



## Clinical trial results:

**A -d-glucan guided antifungal stewardship strategy for the management of patients with severe abdominal sepsis. A monocentric interventional explorative study with a pharmacodynamic/pharmacokinetic substudy entitled:**

**“A Pilot Substudy of Liposomal Amphotericin B Pharmacodynamics in Patients with Abdominal Sepsis”**

### Summary

EudraCT number	2016-002335-14
Trial protocol	IT
Global end of trial date	11 September 2022

### Results information

Result version number	v1 (current)
This version publication date	09 February 2025
First version publication date	09 February 2025

### Trial information

#### Trial identification

Sponsor protocol code	LAMBDA
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	LAMBDA: LAMBDA

Notes:

### Sponsors

Sponsor organisation name	IRCCS Azienda Ospedaliero-Universitaria di Bologna
Sponsor organisation address	Via Albertoni 15, Bologna, Italy, 40138
Public contact	Prof. Pierluigi Viale, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Infectious Diseases Unit, +39 0512143595, pierluigi.viale@unibo.it
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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 March 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 September 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety of pre-emptive therapy with Liposomal Amphotericin B (LamB) 5 mg/kg in the first 24h of treatment followed by LamB 3 mg/kg starting from the third day in patients with predefined high risk for invasive candidiasis (IC)//intra-abdominal candidiasis (IAC)

Protection of trial subjects:

The protection of clinical trial subjects is consistent with the principles set out in the Declaration of Helsinki

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	20
From 65 to 84 years	20
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Adult patients ( $\geq 18$  years) with a severe surgical abdominal disease (SAD), defined as post-operative peritonitis, recurrent gastrointestinal perforation, post-operative hepatobiliary and pancreatic disorders, intra-abdominal abscess and anastomotic leak, and with severe sepsis or septic shock

### Period 1

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

### Arms

Arm title	Overall trial
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Liposomal Amphotericin B (Ambisome)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A loading dose of 5 mg/kg of L-AmB was administered on day 0. No antifungal therapy was given on days 1 and 2. On day 3, the decision to continue antifungal treatment at the standard dosage (3 mg/kg) was based on baseline serum 1,3- $\beta$ -d-glucan (BG) levels (measured on day 0) and clinical criteria as follows:

If baseline BG was negative ( $<80$  pg/mL) and the patient was clinically stable, antifungal therapy was discontinued.

If invasive candidiasis (IC) or intra- abdominal candidiasis (IAC) was confirmed by culture results, antifungal treatment continued at a dosage of 3 mg/kg every 24 hours for 7–14 days, as determined by the attending physician.

If baseline BG was significantly positive ( $>200$  pg/mL) or IC/IAC was confirmed by culture results, antifungal treatment was continued for 7–14 days at the attending physician's discretion.

If baseline BG was between 80 and 200 pg/mL, antifungal treatment continued at the standard dosage.

Number of subjects in period 1	Overall trial
Started	40
Completed	40

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
Units: years			
median	65		
inter-quartile range (Q1-Q3)	49 to 76	-	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	15	15	
Baseline condition			
Units: Subjects			
Septic shock	5	5	
Non Septic shock	35	35	
BDG baseline values			
Units: Subjects			
Positive baseline BDG	15	15	
Negative baseline BDG	25	25	
L-AmB confirmed after first dose			
Units: Subjects			
L-AmB confirmed after first dose	14	14	
L-AmB not confirmed after first dose	26	26	
Comorbidities of enrolled patients at baseline (Charlson comorbidity index)			
Units: Points			
median	3		
inter-quartile range (Q1-Q3)	0 to 4	-	

## End points

### End points reporting groups

Reporting group title	Overall trial
Reporting group description: -	

### Primary: Safety

End point title	Safety <sup>[1]</sup>
End point description: Tolerability of pulse high dose L-AmB as pre-emptive therapy in patients at high risk for intra-abdominal candidiasis	
End point type	Primary
End point timeframe:	
Overall trial	

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: Since the primary endpoint focuses on the safety of the investigational product, no statistical analyses were conducted; instead, the frequency of adverse events in the enrolled population was reported.

<b>End point values</b>	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: N° subjects dead	6			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of invasive candidiasis

End point title	Incidence of invasive candidiasis
End point description: Number of patients with confirmed invasive intra-abdominal candidiasis	
End point type	Secondary
End point timeframe:	
Overall trial	

<b>End point values</b>	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: N° subjects with confirmed invasive IAC	2			

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: During the LAMBDA trial, six serious adverse events (SAE) and no serious adverse reactions (SARs) were reported to the Sponsor. All reported SAEs had a "fatal" outcome and no one of these was considered to be related to the investigational product. Therefore, no actions were taken for safety reasons, throughout the LAMBDA study.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 40 (15.00%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			



subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2021	<p>Change from a multicenter study to a single-center study as the activation of other participating centers was never implemented.</p> <p>Possibility to obtain informed consent to participate in the study/sub-study after the decision to include the subject in the clinical trial in emergency situations, in accordance with Article 35 of EU Regulation No. 536/2014, "Clinical trials in emergency situations".</p> <p>Study duration modification.</p> <p>An addendum was added to the protocol listing the expected Serious Adverse Events (SAEs) for the disease/population under study, for which expedited reporting within 24 hours is deemed unnecessary.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37838147>