



Clinical trial results:

A prospective Phase 3, double-blind, multicenter, randomized study of the efficacy and safety of sulopenem followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infections in adults.

Summary

EudraCT number	2017-003773-34
Trial protocol	LV HU BG CZ
Global end of trial date	02 October 2019

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	IT001-303
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03358576
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Iterum Therapeutics
Sponsor organisation address	20 Research Parkway, Suite A, Old Saybrook, United States, 06475
Public contact	Senior VP and head of Clinical Development, Senior VP and head of Clinical Development, 1 8608762690, saroin@iterumtx.com
Scientific contact	Senior VP and head of Clinical Development, Senior VP and head of Clinical Development, 1 8608762690, saroin@iterumtx.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	08 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2019
Global end of trial reached?	Yes
Global end of trial date	02 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of sulopenem followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infection in adults, on Day 28 (test of cure [TOC]) post randomization.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, adopted by the General Assembly of the World Medical Association (2013), and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy: -

Evidence for comparator:

Ertapenem, the comparator chosen for this study, was approved by the US Food and Drug Administration (FDA) in 2001, for a number of serious infections, including complicated intra-abdominal infections and by the European Medicines Agency (EMA) for complicated intra-abdominal infections in 2002. Unlike sulopenem, however, it does not possess the advantage of being available in oral form; the step-down regimens chosen for those receiving ertapenem were ciprofloxacin + metronidazole or amoxicillin clavulanate, depending on the susceptibility of the pathogen(s) identified at baseline.

Actual start date of recruitment	01 October 2018
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	Bulgaria: 188
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	Estonia: 77
Country: Number of subjects enrolled	Hungary: 46
Country: Number of subjects enrolled	Latvia: 56
Country: Number of subjects enrolled	Georgia: 83
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Ukraine: 118
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	674
EEA total number of subjects	384

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)	443
From 65 to 84 years	212
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 91 study centers in Bulgaria, the Czech Republic, Estonia, Georgia, Hungary, Latvia, Russia, Serbia, Ukraine, and the United States. Study initiation date 28 November 2018.

Study completion date 02 October 2019.

Pre-assignment

Screening details:

A total of 707 potential patients were screened for enrollment. Of these, 33 failed the screening process; the most common reason for screening failure, occurring in 13 patients, was the lack of a cIAI diagnosis as defined in the protocol, ie, not meeting inclusion criterion number 3.

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:

This study was designed to be a double-blind study. The site pharmacist was unblinded in order to prepare the IV study medications and to select the appropriate oral follow on therapy for patients randomized to the ertapenem regimen.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sulopenem

Arm description:

Patients randomized to sulopenem IV followed by oral sulopenem etzadroxil plus probenecid

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

Dosage and administration details:

Patients with normal renal function who were randomized to the sulopenem treatment group were to receive 1000 mg sulopenem IV infused over 3 hours once daily for 5 days and a saline IV infusion over 30 minutes to simulate the comparator; Patients with severe renal impairment who were randomized to the sulopenem treatment group were to receive 250 mg sulopenem IV infused over 3 hours once daily for 5 days and a saline IV infusion over 30 minutes to simulate the comparator.

Arm title	Ertapenem
------------------	-----------

Arm description:

Patients randomized to ertapenem IV followed by oral ciprofloxacin plus metronidazole or oral amoxicillin-clavulanate

Arm type	Active comparator
Investigational medicinal product name	Ertapenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients with normal renal function who were randomized to the comparator treatment group were to

receive 1000 mg of ertapenem IV infused over 30 minutes once daily for 5 days and a saline IV infusion over 3 hours to simulate the sulopenem; Patients with severe renal impairment who were randomized to the comparator treatment group were to receive 500 mg ertapenem IV infused over 30 minutes once daily for 5 days and a saline IV infusion over 3 hours to simulate the sulopenem.

Number of subjects in period 1	Sulopenem	Ertapenem
Started	338	336
Completed	312	311
Not completed	26	25
Adverse event, serious fatal	2	4
Consent withdrawn by subject	7	8
Physician decision	5	3
Adverse event, non-fatal	5	8
Carbapenem-resistant pathogen	3	1
other	3	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Sulopenem
Reporting group description:	
Patients randomized to sulopenem IV followed by oral sulopenem etzadroxil plus probenecid	
Reporting group title	Ertapenem
Reporting group description:	
Patients randomized to ertapenem IV followed by oral ciprofloxacin plus metronidazole or oral amoxicillin-clavulanate	

Reporting group values	Sulopenem	Ertapenem	Total
Number of subjects	338	336	674
Age categorical			
Adult patients ≥18 years of age			
Units: Subjects			
Adults (18-64 years)	226	217	443
From 65-84 years	102	110	212
85 years and over	10	9	19
Gender categorical			
Units: Subjects			
Female	160	155	315
Male	178	181	359
Ethnicity			
Units: Subjects			
Hispanic or Latino	9	8	17
Not Hispanic or Latino	329	328	657
Geographic Region			
Units: Subjects			
U.S.	16	16	32
Non-U.S.	322	320	642
Race			
Units: Subjects			
Black or African American	1	3	4
Asian	0	1	1
White	337	332	669
Baseline APACHE II Score			
Units: Score			
geometric mean	6.6	6.8	
standard deviation	± 3.9	± 3.8	-

End points

End points reporting groups

Reporting group title	Sulopenem
Reporting group description: Patients randomized to sulopenem IV followed by oral sulopenem etzadroxil plus probenecid	
Reporting group title	Ertapenem
Reporting group description: Patients randomized to ertapenem IV followed by oral ciprofloxacin plus metronidazole or oral amoxicillin-clavulanate	
Subject analysis set title	Clinical Set 1
Subject analysis set type	Per protocol
Subject analysis set description: microbiologic modified intention to treat population	
Subject analysis set title	Clinical set 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat population	
Subject analysis set title	Clinical Set 3
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified intention to treat population	
Subject analysis set title	Clinical Set 4
Subject analysis set type	Per protocol
Subject analysis set description: Clinically evaluable at test of cure population	
Subject analysis set title	Clinical Set 5
Subject analysis set type	Per protocol
Subject analysis set description: Microbiologically evaluable at test of cure population	

Primary: Clinical response

End point title	Clinical response
End point description: microbiologic modified intention to treat population	
End point type	Primary
End point timeframe: Test of cure [Day 28]	

End point values	Sulopenem	Ertapenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	266		
Units: Number of patients				
Clinical success	213	240		
Clinical failure	27	17		
Indeterminate	9	9		

Statistical analyses

Statistical analysis title	Statistical outcome
Statistical analysis description:	
Number & % of patients assessed as clinical cure/failure/indeterminate were determined in each treatment group in micro MITT population. Observed difference in % of patients with clinical cure at Day 28 was determined; 95% CI for observed difference was computed using Z statistic. The noninferior hypothesis test was a 1-sided test performed at 2.5% level of significance. If lower limit of 95% CI was greater than -10%, the noninferiority of sulopenem to the comparator group was to be concluded.	
Comparison groups	Ertapenem v Sulopenem
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.025
Method	t-test, 1-sided
Confidence interval	
level	95 %
sides	1-sided
lower limit	-10

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator was to report all directly observed AEs and all AEs spontaneously reported by the study patient from the time that the patient provided informed consent through the Day 28 (TOC) Visit.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	21.0
--------------------	------

Reporting groups

Reporting group title	Sulopenem
-----------------------	-----------

Reporting group description:

Patients randomized to sulopenem IV followed by oral sulopenem etzadroxil plus probenecid

Reporting group title	Ertapenem
-----------------------	-----------

Reporting group description:

Patients randomized to ertapenem IV followed by oral ciprofloxacin plus metronidazole or oral amoxicillin-clavulanate

Serious adverse events	Sulopenem	Ertapenem	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 335 (7.46%)	12 / 333 (3.60%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 335 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 335 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			

subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 335 (0.30%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sudden death			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 335 (0.60%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mesenteric artery thrombosis subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus of small bowel subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (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			
Acute respiratory failure subjects affected / exposed	0 / 335 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure subjects affected / exposed	0 / 335 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Abdominal abscess subjects affected / exposed	9 / 335 (2.69%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess subjects affected / exposed	2 / 335 (0.60%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon gangrene			

subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (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: 1 %

Non-serious adverse events	Sulopenem	Ertapenem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 335 (26.87%)	80 / 333 (24.02%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 335 (0.30%)	5 / 333 (1.50%)	
occurrences (all)	1	5	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 335 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 335 (0.60%)	2 / 333 (0.60%)	
occurrences (all)	2	2	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 335 (0.30%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 335 (0.60%)	5 / 333 (1.50%)	
occurrences (all)	2	5	
Cardiac disorder			
subjects affected / exposed	6 / 335 (1.79%)	7 / 333 (2.10%)	
occurrences (all)	6	7	

Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	3 / 333 (0.90%) 3	
Leukocytosis subjects affected / exposed occurrences (all)	2 / 335 (0.60%) 2	0 / 333 (0.00%) 0	
Thrombocytosis subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	0 / 333 (0.00%) 0	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	15 / 335 (4.48%) 15	8 / 333 (2.40%) 8	
Nausea subjects affected / exposed occurrences (all)	12 / 335 (3.58%) 12	8 / 333 (2.40%) 8	
Vomiting subjects affected / exposed occurrences (all)	6 / 335 (1.79%) 6	5 / 333 (1.50%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 335 (1.19%) 4	1 / 333 (0.30%) 1	
Constipation subjects affected / exposed occurrences (all)	4 / 335 (1.19%) 4	1 / 333 (0.30%) 1	
Ileus subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	1 / 333 (0.30%) 1	
Gastrointestinal hypomotility subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	1 / 333 (0.30%) 1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion subjects affected / exposed occurrences (all)	2 / 335 (0.60%) 2	2 / 333 (0.60%) 2	
Pleurisy			

subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	2 / 333 (0.60%) 2	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	2 / 333 (0.60%) 2	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	3 / 335 (0.90%) 3	0 / 333 (0.00%) 0	
Infections and infestations Postoperative wound infection subjects affected / exposed occurrences (all)	4 / 335 (1.19%) 4	8 / 333 (2.40%) 8	
Pneumonia subjects affected / exposed occurrences (all)	3 / 335 (0.90%) 3	5 / 333 (1.50%) 5	
Abdominal abscess subjects affected / exposed occurrences (all)	6 / 335 (1.79%) 6	0 / 333 (0.00%) 0	
Wound infection subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	4 / 333 (1.20%) 4	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 335 (0.00%) 0	2 / 333 (0.60%) 2	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	4 / 335 (1.19%) 4	6 / 333 (1.80%) 6	
Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 335 (1.49%) 5	0 / 333 (0.00%) 0	
Hypomagnesaemia subjects affected / exposed occurrences (all)	3 / 335 (0.90%) 3	1 / 333 (0.30%) 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

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

Initial review of primary efficacy tables raised concerns about imbalances that didn't have a reasonable medical explanation. This prompted reexamination of programming and ultimately reanalysis of database to address identified deficiencies.
--

Notes: