravacycline to levofloxacin was declared.

Primary: Participants In The ME Population With A Microbiologic Response

End point title	Participants In The ME Population With A Microbiologic Response

End point description:

This outcome measure (FDA and EMA) compared the microbiological responses of eravacycline to levofloxacin for both treatment groups in the ME population. Responses were either success or failure. Indeterminate/missing responses were not included. Success was considered a reduction of the baseline pathogen(s) to <10^4 CFU/mL. Failure required blood cultures at or beyond EOT to be positive for baseline pathogen(s), or urine culture to grow ≥10^4 CFU/mL of the baseline pathogen(s). Indeterminate/missing indicated no interpretable culture data available.

End point type	Primary

End point timeframe:

PT Visit

End point values	Eravacycline	Levofloxacin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	276		
Units: Participant				
Success	180	203		
Failure	75	73		

Statistical analyses

Statistical analysis title	ME Population and Microbiologic Response

Statistical analysis description:

For the EMA, a 10% NI margin was used to determine success and the primary efficacy analysis was based on the ME population (co-primary efficacy outcome). The primary efficacy outcome was microbiological success at the PT visit in the ME population.

Since the lower limit of the 99% CI did not exceed the established NI margin, NI of eravacycline to levofloxacin in the ME population was not declared.

Comparison groups	Eravacycline v Levofloxacin
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Treatment Difference
Point estimate	-3
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-12
upper limit	7.7

Notes:

[2] - To test the null hypothesis, an adjusted 2-sided 99% CI (using the Miettinen-Nurminen method) for the observed difference in microbiological success rates (eravacycline treatment group minus levofloxacin treatment group) was calculated for the ME population. If the lower limit of the 99% CI for the difference in microbiological success rates in the ME population exceeded –10%, then the null hypothesis was rejected and the NI of eravacycline to levofloxacin was declared.

Secondary: Participants In The Micro-ITT Population With A Responder Outcome At The PT Visit

End point title	Participants In The Micro-ITT Population With A Responder Outcome At The PT Visit

End point description:

This was the primary outcome measure for the FDA. Clinical responses were either cure, failure, or indeterminate/missing; microbiological responses were characterized programmatically as either success, failure, or indeterminate/missing. Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the infection; microbiological success was a reduction of the baseline pathogen(s) to <10^4 CFU/mL. An outcome of Responder required a clinical response of cure and a microbiological response of success. Any other combination of the clinical and microbiological responses was considered either Non-responder or Indeterminate.

End point type	Secondary

End point timeframe:

PT Visit

End point values	Eravacycline	Levofloxacin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	302		
Units: Participants				
Responder	180	202		
Non-responder	100	91		
Indeterminate	18	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for adverse event reporting was from the first dose of study drug through 30 days after the last dose of study drug or the late PT visit (whichever was later).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Eravacycline

Reporting group description:

Eravacycline was administered IV at a dose of 1.5 mg/kg q24h. At minimum, the first 3 doses were administered IV. After an IV-to-PO transition, provided adequate clinical improvement, participants were administered 200 mg PO BID for a total therapy of 7 dosing cycles.

Reporting group title	Levofloxacin

Reporting group description:

Levofloxacin (750 mg) was administered IV q24h. At minimum, the first 3 doses were administered IV. After an IV-to-PO transition, provided adequate clinical improvement, participants were administered 750 mg PO QD for a total therapy of 7 dosing cycles.

Serious adverse events	Eravacycline	Levofloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 455 (1.54%)	6 / 450 (1.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
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			
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (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			
Dyspnoea			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (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			
Renal colic			
subjects affected / exposed	1 / 455 (0.22%)	0 / 450 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Orchitis			
subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			
subjects affected / exposed	0 / 455 (0.00%)	1 / 450 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Eravacycline	Levofloxacin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 455 (28.35%)	26 / 450 (5.78%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 455 (3.08%)	6 / 450 (1.33%)	
occurrences (all)	14	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	82 / 455 (18.02%)	14 / 450 (3.11%)	
occurrences (all)	111	15	
Vomiting			
subjects affected / exposed	33 / 455 (7.25%)	6 / 450 (1.33%)	
occurrences (all)	35	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2014	Amendment 1.0 (Version 2.0 dated 08 May 2014): • Clarification of eligibility criteria • Clarification of sample size calculations • Clarification of statistical methods and efficacy assessments • Clarification of primary population to be used in analysis for the EMA to comply with guidance document • Addition of collection of clinical response data for participants who discontinue early from study drug administration • Clarification of microbiologic response criteria to align with United States (US) FDA guidance • Clarification of timing and criteria for IV-to-PO step-down • Clarification of timing of verification of PO study drug compliance, and • Other global administrative changes and clarifications
12 March 2015	Amendment 2.0 (Version 3.0 dated 12 March 2015): • Clarification of timing for study procedures and for procedures used to establish eligibility • Extension of blood culture collection through late PT visit (rather than the EOT visit) • Clarification of criteria for positive and negative leukocyte esterase • Clarification of microbiological failure as related to inclusion • Enrollment cap for participants with pyelonephritis with normal urinary tract anatomy changed based on US and European Union (EU) regulatory guidances • Introduction of alternative method for establishing eligibility related to creatinine clearance, for Investigator flexibility • Clarification of circumstances in which antibiotics may be used prior to study enrollment • Clarification of definition of "clinical failure" to include participants who required concomitant systemic antibiotics for a condition other than cUTI • Microbiological threshold changed to align with US and EU regulatory guidances • Clarification of analysis populations in alignment with the statistical analysis plan (SAP) and with US and EU regulatory guidances • Clarification of efficacy evaluations in alignment with the SAP, and • Other global administrative changes and clarifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported