Clinical trial results:
A randomized, controlled, evaluator-blinded, multi-center study to evaluate LYS228 pharmacokinetics, clinical response, safety, and tolerability in patients with complicated intra-abdominal infection

Summary

EudraCT number	2017-003130-90
Trial protocol	CZ DE
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	CLYS228X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03354754
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	24 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the plasma pharmacokinetics of LYS228 in patients with cIAI and to evaluate the clinical response to LYS228 in combination with vancomycin and metronidazole compared to standard of care antibiotics for treating patients with cIAI

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 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	United States: 3
Worldwide total number of subjects	3
EEA total number of subjects	0

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 60 patients were planned to be randomized to LYS228 or a comparator (standard of care therapy preferably piperacillin/tazobactam) in a 2:1 ratio.

Pre-assignment

Screening details:

Due to the study being terminated early, only 3 patients were enrolled and randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LYS228

Arm description:

IV infusion every 6 hours for at least 5 days

Arm type	Experimental
Investigational medicinal product name	LYS228
Investigational medicinal product code	LYS228
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2000 mg every 6 Hours or 3000 mg every 6 hours administered intravenously in normal saline solution.

Arm title	Standard of care

Arm description:

IV infusion of standard of care antibiotics for at least 5 days

Arm type	Active comparator
Investigational medicinal product name	Standard of care
Investigational medicinal product code	Standard of care
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were dosed according to local practices

Number of subjects in period 1	LYS228	Standard of care
Started	2	1
Completed	2	1

Baseline characteristics

Reporting groups	
Reporting group title	LYS228
Reporting group description:	
IV infusion every 6 hours for at least 5 days	
Reporting group title	Standard of care
Reporting group description:	
IV infusion of standard of care antibiotics for at least 5 days	

Reporting group values	LYS228	Standard of care	Total
Number of subjects	2	1	3
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)	2	1	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
median	63.5	63	
full range (min-max)	63 to 64	63 to 63	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	2	1	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	2	1	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	LYS228
Reporting group description:	
IV infusion every 6 hours for at least 5 days	
Reporting group title	Standard of care
Reporting group description:	
IV infusion of standard of care antibiotics for at least 5 days	

Primary: Clinical Success at Day 28

End point title	Clinical Success at Day 28[1]
End point description:	
Clinical success is defined as resolution, or substantial improvement (i.e. reduction of severity of all baseline signs and symptoms and worsening of none) of all or most baseline signs and symptoms of cIAI infection without the need for additional antibiotic therapy other than any oral antibiotics given to complete treatment at home following discontinuation of Study Drug and no drainage or surgical reintervention required 96 hours after the start of Study Drug.	
End point type	Primary
End point timeframe:	
Day 28	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Participants	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: Area Under the Plasma Concentration-time Curve from time zero to the end of the dosing interval tau (AUCtau)

End point title	Plasma Pharmacokinetics (PK) of LYS228: Area Under the Plasma Concentration-time Curve from time zero to the end of the dosing interval tau (AUCtau)[2]
End point description:	
Calculated based on LYS228 concentration in blood at different time points following drug administration on Day 5	
End point type	Primary
End point timeframe:	
Day 5	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: h*ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - PK analysis not conducted as per protocol the first analysis required 8 patients

[4] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: The observed maximum plasma concentration following drug administration (Cmax)

End point title	Plasma Pharmacokinetics (PK) of LYS228: The observed maximum plasma concentration following drug administration (Cmax)[5]

End point description:

Calculated based on LYS228 concentration in blood at different time points following drug administration on Day 5

End point type	Primary

End point timeframe:

Day 5

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - PK analysis not conducted as per protocol the first analysis required 8 patients

[7] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: The time to reach the maximum concentration after drug administration (Tmax)

End point title	Plasma Pharmacokinetics (PK) of LYS228: The time to reach the maximum concentration after drug administration (Tmax)[8]

End point description:

Calculated based on LYS228 concentration in blood at different time points following drug administration

on Day 5

End point type	Primary

End point timeframe:

Day 5

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Hours				
arithmetic mean (standard deviation)	()	()		

Notes:

[9] - PK analysis not conducted as per protocol the first analysis required 8 patients

[10] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: The systemic (or total body) clearance from plasma following intravenous administration (CL)

End point title	Plasma Pharmacokinetics (PK) of LYS228: The systemic (or total body) clearance from plasma following intravenous administration (CL)[11]

End point description:

Calculated based on LYS228 concentration in blood at different time points following drug administration on Day 5

End point type	Primary

End point timeframe:

Day 5

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: L/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[12] - PK analysis not conducted as per protocol the first analysis required 8 patients

[13] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: The volume of distribution at steady state following intravenous administration (Vss)

End point title	Plasma Pharmacokinetics (PK) of LYS228: The volume of distribution at steady state following intravenous administration (Vss)[14]

End point description:

Calculated based on LYS228 concentration in blood at different time points following drug administration on Day 5

End point type	Primary

End point timeframe:

Day 5

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: L/h				
arithmetic mean (standard deviation)	()	()		

Notes:

[15] - PK analysis not conducted as per protocol the first analysis required 8 patients

[16] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Pharmacokinetics (PK) of LYS228: The terminal elimination half-life (T1/2)

End point title	Plasma Pharmacokinetics (PK) of LYS228: The terminal elimination half-life (T1/2)[17]

End point description:

Calculated based on LYS228 concentration in blood at different time points following drug administration on Day 5

End point type	Primary

End point timeframe:

Day 5

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses as trial terminated after three patients

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: Hours				
arithmetic mean (standard deviation)	()	()		

Notes:

[18] - PK analysis not conducted as per protocol the first analysis required 8 patients

[19] - PK analysis was not planned to be conducted for patients that received Standard of Care

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Adverse Events

End point title	Number of patients with Adverse Events

End point description:

Number of patients with at least one Adverse Event

End point type	Secondary

End point timeframe:

Daily

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological Response at Day 28

End point title	Microbiological Response at Day 28

End point description:

Microbiologic success at 28 days after randomization determined by microbial growth in culture from the intra-abdominal focus of infection when available or presumed eradication based on clinical success

End point type	Secondary

End point timeframe:

Day 28

End point values	LYS228	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	0[20]		
Units: Participants	2			

Notes:

[20] - Assessment not performed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first dose of study treatment until day 28.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	LYS228
Reporting group description:	
IV infusion every 6 hours for at least 5 days	
Reporting group title	Standard of care
Reporting group description:	
IV infusion of standard of care antibiotics for at least 5 days	

Serious adverse events	LYS228	Standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
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: 0 %

Non-serious adverse events	LYS228	Standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 1 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Blood phosphorus decreased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 2 (50.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2017	The purpose of this amendment was to collect additional pharmacokinetics (PK) samples in order to better characterize LYS228 PK parameters in patients during the treatment course.
11 June 2018	The purpose of this amendment was to specify a preferred and alternative choice of standard of care antibiotics used as controls. Additional details on planned interim analysis were added.

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.

Due to the study being terminated early, only 3 patients were enrolled and randomized.

Notes: