



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 |
|-----------------------|--------|

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 (≥ 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- β -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 ^[1] |
| 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.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | 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 | |

| | | | | |
|--|-----------------|--|--|--|
| End point values | Overall trial | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 40 | | | |
| Units: N° subjects with confirmed invasive IAC | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Overall trial

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall trial |
|-----------------------|---------------|

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 %

| | | | |
|---|----------------|--|--|
| Non-serious adverse events | 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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