Clinical trial results:
A randomized, observer-blinded, active-controlled, Phase IIIb study to compare IV / Oral delafloxacin fixed-dose monotherapy with best available treatments in a microbiologically enriched population with surgical site infections

Summary

EudraCT number	2018-001082-17
Trial protocol	CZ GB HU LV SI ES AT PL EE BG HR IT RO
Global end of trial date	28 October 2020

Results information

Result version number	v1 (current)
This version publication date	15 October 2021
First version publication date	15 October 2021

Trial information

Trial identification

Sponsor protocol code	DELA-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04042077
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A
Sponsor organisation address	via Sette Santi 1, Firenze, Italy, 50131
Public contact	Corp. Director Of Clinical Sciences, MENARINI RICERCHE S.p.A., +39 0555680 9933, ACapriati@menarini-ricerche.it
Scientific contact	Corp. Director Of Clinical Sciences, MENARINI RICERCHE S.p.A., +39 0555680 9933, ACapriati@menarini-ricerche.it

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	31 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2020
Global end of trial reached?	Yes
Global end of trial date	28 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the comparability of delafloxacin and best available therapy (BAT) in terms of Clinical Success response in patients with superficial or deep incisional Surgical site infection (SSI) following a cardiothoracic / related leg or abdominal surgical procedure.

Protection of trial subjects:

Patients underwent standard procedures, no specific measures were put in place. Procedures and examinations were done according to the local hospital standards.

Background therapy:

No background therapy planned.

Evidence for comparator:

DELA-01 has been designed to assess the efficacy and the effectiveness of delafloxacin compared to well-known best available treatments, that have been selected to address the microbiological flora causative of post cardiothoracic and abdominal SSI, on the basis of the current international guidances.

Actual start date of recruitment	25 September 2019
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	Poland: 7
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 91
Country: Number of subjects enrolled	Czechia: 24
Country: Number of subjects enrolled	Estonia: 77
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Romania: 13
Worldwide total number of subjects	266
EEA total number of subjects	247

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)	116
From 65 to 84 years	137
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Recruitment started in Estonia on 25 September 2019 with the FPI. It was stopped on 15 September 2020 due to COVID-19 pandemic. Overall, it lasted 13 months and was mostly conducted at Abdominal and General surgery departments.

Pre-assignment

Screening details:

In total, 274 patients were screened while 266 were randomized and treated. The Screening Visit was performed within 30 days after the surgical intervention.

Period 1

Period 1 title	Screening/Visit 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open-label, however an observer-blinded was selected in order to increase the objectivity in the clinical assessments and to minimize the intentional or unintentional Investigator's bias with respect to the assigned treatment. This observer blinded role was assigned by PI to a physician who was responsible for the assessment of parameters relevant for defining the patient as eligible to IV/PO switch of therapy and dischargeable from the hospital.

Arms

Are arms mutually exclusive?	Yes
Arm title	Delafloxacin

Arm description:

Delafloxacin arm was the Test arm. Patients started the treatment IV with the option to switch to oral formulation.

Arm type	Experimental
Investigational medicinal product name	Delafloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion, Tablet
Routes of administration	Infusion , Oral use

Dosage and administration details:

Delafloxacin 300 mg IV given every 12 hours, with the option to switch to delafloxacin 450 mg OS every 12 hours as soon as patient met the eligibility criteria to switch to oral formulation

Arm title	Best Available Therapy

Arm description:

Best Available Therapy was the Reference arm.
Reference Treatments for cardiothoracic / related leg SSI
● Vancomycin OR
● Linezolid
Reference Treatments for abdominal SSI
● Piperacillin / tazobactam OR
● Tigecycline
In case of suspicion of Gram-negative in the cardiothoracic SSI or MRSA in patients treated with piperacillin/tazobactam, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones).

Arm type	Active comparator

Investigational medicinal product name	Vancomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion
Dosage and administration details: 15 mg/kg given IV every 12 hours	
Investigational medicinal product name	Linezolid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet
Routes of administration	Infusion , Oral use
Dosage and administration details: 600 mg IV or OS every 12 hours	
Investigational medicinal product name	Piperacillin/tazobactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion
Dosage and administration details: 4/0,5g every 8 hours	
Investigational medicinal product name	Tigecycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Infusion
Dosage and administration details: 100 mg loading, then 50 mg every 12 hours	

Number of subjects in period 1	Delafloxacin	Best Available Therapy
Started	134	132
Completed	125	123
Not completed	9	9
Consent withdrawn by subject	4	2
Physician decision	-	2
Adverse event, non-fatal	2	2
Lack of efficacy	2	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Delafloxacin
Reporting group description:	
Delafloxacin arm was the Test arm. Patients started the treatment IV with the option to switch to oral formulation.	
Reporting group title	Best Available Therapy
Reporting group description:	
Best Available Therapy was the Reference arm. Reference Treatments for cardiothoracic / related leg SSI ● Vancomycin OR ● Linezolid Reference Treatments for abdominal SSI ● Piperacillin / tazobactam OR ● Tigecycline In case of suspicion of Gram-negative in the cardiothoracic SSI or MRSA in patients treated with piperacillin/tazobactam, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones).	

Reporting group values	Delafloxacin	Best Available Therapy	Total
Number of subjects	134	132	266
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)	61	55	116
From 65-84 years	60	77	137
85 years and over	13	0	13
Age continuous Units: years			
arithmetic mean	66	63.7	
standard deviation	± 13.65	± 13.71	-
Gender categorical			
Gender was collected at Screening within the demographic data.			
Units: Subjects			
Female	61	53	114
Male	73	79	152
Site of infection			
The category distinguishes among abdominal and cardiothoracic/related leg site.			
Units: Subjects			
Abdominal SSI	124	122	246
Cardiothoracic SSI	10	10	20
Depth of infection			
The category distinguishes between the superfical and deep SSI.			
Units: Subjects			

Superficial SSI	82	79	161
Deep SSI	52	53	105
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	131	131	262
Unknown or Not reported	0		0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Natve Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	133	132	265
More than one race	0	0	0
Unknown or not reported	0	0	0

Subject analysis sets

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

Subject analysis set description:

All randomized and treated subjects analyzed according to the randomized treatment arm (Test or Reference).

Reporting group values	ITT analysis set		
Number of subjects	266		
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)	116		
From 65-84 years	137		
85 years and over	13		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Gender was collected at Screening within the demographic data.			
Units: Subjects			
Female			
Male			

Site of infection			
The category distinguishes among abdominal and cardiothoracic/related leg site.			
Units: Subjects			
Abdominal SSI			
Cardiothoracic SSI			
Depth of infection			
The category distinguishes between the superfical and deep SSI.			
Units: Subjects			
Superficial SSI			
Deep SSI			
Ethnicity Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	262		
Unknown or Not reported	0		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Natve Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	265		
More than one race	0		
Unknown or not reported	0		

End points

End points reporting groups

Reporting group title	Delafloxacin

Reporting group description:

Delafloxacin arm was the Test arm. Patients started the treatment IV with the option to switch to oral formulation.

Reporting group title	Best Available Therapy

Reporting group description:

Best Available Therapy was the Reference arm.
Reference Treatments for cardiothoracic / related leg SSI
● Vancomycin OR
● Linezolid
Reference Treatments for abdominal SSI
● Piperacillin / tazobactam OR
● Tigecycline
In case of suspicion of Gram-negative in the cardiothoracic SSI or MRSA in patients treated with piperacillin/tazobactam, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones).

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

Subject analysis set description:

All randomized and treated subjects analyzed according to the randomized treatment arm (Test or Reference).

Primary: Clinical Success at TOC in the Intent-to-Treat (ITT) and the Clinical Evaluable (CE) populations.

End point title	Clinical Success at TOC in the Intent-to-Treat (ITT) and the Clinical Evaluable (CE) populations.

End point description:

Clinical success is defined as the clinical response of “Cure” or “Improved”

End point type	Primary

End point timeframe:

Test of Cure Visit, i.e. 7 - 14 days after last dose

End point values	Delafloxacin	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	132		
Units: N. of pts achieving the clinical success				
Success at TOC Visit	123	119		

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

The clinical success response at TOC is defined as cure or improved response within 7 - 14 days after last dose.
The rate of the efficacy variable is the sample responder rate defined in the following equation:

responder rate=(number of responder)/(number of responder+number of nonresponder)
All the statistical comparisons will be a test for non-inferiority of delafloxacin versus the Reference arm at a 10% non-inferiority margin, with the possibility of switching to the superiority.

Comparison groups	Delafloxacin v Best Available Therapy
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6 [1]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.0171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0568
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.0377

Notes:

[1] - P-value is referred to superiority testing (not achieved); non-inferiority achieved (95% CI[-0.05; 0.09])

Secondary: Hospital Infection Related Length of Stay (IRLOS)

End point title	Hospital Infection Related Length of Stay (IRLOS)

End point description:

The endpoint measures the lenght of stay since beginning of therapy till patient stabilization and eligibility to discharge based on blinded oberver assessment.

End point type	Secondary

End point timeframe:

Starting from Day 2 up to end of treatment (ie. 14 days maximum)

End point values	Delafloxacin	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	132		
Units: N. of patients				
IRLOS	119	115		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Length of Stay (LOS)

End point title	Hospital Length of Stay (LOS)

End point description:

Lenght of Stay since Screening till actual hospital discharge

End point type	Secondary

End point timeframe:
up to 45 days (i.e. Late Follow Up visit)

End point values	Delafloxacin	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	132		
Units: hours				
arithmetic mean (standard deviation)				
Lenght of Stay	178.8 (± 95.44)	193.5 (± 119.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Eligibility to switch to oral formulation

End point title	Eligibility to switch to oral formulation

End point description:
Blinded observer assessment based on patient stabilization and ability to tolerate OS diet

End point type	Secondary

End point timeframe:
Starting from Day 2 up to the end of treatment (i.e. 14 days maximum)

End point values	Delafloxacin	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	132		
Units: N. of patients				
Eligibility to switch to oral formulation	129	129		

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological response

End point title	Microbiological response

End point description:
Documented or presumed pathogen eradication or persistence

End point type	Secondary

End point timeframe:
up to 14 days (End of Treatment Visit) and 7-14 days after last dose (Test of Cure Visit)

End point values	Delafloxacin	Best Available Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	102		
Units: N.of patients				
Eradicated	94	81		
Persisted	11	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected starting from the FPFV up to LPLV.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Delafloxacin

Reporting group description:

Delafloxacin arm was the Test arm. Patients started the treatment IV with the option to switch to oral formulation.

Reporting group title	Best Available Therapy

Reporting group description:

Best Available Therapy was the Reference arm.
Reference Treatments for cardiothoracic / related leg SSI
● Vancomycin OR
● Linezolid
Reference Treatments for abdominal SSI
● Piperacillin / tazobactam OR
● Tigecycline
In case of suspicion of Gram-negative in the cardiothoracic SSI or MRSA in patients treated with piperacillin/tazobactam, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones).

Serious adverse events	Delafloxacin	Best Available Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 134 (6.72%)	14 / 132 (10.61%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	2	1	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound dehiscence			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
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	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 134 (0.75%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (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	0 / 134 (0.00%)	1 / 132 (0.76%)	
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			
Death			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malaise			

subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocutaneous fistula			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
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			
Pleural effusion			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 134 (0.75%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 134 (0.75%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 132 (0.76%)	
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: 1 %

Non-serious adverse events	Delafloxacin	Best Available Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 134 (14.18%)	13 / 132 (9.85%)	
Investigations			
Hypokalaemia			

subjects affected / exposed	3 / 134 (2.24%)	2 / 132 (1.52%)	
occurrences (all)	3	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 134 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Phlebitis			
subjects affected / exposed	2 / 134 (1.49%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 134 (1.49%)	3 / 132 (2.27%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 134 (1.49%)	1 / 132 (0.76%)	
occurrences (all)	2	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 134 (2.24%)	3 / 132 (2.27%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	2 / 134 (1.49%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 134 (0.75%)	2 / 132 (1.52%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 134 (1.49%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	2 / 134 (1.49%)	0 / 132 (0.00%)	
occurrences (all)	2	0	

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.

The study was prematurely closed due to COVID-19 pandemic affecting both the recruitment and the patient distribution. 266 patients were treated instead of the planned 600.

Notes: