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

Summary

EudraCT number	2016-002208-21
Trial protocol	HU CZ LV EE LT BG
Global end of trial date	19 May 2017

Results information

Result version number	v1 (current)
This version publication date	25 December 2021
First version publication date	25 December 2021

Trial information

Trial identification

Sponsor protocol code	TP-434-025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02784704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tetraphase Pharmaceuticals, Inc.
Sponsor organisation address	201 Jones Road, Suite 400, Waltham, United States, 02451
Public contact	Stew Kroll, Tetraphase Pharmaceuticals, Inc., 1 858-207-4264, ljpcregulatory@ljpc.com
Scientific contact	Stew Kroll, Tetraphase Pharmaceuticals, Inc., 1 858-207-4264, ljpcregulatory@ljpc.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	15 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2017
Global end of trial reached?	Yes
Global end of trial date	19 May 2017
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 meropenem in clinical response at the test-of-cure (TOC) visit in the all-treated (MITT) and the clinically evaluable (CE) populations

Protection of trial subjects:

This study was conducted in compliance with ICH E6 GCP (consolidated guidelines and the ethical principles of the Declaration of Helsinki), and any additional national or IRB/IED- required procedures

Background therapy: -

Evidence for comparator:

The comparator, meropenem, was chosen because it is approved by the FDA and other regulatory authorities for the treatment of cIAI. It was given at the recommended dose of 1g q8 for a minimum of four-24h dose cycles

Actual start date of recruitment	13 October 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	Bulgaria: 93
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Estonia: 31
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Latvia: 68
Country: Number of subjects enrolled	Lithuania: 40
Country: Number of subjects enrolled	Romania: 57
Country: Number of subjects enrolled	Georgia: 24
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Ukraine: 82
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	500
EEA total number of subjects	348

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)	355
From 65 to 84 years	140
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants at least 18 years of age with a diagnosis of cIAI were recruited into the study

Pre-assignment

Screening details:

Screening and baseline were performed after informed consent was obtained and within 48 hours prior to initial dose. Participants were eligible to participate if they met all of the inclusion criteria and none of the exclusion criteria at the Screening visit.

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, Carer, Assessor

Blinding implementation details:

Subjects were assigned to study drug regimens using computerized randomization. Except for the responsible study site pharmacist or designee, and separate unblinded clinical research associates (CRAs) to monitor drug supply and adherence to study drug blinding and randomization procedures, all study staff and participants were blinded to the IV dosing regimens of subjects. 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 (MITT)

Arm description:

Eravacycline IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug.

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

Dosage and administration details:

Eravacycline was administered intravenously (IV) at a dose of 1.0 milligrams per kilogram (mg/kg) of body weight every 12 hours (q12h) for a minimum of 4 days and a maximum of 14 days.

Arm title	Meropenem (MITT)

Arm description:

Meropenem IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug. Please note that one subject randomized to Meropenem did not receive study drug.

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

Dosage and administration details:

Meropenem was administered intravenously (IV) at a dose of 1.0 grams (g) every 8 hours (q8h) for minimum of 4 days and a maximum of 14 days.

Number of subjects in period 1[1]	Eravacycline (MITT)	Meropenem (MITT)
Started	250	249
Completed	237	241
Not completed	13	8
Consent withdrawn by subject	1	2
Adverse event, non-fatal	4	2
noncompliance	2	-
Lost to follow-up	6	4

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: The number reported in the baseline period differs by 1 subject versus the worldwide number enrolled due to 1 subject being enrolled in the meropenem group who did not receive study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Eravacycline (MITT)
Reporting group description:	
Eravacycline IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug.	
Reporting group title	Meropenem (MITT)
Reporting group description:	
Meropenem IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug. Please note that one subject randomized to Meropenem did not receive study drug.	

Reporting group values	Eravacycline (MITT)	Meropenem (MITT)	Total
Number of subjects	250	249	499
Age categorical			
Units: Subjects			
Adults (18-64 years)	180	174	354
From 65-84 years	68	72	140
85 years and over	2	3	5
Age continuous			
Units: years			
arithmetic mean	52.1	52.8	
standard deviation	± 17.69	± 18.24	-
Gender categorical			
Units: Subjects			
Female	111	120	231
Male	139	129	268

End points

End points reporting groups

Reporting group title	Eravacycline (MITT)
Reporting group description:	
Eravacycline IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug.	
Reporting group title	Meropenem (MITT)
Reporting group description:	
Meropenem IV (MITT) modified intent-to treat population defined as subjects that were randomized and received at least 1 dose of study drug. Please note that one subject randomized to Meropenem did not receive study drug.	

Primary: Clinical Response at the test of cure (TOC) visit in the MITT population

End point title	Clinical Response at the test of cure (TOC) visit in the MITT population
End point description:	
This was a co-primary outcome measure for the European Medicines Agency (EMA). Clinical response was classified as cure (complete resolution or significant improvement of signs and symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required), failure (death related to complicated intra-abdominal infection (cIAI), persistence of clinical symptoms of cIAI, unplanned surgical or percutaneous drainage procedures for complication or recurrence of cIAI, post-surgical wound infections requiring systemic antibiotics, or initiation of rescue antibacterial drug therapy for treatment of cIAI), or indeterminate (outcome was neither cure nor failure, or assessment was not available). The number of participants with a clinical response classification of cure, failure, or indeterminate is presented.	
End point type	Primary
End point timeframe:	
TOC visit: 25-31 days after the first study dose	

End point values	Eravacycline (MITT)	Meropenem (MITT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: subjects				
Clinical Cure	231	228		
Clinical Failure	7	9		
Indeterminate/Missing	12	12		

Statistical analyses

Statistical analysis title	MITT
Statistical analysis description:	
A 2-sided 95% confidence interval (CI) for the observed difference in primary outcome rates (eravacycline treatment group minus meropenem treatment group) was calculated. If the lower limit of the 95% CI for the difference in clinical cure rates exceeded −12.5%, then the null hypothesis was rejected, and the non-inferiority of eravacycline to meropenem was declared	
Comparison groups	Eravacycline (MITT) v Meropenem (MITT)

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	5.8
Variability estimate	Standard deviation

Notes:

[1] - pre-specified

Primary: Clinical Response at the TOC visit in the CE population

End point title	Clinical Response at the TOC visit in the CE population

End point description:

This was a co-primary outcome measure for the European Medicines Agency (EMA). Clinical response was classified as cure (complete resolution or significant improvement of signs and symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required) or failure (death related to complicated intra-abdominal infection (cIAI), persistence of clinical symptoms of cIAI, unplanned surgical or percutaneous drainage procedures for complication or recurrence of cIAI, post-surgical wound infections requiring systemic antibiotics, or initiation of rescue antibacterial drug therapy for treatment of cIAI). The number of participants with a clinical response classification of cure or failure is presented.

End point type	Primary

End point timeframe:

TOC visit: 25-31 days after the first dose of study drug

End point values	Eravacycline (MITT)	Meropenem (MITT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	231		
Units: subjects				
Clinical Cure	218	222		
Clinical Failure	7	9		

Statistical analyses

Statistical analysis title	CE

Statistical analysis description:

A 2-sided 95% confidence interval (CI) for the observed difference in primary outcome rates (eravacycline treatment group minus meropenem treatment group) was calculated. If the lower limit of the 95% CI for the difference in clinical cure rates exceeded −12.5%, then the null hypothesis was rejected, and the non-inferiority of eravacycline to meropenem was declared.

Comparison groups	Eravacycline (MITT) v Meropenem (MITT)

Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	4.5
Variability estimate	Standard deviation

Notes:

[2] - treatment difference

Secondary: Clinical Response at the test of cure (TOC) visit in the micro-ITT population

End point title	Clinical Response at the test of cure (TOC) visit in the micro-ITT population

End point description:

This was the primary outcome measure for the United States Food and Drug Administration (FDA). Clinical response was classified as cure (complete resolution or significant improvement of signs and symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required), failure (death related to complicated intra-abdominal infection (cIAI), persistence of clinical symptoms of cIAI, unplanned surgical or percutaneous drainage procedures for complication or recurrence of cIAI, post-surgical wound infections requiring systemic antibiotics, or initiation of rescue antibacterial drug therapy for treatment of cIAI), or indeterminate (outcome was neither cure nor failure, or assessment was not available). The number of participants with a clinical response classification of cure, failure, or indeterminate is presented.

End point type	Secondary

End point timeframe:

TOC visit: 25-31 days after the first dose of study drug

End point values	Eravacycline (MITT)	Meropenem (MITT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	205		
Units: subjects				
Clinical Cure	177	187		
Clinical Failure	7	7		
Indeterminate/Missing	11	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the first dose of study drug through 30 days after the last dose of study drug or the follow-up visit, which occurred 38 to 50 days after the first dose of study drug (whichever was later).

Adverse event reporting additional description:

Eravacycline was administered intravenously (IV) at a dose of 1.0 milligrams per kilogram (mg/kg) of body weight every 12 hours (q12h) for a minimum of 4 days and maximum of 14 days. Meropenem was administered intravenously (IV) at a dose of 1.0 grams (g) every 8 hours (q8h) for a minimum of 4 days and a maximum of 14 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Eravacycline

Reporting group description:

Eravacycline was administered intravenously (IV) at a dose of 1.0 milligrams per kilogram (mg/kg) of body weight every 12 hours (q12h) for a minimum of 4 days and maximum of 14 days.

Reporting group title	Meropenem

Reporting group description:

Meropenem was administered intravenously (IV) at a dose of 1.0 grams (g) every 8 hours (q8h) for a minimum of 4 days and a maximum of 14 days

Serious adverse events	Eravacycline	Meropenem	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 250 (6.00%)	16 / 249 (6.43%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disorders			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			

subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture related complication			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound decomposition			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
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			
Splenic haematoma			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Duodenal ulcer			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric rupture			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 250 (0.80%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eravacycline	Meropenem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 250 (11.60%)	8 / 249 (3.21%)	
General disorders and administration site conditions			
Infusion site phlebitis			
subjects affected / exposed	8 / 250 (3.20%)	1 / 249 (0.40%)	
occurrences (all)	10	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 250 (4.80%)	2 / 249 (0.80%)	
occurrences (all)	13	3	
Vomiting			
subjects affected / exposed	9 / 250 (3.60%)	5 / 249 (2.01%)	
occurrences (all)	10	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2017	Amendment number 1 was implemented to documented the following: the increase in study sample size based on the pre-specified, blinded assessment of the proportion of participants who qualified for the micro-ITT population; global administrative changes and clarifications

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.

None reported

Notes: