Clinical trial results:
A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis.

Summary

EudraCT number	2017-002608-29
Trial protocol	BG
Global end of trial date	17 May 2018

Results information

Result version number	v1 (current)
This version publication date	25 May 2019
First version publication date	25 May 2019

Trial information

Trial identification

Sponsor protocol code	CS2514-2017-0003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Entasis Therapeutics
Sponsor organisation address	Gatehouse Park BioHub, 35 Gatehouse Drive, Waltham, United States, MA 02451
Public contact	Robin Isaacs, Entasis Therapeutics, 001 781-810-8940, Enquiries@entasistx.com
Scientific contact	Robin Isaacs, Entasis Therapeutics, 001 781-810-8940 , Enquiries@entasistx.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	21 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2018
Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety profile of sulbactam-ETX2514 (ETX2514SUL) versus placebo in patients with complicated urinary tract infection (cUTI), including acute pyelonephritis (AP).
The efficacy (secondary) objectives of this study were the following:
· To evaluate the efficacy of ETX2514SUL in patients with cUTI, including AP, for the Microbiologically Modified Intent-to-Treat (m-MITT) Population
· To compare the clinical cure rate in the 2 treatment groups for the Modified Intent-to-Treat (MITT), m-MITT, Clinically Evaluable (CE), and Microbiologically Evaluable (ME) Populations at the Test-of-Cure (TOC) Visit
· To compare the microbiological eradication rate for the m-MITT and ME Populations at the TOC Visit.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice (GCP) Guidelines.
The rationale of the study, procedural details, and investigational goals were explained to each patient, along with potential risks and benefits. Each patient was assured of his/her right to withdraw from the study at any time. Prior to the initiation of any study procedures, each patient signed and dated an approved Informed Consent Form (ICF). The original was kept on file by the Investigator with the patient’s records, and a copy was given to each patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2018
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	Belarus: 15
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Ukraine: 24
Country: Number of subjects enrolled	Bulgaria: 19
Worldwide total number of subjects	80
EEA total number of subjects	19

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)	55
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were performed as standard of care within 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which was obtained at the local laboratory within 24 hours prior to the first dose of Study Drug.

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

Blinding implementation details:

The Investigator, site personnel, Sponsor, and the Sponsor's designees involved in monitoring, data management, and other aspects of the study were blinded to treatment assignment. An unblinded site monitor was assigned to review unblinded pharmacy data and followed documented procedures to ensure that the blind was maintained throughout the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	ETX2514SUL+ IMI

Arm description:

ETX2514/sulbactam (ETX2514SUL) + imipenem/cilastatin (IMI)

Arm type	Experimental
Investigational medicinal product name	ETX2514
Investigational medicinal product code	
Other name	ETX2514
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 1 g ETX2514/1 g sulbactam intravenous (IV) administered every 6 hours (q6h) over 3 hours. In addition, all patients were administered background therapy with 500 mg/500 mg IMI IV q6h infused over 30 minutes. Infusions occurred q6h for 7 calendar days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

Investigational medicinal product name	Sulbactam sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 1 g ETX2514/1 g sulbactam intravenous (IV) administered every 6 hours (q6h) over 3 hours. In addition, all patients were administered background therapy with 500 mg/500 mg IMI IV q6h infused over 30 minutes. Infusions of Study Drug occurred for 7 calendar days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

Investigational medicinal product name	IMI
Investigational medicinal product code	
Other name	Imipenem/cilastatin
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients were administered background therapy with 500 mg/500 mg IMI administered intravenous infused over 30 minutes every 6 hours for 7 calendar days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

Arm title	Placebo + IMI

Arm description:

Matching placebo + imipenem/cilastatin (IMI)

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received matching placebo (0.9% sodium chloride) IV administered q6h over 3 hours. In addition, all patients were administered background therapy with 500 mg/500 mg IMI IV q6h infused over 30 minutes. Infusions occurred q6h for 7 calendar days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

Investigational medicinal product name	IMI
Investigational medicinal product code	
Other name	Imipenem/cilastatin
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients were administered background therapy with 500 mg/500 mg IMI administered intravenous infused over 30 minutes every 6 hours for 7 calendar days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

Number of subjects in period 1	ETX2514SUL+ IMI	Placebo + IMI
Started	53	27
Completed	52	27
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ETX2514SUL+ IMI
Reporting group description: ETX2514/sulbactam (ETX2514SUL) + imipenem/cilastatin (IMI)	
Reporting group title	Placebo + IMI
Reporting group description: Matching placebo + imipenem/cilastatin (IMI)	

Reporting group values	ETX2514SUL+ IMI	Placebo + IMI	Total
Number of subjects	53	27	80
Age categorical Units: Subjects			
Adults (18-64 years)	36	19	55
From 65-84 years	17	8	25
Gender categorical Units: Subjects			
Female	27	11	38
Male	26	16	42

End points

End points reporting groups

Reporting group title	ETX2514SUL+ IMI
Reporting group description: ETX2514/sulbactam (ETX2514SUL) + imipenem/cilastatin (IMI)	
Reporting group title	Placebo + IMI
Reporting group description: Matching placebo + imipenem/cilastatin (IMI)	

Primary: Overall Response at TOC Visit Based on FDA Criteria (m-MITT Population)

End point title	Overall Response at TOC Visit Based on FDA Criteria (m-MITT Population)

End point description:

This endpoint was defined as the proportion of patients with an overall success (clinical cure and microbiologic eradication) for the m-MITT Population (patients who met MITT criteria and had at least 1 baseline uropathogen from an appropriately collected pretreatment baseline urine or blood sample) at the Test-of-Cure (TOC) Visit.
This endpoint was programmatically determined based on the clinical and microbiologic outcomes from the FDA criteria (demonstration that the baseline bacterial pathogen(s) was reduced to <10E4 CFU/mL on urine culture and negative on repeat blood culture [if positive at baseline]) as 1 of the following overall responses:
- Overall success: A patient who was deemed a clinical cure AND who achieved microbiologic eradication.
- Overall failure: A patient who was deemed a clinical failure OR was deemed to have microbiological persistence.
- Overall indeterminate: Insufficient data were available to determine if the patient was an overall success or failure.

End point type	Primary

End point timeframe:

From the start of treatment until the TOC Visit. The TOC Visit was to be completed 7 days (±1 day) after the end of treatment for all patients.

End point values	ETX2514SUL+ IMI	Placebo + IMI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	21		
Units: Patients				
Success	36	17		
Failure	9	4		
Indeterminate	2	0		

Statistical analyses

Statistical analysis title	Difference in the overall success rate per FDA
Comparison groups	ETX2514SUL+ IMI v Placebo + IMI

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	19.8

Primary: Overall Response at TOC Visit Based on EMA Criteria (m-MITT Population)

End point title	Overall Response at TOC Visit Based on EMA Criteria (m-MITT Population)

End point description:

This endpoint was defined as the proportion of patients with an overall success (clinical cure and microbiologic eradication) for the m-MITT Population (patients who met MITT criteria and had at least 1 baseline uropathogen from an appropriately collected pretreatment baseline urine or blood sample) at TOC Visit.
This endpoint was programmatically determined based on the clinical and microbiologic outcomes from the EMA criteria (demonstration that the baseline bacterial pathogen(s) was reduced to <10E3 CFU/mL on urine culture and negative on repeat blood culture [if positive at baseline]) as 1 of the following overall responses:
- Overall success: A patient who was deemed a clinical cure AND who achieved microbiologic eradication.
- Overall failure: A patient who was deemed a clinical failure OR was deemed to have microbiological persistence.
- Overall indeterminate: Insufficient data were available to determine if the patient was an overall success or failure.

End point type	Primary

End point timeframe:

From the start of treatment until the TOC Visit. The TOC Visit was to be completed 7 days (±1 day) after the end of treatment for all patients.

End point values	ETX2514SUL+ IMI	Placebo + IMI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	21		
Units: Patients				
Success	35	17		
Failure	10	4		
Indeterminate	2	0		

Statistical analyses

Statistical analysis title	Difference in the overall success rate per EMA
Comparison groups	ETX2514SUL+ IMI v Placebo + IMI

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.8
upper limit	17.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected from the first dose of Study Drug until the Late Follow-up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	ETX2514SUL+ IMI
Reporting group description: ETX2514/sulbactam (ETX2514SUL) + imipenem/cilastatin (IMI)	
Reporting group title	Placebo + IMI
Reporting group description: Matching placebo + imipenem/cilastatin (IMI)	

Serious adverse events	ETX2514SUL+ IMI	Placebo + IMI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)	0 / 27 (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: 2 %

Non-serious adverse events	ETX2514SUL+ IMI	Placebo + IMI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 53 (37.74%)	8 / 27 (29.63%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	3 / 53 (5.66%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Vascular pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 53 (9.43%)	2 / 27 (7.41%)	
occurrences (all)	7	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 53 (1.89%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	2 / 53 (3.77%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Dysbacteriosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 53 (3.77%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Infections and infestations			
Pseudomembranous colitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported