



## Clinical trial results:

### A Phase 3, Double-Blind, Multicenter, Randomized, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Prophylactic Liposomal Amphotericin B (AmBisome®) for the Prevention of Invasive Fungal Infections (IFIs) in Subjects Receiving Remission-Induction Chemotherapy for Acute Lymphoblastic Leukemia (ALL)

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2010-019562-91       |
| Trial protocol           | AT PT ES DE GR BE IT |
| Global end of trial date | 29 January 2014      |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 22 March 2016  |
| First version publication date | 05 August 2015 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | GS-EU-131-0247 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01259713 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Gilead Sciences  |
| Sponsor organisation address | Flowers Building, Granta Park, Abington, Cambridge, United Kingdom, CB21 6GT                   |
| Public contact               | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact           | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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                       | 29 January 2014 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 29 January 2014 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The study investigated whether prophylaxis with liposomal amphotericin B (AmBisome®) can reduce the incidence of invasive fungal infections (IFIs) in patients with Acute Lymphoblastic Leukemia (ALL) who are undergoing their first remission induction.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 13 April 2011 |
| 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 | Greece: 27     |
| Country: Number of subjects enrolled | Italy: 66      |
| Country: Number of subjects enrolled | Turkey: 11     |
| Country: Number of subjects enrolled | Israel: 9      |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Brazil: 15     |
| Country: Number of subjects enrolled | Argentina: 8   |
| Country: Number of subjects enrolled | Portugal: 17   |
| Country: Number of subjects enrolled | Spain: 28      |
| Country: Number of subjects enrolled | Austria: 9     |
| Country: Number of subjects enrolled | Belgium: 31    |
| Country: Number of subjects enrolled | France: 52     |
| Country: Number of subjects enrolled | Germany: 75    |
| Worldwide total number of subjects   | 355            |
| EEA total number of subjects         | 305            |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 313 |
| From 65 to 84 years                       | 42  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at a total of 86 study sites. The first participant was screened on 13 April 2011. The last study visit occurred on 29 January 2014.

### Pre-assignment

Screening details:

391 participants were screened.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall Study (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 |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Liposomal amphotericin B |
|------------------|--------------------------|

Arm description:

Liposomal amphotericin B twice weekly during induction chemotherapy

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Liposomal amphotericin B         |
| Investigational medicinal product code |                                  |
| Other name                             | AmBisome®                        |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Liposomal amphotericin B 5 mg/kg administered by IV route over 2 hours twice weekly (each dose separated alternately by 2 and 3 days each week)

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo to match liposomal amphotericin B twice weekly during induction chemotherapy

|  |   |
|--|---|
| Arm type                               | Placebo                                   |
| Investigational medicinal product name | Placebo to match liposomal amphotericin B |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder for solution for infusion          |
| Routes of administration               | Intravenous use                           |

Dosage and administration details:

Placebo to match liposomal amphotericin B administered by IV route over 2 hours twice weekly (each dose separated alternately by 2 and 3 days each week)

| <b>Number of subjects in period 1</b> | Liposomal<br>amphotericin B | Placebo |
|---------------------------------------|-----------------------------|---------|
| Started                               | 237                         | 118     |
| Completed                             | 142                         | 77      |
| Not completed                         | 95                          | 41      |
| Subject Withdrew Consent              | 12                          | 7       |
| Adverse event, non-fatal              | 54                          | 23      |
| Protocol violation                    | 5                           | 4       |
| Investigators Discretion              | 14                          | 6       |
| Death Not Related to IFI              | 8                           | 1       |
| Lack of efficacy                      | 2                           | -       |

## Baseline characteristics

### Reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Liposomal amphotericin B |
| Reporting group description:<br>Liposomal amphotericin B twice weekly during induction chemotherapy                  |                          |
| Reporting group title  | Placebo                  |
| Reporting group description:<br>Placebo to match liposomal amphotericin B twice weekly during induction chemotherapy |                          |

| Reporting group values                        | Liposomal amphotericin B | Placebo | Total |
|---|--------------------------|---------|-------|
| Number of subjects                            | 237                      | 118     | 355   |
| Age categorical<br>Units: Subjects            |                          |         |       |
| ≤ 25 years                                    | 37                       | 25      | 62    |
| > 25 to ≤ 60 years                            | 160                      | 64      | 224   |
| > 60 years                                    | 40                       | 29      | 69    |
| Age Continuous<br>Units: years                |                          |         |       |
| arithmetic mean                               | 44.5                     | 44.8    |       |
| standard deviation                            | ± 15.16                  | ± 17.52 | -     |
| Gender, Male/Female<br>Units: participants    |                          |         |       |
| Female  | 98                       | 58      | 156   |
| Male  | 139                      | 60      | 199   |
| Race/Ethnicity, Customized<br>Units: Subjects |                          |         |       |
| Asian   | 1                        | 0       | 1     |
| Black   | 4                        | 3       | 7     |
| White   | 211                      | 100     | 311   |
| Not Permitted                                 | 17                       | 15      | 32    |
| Other   | 4                        | 0       | 4     |
| Region of Enrollment<br>Units: Subjects       |                          |         |       |
| Germany                                       | 52                       | 23      | 75    |
| Italy   | 41                       | 25      | 66    |
| France  | 33                       | 19      | 52    |
| Belgium                                       | 20                       | 11      | 31    |
| Spain   | 21                       | 7       | 28    |
| Greece  | 14                       | 13      | 27    |
| Portugal                                      | 13                       | 4       | 17    |
| Turkey  | 7                        | 4       | 11    |
| Austria                                       | 6                        | 3       | 9     |
| Israel  | 9                        | 0       | 9     |
| Switzerland                                   | 6                        | 1       | 7     |
| Brazil  | 8                        | 7       | 15    |
| Argentina                                     | 7                        | 1       | 8     |



## End points

### End points reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Liposomal amphotericin B |
| Reporting group description:<br>Liposomal amphotericin B twice weekly during induction chemotherapy                  |                          |
| Reporting group title  | Placebo                  |
| Reporting group description:<br>Placebo to match liposomal amphotericin B twice weekly during induction chemotherapy |                          |

### Primary: Percentage of participants with proven or probable IFIs during remission-induction chemotherapy for acute lymphoblastic leukemia (ALL)

|  |  |
|--|--|
| End point title  | Percentage of participants with proven or probable IFIs during remission-induction chemotherapy for acute lymphoblastic leukemia (ALL) |
| End point description:<br>Diagnoses of proven or probable invasive fungal infections (IFI) were assessed according to European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria by the independent data review board (IDRB) who were blinded to treatment assignment.<br><br>The duration of remission-induction chemotherapy was defined as the period from the initiation of remission-induction chemotherapy administration to the start of consolidation or salvage therapy. |  |
| End point type   | Primary  |
| End point timeframe:<br>During remission-induction chemotherapy (average 7 weeks)  |  |

| End point values                  | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 7.9                      | 11.7            |  |  |

### Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title  | Difference in relative risk reduction |
| Statistical analysis description:<br>A two-group Cochran-Mantel-Haenszel (CMH) test with a 0.05 two-sided significance level and 2:1 allocation of 354 randomized subjects (236 AmBisome, 118 placebo) would have 81% power to detect a relative reduction of 75% if the rate of IFI is 10% in the placebo group (based on unpublished data from the German Multicenter Acute Lymphoblastic Leukemia Working Group (GMALL) and consistent with the published rate of 16.4% in patients with hematological malignancies undergoing remission induction). |                                       |
| Comparison groups   | Placebo v Liposomal amphotericin B    |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 339                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| P-value                                 | = 0.24 <sup>[2]</sup>          |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Relative risk reduction        |
| Point estimate                          | 0.33                           |
| Confidence interval                     |                                |
| level                                   | 95.03 %                        |
| sides                                   | 2-sided                        |
| lower limit                             | -0.32                          |
| upper limit                             | 0.66                           |

Notes:

[1] - For the interim analysis performed when 50% of the subjects had completed the study, an alpha of 0.0003 was spent. Therefore, the significance level for the 2-sided test in the primary analysis at the end of the study was 0.0497 (corresponding to 95.03% confidence interval (CI)). Relative risk reduction = 1- risk ratio.

[2] - P-value was from a stratum-adjusted (stratified by region) CMH test.

## Secondary: Percentage of participants with pulmonary infiltrates according to the Central Image Reader

|   |   |
|---|---|
| End point title   | Percentage of participants with pulmonary infiltrates according to the Central Image Reader |
| End point description:                                    |   |
| End point type  | Secondary   |
| End point timeframe:                                      |   |
| During remission-induction chemotherapy (average 7 weeks) |   |

| End point values                  | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 20.2                     | 27              |  |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| Statistical analysis title              | Difference in relative risk reduction |
| Comparison groups                       | Liposomal amphotericin B v Placebo    |
| Number of subjects included in analysis | 339                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other                                 |
| P-value                                 | = 0.15 <sup>[3]</sup>                 |
| Method                                  | Cochran-Mantel-Haenszel               |
| Parameter estimate                      | Relative risk reduction               |
| Point estimate                          | 0.25                                  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.11   |
| upper limit         | 0.5     |

Notes:

[3] - P-value was from a stratum-adjusted (stratified by region) CMH test. Relative risk reduction = 1 - risk ratio.

### Secondary: Percentage of participants diagnosed with proven or probable IFIs according to the EORTC/MSG criteria, as assessed by the investigator

|                 |  |
|-----------------|--|
| End point title | Percentage of participants diagnosed with proven or probable IFIs according to the EORTC/MSG criteria, as assessed by the investigator |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During remission-induction chemotherapy (average 7 weeks)

| End point values                  | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 11                       | 10.8            |  |  |

### Statistical analyses

|   |                                    |
|---|------------------------------------|
| Statistical analysis title              | Difference in risk reduction       |
| Comparison groups                       | Placebo v Liposomal amphotericin B |
| Number of subjects included in analysis | 339                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other                              |
| P-value                                 | = 0.97 <sup>[4]</sup>              |
| Method                                  | Cochran-Mantel-Haenszel            |
| Parameter estimate                      | Relative risk reduction            |
| Point estimate                          | -0.01                              |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -0.94                              |
| upper limit                             | 0.47                               |

Notes:

[4] - P-value was from a stratum-adjusted (stratified by region) CMH test. Relative risk reduction = 1 - risk ratio.

### Secondary: Percentage of Participants Requiring Antifungal Treatment During

## Remission-Induction Chemotherapy

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Requiring Antifungal Treatment During Remission-Induction Chemotherapy |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During remission-induction chemotherapy (average 7 weeks)

| End point values                  | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 16.2                     | 21.6            |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Difference in rates of antifungal treatment |
| Comparison groups                       | Placebo v Liposomal amphotericin B          |
| Number of subjects included in analysis | 339   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other                                       |
| P-value                                 | = 0.22 <sup>[5]</sup>                       |
| Method                                  | Cochran-Mantel-Haenszel                     |
| Parameter estimate                      | Relative risk reduction                     |
| Point estimate                          | 0.25  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | -0.19                                       |
| upper limit                             | 0.53  |

Notes:

[5] - P-value was from a stratum-adjusted (stratified by region) CMH test. Relative risk reduction = 1-risk ratio.

## Secondary: Percentage of participants who died due to fungal infection; causality as assessed by the IDRB.

|                 |   |
|-----------------|---|
| End point title | Percentage of participants who died due to fungal infection; causality as assessed by the IDRB. |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During remission-induction chemotherapy (average 7 weeks)

| <b>End point values</b>           | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 0.9                      | 0               |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Difference in rates of death due to IFI |
| Comparison groups                       | Placebo v Liposomal amphotericin B      |
| Number of subjects included in analysis | 339                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other                                   |
| P-value                                 | = 0.32 <sup>[6]</sup>                   |
| Method                                  | Cochran-Mantel-Haenszel                 |
| Confidence interval                     |   |
| sides                                   | 2-sided                                 |

Notes:

[6] - P-value was from a stratum-adjusted (stratified by region) CMH test.

### Secondary: Percentage of participants who died due to fungal infection; causality as assessed by the investigator.

|   |   |
|---|---|
| End point title   | Percentage of participants who died due to fungal infection; causality as assessed by the investigator. |
| End point description:                                    |   |
| End point type  | Secondary   |
| End point timeframe:                                      |   |
| During remission-induction chemotherapy (average 7 weeks) |   |

| <b>End point values</b>           | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 0.9                      | 0               |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Difference in rates of death due to IFI |
| Comparison groups                       | Placebo v Liposomal amphotericin B      |
| Number of subjects included in analysis | 339                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other                                   |
| P-value                                 | = 0.32 [7]                              |
| Method                                  | Cochran-Mantel-Haenszel                 |

Notes:

[7] - P-value was from a stratum-adjusted (stratified by region) CMH test.

### Secondary: Time from beginning of remission-induction chemotherapy until the beginning of consolidation therapy

|                 |  |
|-----------------|--|
| End point title | Time from beginning of remission-induction chemotherapy until the beginning of consolidation therapy |
|-----------------|--|

End point description:

This endpoint was to evaluate the potential impact of IFI prevention on the efficacy of remission-induction chemotherapy for ALL.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During remission-induction chemotherapy (average 7 weeks)

| End point values                      | Liposomal amphotericin B | Placebo         |  |  |
|---------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                    | Reporting group          | Reporting group |  |  |
| Number of subjects analysed           | 228                      | 111             |  |  |
| Units: days                           |                          |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 50 (38 to 75)            | 55 (36 to 75)   |  |  |

### Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Difference in days                 |
| Comparison groups                       | Placebo v Liposomal amphotericin B |
| Number of subjects included in analysis | 339                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other                              |
| P-value                                 | = 0.69 [8]                         |
| Method                                  | Logrank                            |

Notes:

[8] - The p-value was from the log-rank test stratified by region.

### Secondary: Percentage of participants with complete remission at the end of remission induction

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with complete remission at the end of remission induction |
|-----------------|--|

End point description:

This endpoint was to evaluate the potential impact of IFI prevention on the efficacy of remission-induction chemotherapy for ALL.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                      |           |
| During remission-induction chemotherapy (average 7 weeks) |           |

| End point values                  | Liposomal amphotericin B | Placebo         |  |  |
|-----------------------------------|--------------------------|-----------------|--|--|
| Subject group type                | Reporting group          | Reporting group |  |  |
| Number of subjects analysed       | 228                      | 111             |  |  |
| Units: percentage of participants |                          |                 |  |  |
| number (not applicable)           | 72.8                     | 79.3            |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>                   | Difference in rate of remission-induction response |
| Statistical analysis description:                   |  |
| Participants were not stratified for leukemia risk. |  |
| Comparison groups                                   | Placebo v Liposomal amphotericin B                 |
| Number of subjects included in analysis             | 339  |
| Analysis specification                              | Pre-specified                                      |
| Analysis type                                       | other  |
| P-value   | = 0.2 <sup>[9]</sup>                               |
| Method  | Cochran-Mantel-Haenszel                            |
| Parameter estimate                                  | Relative risk reduction                            |
| Point estimate                                      | 0.08   |
| Confidence interval                                 |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -0.04  |
| upper limit   | 0.19   |

Notes:

[9] - P-value was from a stratum-adjusted (stratified by region) CMH test. Relative risk reduction = 1-risk ratio.

## Secondary: Time to Diagnosis of Proven or Probable IFIs According to the EORTC/MSG Criteria, as Assessed by the IDRB.

|                 |  |
|-----------------|--|
| End point title | Time to Diagnosis of Proven or Probable IFIs According to the EORTC/MSG Criteria, as Assessed by the IDRB. |
|-----------------|--|

End point description:

Time to diagnosis of proven or probable IFIs is presented as the median (Q1,Q3) days to diagnosis of those participants who experienced a proven or probable IFI. Median was not reached if < 50% of participants had an event; Q1 was not reached if < 25% of participants had an event; Q3 was not reached if < 75% of participants had an event.

999 / 9999 / 99999 = not reached due to insufficient number of events

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                      |           |
| During remission-induction chemotherapy (average 7 weeks) |           |

| <b>End point values</b>               | Liposomal amphotericin B | Placebo             |  |  |
|---------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed           | 228                      | 111                 |  |  |
| Units: days                           |                          |                     |  |  |
| median (inter-quartile range (Q1-Q3)) | 9999 (999 to 99999)      | 9999 (999 to 99999) |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Difference in time to IFI          |
|---|------------------------------------|
| Comparison groups                       | Placebo v Liposomal amphotericin B |
| Number of subjects included in analysis | 339                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other <sup>[10]</sup>              |
| P-value                                 | = 0.33 <sup>[11]</sup>             |
| Method                                  | Logrank                            |

Notes:

[10] - Comparative analysis.

[11] - The p-value is from the log-rank test stratified by region.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose to last dose of study drug plus 30 days.

Adverse event reporting additional description:

Safety Analysis Set; participants were randomized and received at least 1 dose of study drug. MedDRA version 11.1 was used for the Tenofovir and Placebo columns; MedDRA version 16.1 was used for the All TDF column.

All AEs are reported by system order class and preferred term as determined by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Liposomal amphotericin B |
|-----------------------|--------------------------|

Reporting group description:

Liposomal amphotericin B 5 mg/kg twice weekly administered by IV route over 2 hours twice weekly (each dose separated alternately by 2 and 3 days each week) during induction chemotherapy

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo to match liposomal amphotericin B twice weekly administered by IV route over 2 hours twice weekly (each dose separated alternately by 2 and 3 days each week) during induction chemotherapy

| Serious adverse events  | Liposomal amphotericin B | Placebo           |  |
|---|--------------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                          |                   |  |
| subjects affected / exposed   | 79 / 237 (33.33%)        | 38 / 118 (32.20%) |  |
| number of deaths (all causes)                                       | 17                       | 8                 |  |
| number of deaths resulting from adverse events                      | 0                        | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |                   |  |
| Metastases to bone marrow   |                          |                   |  |
| subjects affected / exposed   | 1 / 237 (0.42%)          | 0 / 118 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0             |  |
| Metastases to central nervous system                                |                          |                   |  |
| subjects affected / exposed   | 1 / 237 (0.42%)          | 0 / 118 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0             |  |
| Vascular disorders  |                          |                   |  |
| Deep vein thrombosis  |                          |                   |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypotension  |                 |                 |  |
| subjects affected / exposed                          | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombosis   |                 |                 |  |
| subjects affected / exposed                          | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| 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 |                 |                 |  |
| Pyrexia  |                 |                 |  |
| subjects affected / exposed                          | 2 / 237 (0.84%) | 3 / 118 (2.54%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Systemic inflammatory response syndrome              |                 |                 |  |
| subjects affected / exposed                          | 0 / 237 (0.00%) | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chills   |                 |                 |  |
| subjects affected / exposed                          | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Inflammation   |                 |                 |  |
| subjects affected / exposed                          | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Allergic oedema                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Pulmonary haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bronchial obstruction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 237 (1.27%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Creatinine renal clearance decreased            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| White blood cell count decreased                |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphocyte count decreased                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Post lumbar puncture syndrome                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 4 / 237 (1.69%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (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                        |                 |                 |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hepatic encephalopathy                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial venous sinus thrombosis            |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Meningism                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Somnolence                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%)  | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Febrile neutropenia                             |                  |                 |  |
| subjects affected / exposed                     | 10 / 237 (4.22%) | 6 / 118 (5.08%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anaemia   |                  |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neutropenia                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancytopenia                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Visual acuity reduced                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Colitis   |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Caecitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileitis   |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| 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 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intra-abdominal haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic steatosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular injury                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Rash papular                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 237 (1.69%) | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 237 (1.27%) | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nephropathy toxic                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Joint swelling                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Septic shock                                    |                  |                 |  |
| subjects affected / exposed                     | 13 / 237 (5.49%) | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 7            | 0 / 2           |  |
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 7 / 237 (2.95%)  | 3 / 118 (2.54%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Sepsis  |                  |                 |  |
| subjects affected / exposed                     | 4 / 237 (1.69%)  | 6 / 118 (5.08%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3           |  |
| Device related infection                        |                  |                 |  |
| subjects affected / exposed                     | 3 / 237 (1.27%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bacterial sepsis                                |                  |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pneumonia bacterial                             |                  |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%)  | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Escherichia sepsis                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%)  | 2 / 118 (1.69%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pseudomonal sepsis                              |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| 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 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal bacteraemia                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella infection                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii infection                |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia klebsiella                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia necrotising                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory moniliasis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 118 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal sepsis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyperammonaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 237 (0.84%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 118 (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: 5 %

| <b>Non-serious adverse events</b>                     | Liposomal amphotericin B | Placebo            |  |
|---|--------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                          |                    |  |
| subjects affected / exposed                           | 233 / 237 (98.31%)       | 114 / 118 (96.61%) |  |
| Vascular disorders                                    |                          |                    |  |
| Hypotension   |                          |                    |  |
| subjects affected / exposed                           | 17 / 237 (7.17%)         | 15 / 118 (12.71%)  |  |
| occurrences (all)                                     | 21                       | 18                 |  |
| Hypertension  |                          |                    |  |
| subjects affected / exposed                           | 12 / 237 (5.06%)         | 7 / 118 (5.93%)    |  |
| occurrences (all)                                     | 14                       | 7                  |  |
| Haematoma   |                          |                    |  |
| subjects affected / exposed                           | 15 / 237 (6.33%)         | 3 / 118 (2.54%)    |  |
| occurrences (all)                                     | 18                       | 3                  |  |
| General disorders and administration site conditions  |                          |                    |  |
| Pyrexia   |                          |                    |  |
| subjects affected / exposed                           | 65 / 237 (27.43%)        | 37 / 118 (31.36%)  |  |
| occurrences (all)                                     | 98                       | 50                 |  |
| Mucosal inflammation                                  |                          |                    |  |
| subjects affected / exposed                           | 61 / 237 (25.74%)        | 32 / 118 (27.12%)  |  |
| occurrences (all)                                     | 69                       | 39                 |  |
| Oedema peripheral                                     |                          |                    |  |
| subjects affected / exposed                           | 56 / 237 (23.63%)        | 18 / 118 (15.25%)  |  |
| occurrences (all)                                     | 69                       | 21                 |  |
| Asthenia  |                          |                    |  |
| subjects affected / exposed                           | 32 / 237 (13.50%)        | 19 / 118 (16.10%)  |  |
| occurrences (all)                                     | 36                       | 22                 |  |
| Fatigue   |                          |                    |  |
| subjects affected / exposed                           | 17 / 237 (7.17%)         | 10 / 118 (8.47%)   |  |
| occurrences (all)                                     | 20                       | 13                 |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 18 / 237 (7.59%)<br>21  | 8 / 118 (6.78%)<br>10   |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 17 / 237 (7.17%)<br>19  | 9 / 118 (7.63%)<br>11   |  |
| Oedema<br>subjects affected / exposed<br>occurrences (all)  | 15 / 237 (6.33%)<br>18  | 6 / 118 (5.08%)<br>9    |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 10 / 237 (4.22%)<br>11  | 11 / 118 (9.32%)<br>14  |  |
| Reproductive system and breast disorders<br>Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 2 / 237 (0.84%)<br>2    | 6 / 118 (5.08%)<br>7    |  |
| Respiratory, thoracic and mediastinal disorders<br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)    | 20 / 237 (8.44%)<br>28  | 16 / 118 (13.56%)<br>21 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 29 / 237 (12.24%)<br>32 | 17 / 118 (14.41%)<br>19 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 19 / 237 (8.02%)<br>21  | 10 / 118 (8.47%)<br>14  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 15 / 237 (6.33%)<br>16  | 13 / 118 (11.02%)<br>14 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                                | 19 / 237 (8.02%)<br>22  | 15 / 118 (12.71%)<br>17 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 32 / 237 (13.50%)<br>35 | 17 / 118 (14.41%)<br>17 |  |

|  |                          |                         |  |
|--|--------------------------|-------------------------|--|
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 12 / 237 (5.06%)<br>12   | 5 / 118 (4.24%)<br>5    |  |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                            | 5 / 237 (2.11%)<br>7     | 7 / 118 (5.93%)<br>8    |  |
| Investigations   |                          |                         |  |
| Antithrombin III decreased<br>subjects affected / exposed<br>occurrences (all)           | 33 / 237 (13.92%)<br>34  | 14 / 118 (11.86%)<br>15 |  |
| Blood fibrinogen decreased<br>subjects affected / exposed<br>occurrences (all)           | 19 / 237 (8.02%)<br>21   | 8 / 118 (6.78%)<br>8    |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 17 / 237 (7.17%)<br>21   | 9 / 118 (7.63%)<br>9    |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 19 / 237 (8.02%)<br>21   | 4 / 118 (3.39%)<br>4    |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 16 / 237 (6.75%)<br>24   | 4 / 118 (3.39%)<br>4    |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)           | 20 / 237 (8.44%)<br>26   | 0 / 118 (0.00%)<br>0    |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 13 / 237 (5.49%)<br>13   | 4 / 118 (3.39%)<br>5    |  |
| Cardiac disorders  |                          |                         |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                          | 13 / 237 (5.49%)<br>15   | 8 / 118 (6.78%)<br>11   |  |
| Nervous system disorders   |                          |                         |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 84 / 237 (35.44%)<br>126 | 45 / 118 (38.14%)<br>60 |  |

|   |                           |                         |  |
|---|---------------------------|-------------------------|--|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)           | 11 / 237 (4.64%)<br>12    | 12 / 118 (10.17%)<br>14 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)        | 14 / 237 (5.91%)<br>14    | 9 / 118 (7.63%)<br>9    |  |
| Blood and lymphatic system disorders                                    |                           |                         |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)             | 49 / 237 (20.68%)<br>97   | 27 / 118 (22.88%)<br>44 |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all) | 50 / 237 (21.10%)<br>63   | 26 / 118 (22.03%)<br>34 |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)         | 40 / 237 (16.88%)<br>58   | 26 / 118 (22.03%)<br>33 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)    | 42 / 237 (17.72%)<br>72   | 14 / 118 (11.86%)<br>21 |  |
| Coagulopathy<br>subjects affected / exposed<br>occurrences (all)        | 13 / 237 (5.49%)<br>14    | 9 / 118 (7.63%)<br>10   |  |
| Ear and labyrinth disorders   |                           |                         |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)             | 14 / 237 (5.91%)<br>16    | 8 / 118 (6.78%)<br>12   |  |
| Gastrointestinal disorders  |                           |                         |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)              | 118 / 237 (49.79%)<br>157 | 50 / 118 (42.37%)<br>80 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)            | 75 / 237 (31.65%)<br>101  | 43 / 118 (36.44%)<br>60 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)        | 74 / 237 (31.22%)<br>91   | 40 / 118 (33.90%)<br>41 |  |
| Diarrhoea   |                           |                         |  |



|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 66 / 237 (27.85%) | 36 / 118 (30.51%) |  |
| occurrences (all)                               | 83                | 49                |  |
| Abdominal pain                                  |                   |                   |  |
| subjects affected / exposed                     | 55 / 237 (23.21%) | 35 / 118 (29.66%) |  |
| occurrences (all)                               | 78                | 44                |  |
| Abdominal pain upper                            |                   |                   |  |
| subjects affected / exposed                     | 39 / 237 (16.46%) | 14 / 118 (11.86%) |  |
| occurrences (all)                               | 44                | 19                |  |
| Haemorrhoids                                    |                   |                   |  |
| subjects affected / exposed                     | 18 / 237 (7.59%)  | 12 / 118 (10.17%) |  |
| occurrences (all)                               | 19                | 12                |  |
| Stomatitis                                      |                   |                   |  |
| subjects affected / exposed                     | 14 / 237 (5.91%)  | 11 / 118 (9.32%)  |  |
| occurrences (all)                               | 14                | 11                |  |
| Dyspepsia                                       |                   |                   |  |
| subjects affected / exposed                     | 14 / 237 (5.91%)  | 4 / 118 (3.39%)   |  |
| occurrences (all)                               | 16                | 4                 |  |
| Hepatobiliary disorders                         |                   |                   |  |
| Hyperbilirubinaemia                             |                   |                   |  |
| subjects affected / exposed                     | 6 / 237 (2.53%)   | 7 / 118 (5.93%)   |  |
| occurrences (all)                               | 7                 | 7                 |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Rash  |                   |                   |  |
| subjects affected / exposed                     | 39 / 237 (16.46%) | 11 / 118 (9.32%)  |  |
| occurrences (all)                               | 46                | 11                |  |
| Erythema  |                   |                   |  |
| subjects affected / exposed                     | 19 / 237 (8.02%)  | 5 / 118 (4.24%)   |  |
| occurrences (all)                               | 21                | 6                 |  |
| Alopecia  |                   |                   |  |
| subjects affected / exposed                     | 17 / 237 (7.17%)  | 6 / 118 (5.08%)   |  |
| occurrences (all)                               | 17                | 6                 |  |
| Pruritus  |                   |                   |  |
| subjects affected / exposed                     | 13 / 237 (5.49%)  | 4 / 118 (3.39%)   |  |
| occurrences (all)                               | 18                | 4                 |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |

|   |                          |                         |  |
|---|--------------------------|-------------------------|--|
| Back pain<br>subjects affected / exposed<br>occurrences (all)           | 34 / 237 (14.35%)<br>37  | 16 / 118 (13.56%)<br>20 |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)           | 14 / 237 (5.91%)<br>15   | 9 / 118 (7.63%)<br>10   |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 8 / 237 (3.38%)<br>9     | 10 / 118 (8.47%)<br>11  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)           | 11 / 237 (4.64%)<br>13   | 6 / 118 (5.08%)<br>7    |  |
| Infections and infestations   |                          |                         |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)         | 22 / 237 (9.28%)<br>24   | 7 / 118 (5.93%)<br>7    |  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)    | 8 / 237 (3.38%)<br>8     | 11 / 118 (9.32%)<br>11  |  |
| Bacterial infection<br>subjects affected / exposed<br>occurrences (all) | 12 / 237 (5.06%)<br>17   | 6 / 118 (5.08%)<br>6    |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)           | 15 / 237 (6.33%)<br>15   | 3 / 118 (2.54%)<br>3    |  |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)        | 10 / 237 (4.22%)<br>10   | 6 / 118 (5.08%)<br>6    |  |
| Metabolism and nutrition disorders                                      |                          |                         |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)        | 83 / 237 (35.02%)<br>115 | 21 / 118 (17.80%)<br>32 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)      | 22 / 237 (9.28%)<br>22   | 11 / 118 (9.32%)<br>12  |  |
| Hypoalbuminaemia  |                          |                         |  |

|                             |                   |                 |  |
|-----------------------------|-------------------|-----------------|--|
| subjects affected / exposed | 24 / 237 (10.13%) | 9 / 118 (7.63%) |  |
| occurrences (all)           | 30                | 9               |  |
| Decreased appetite          |                   |                 |  |
| subjects affected / exposed | 18 / 237 (7.59%)  | 9 / 118 (7.63%) |  |
| occurrences (all)           | 19                | 9               |  |
| Hypocalcaemia               |                   |                 |  |
| subjects affected / exposed | 18 / 237 (7.59%)  | 7 / 118 (5.93%) |  |
| occurrences (all)           | 18                | 7               |  |
| Fluid retention             |                   |                 |  |
| subjects affected / exposed | 15 / 237 (6.33%)  | 6 / 118 (5.08%) |  |
| occurrences (all)           | 27                | 7               |  |
| Hyperuricaemia              |                   |                 |  |
| subjects affected / exposed | 13 / 237 (5.49%)  | 4 / 118 (3.39%) |  |
| occurrences (all)           | 14                | 4               |  |
| Hypomagnesaemia             |                   |                 |  |
| subjects affected / exposed | 12 / 237 (5.06%)  | 5 / 118 (4.24%) |  |
| occurrences (all)           | 20                | 7               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 13 October 2010 | Removed the restriction that the duration of study treatment be a maximum of 12 weeks; updated the duration of clinical monitoring for IFIs such that it continued until a subject had started consolidation therapy, and was not restricted to 12 weeks; added an interim analysis to the study which allowed for stopping due to futility. |
| 10 May 2011     | Clarified the end of study-drug administration and the use of salvage therapy for subjects not recovering from neutropenia; adjusted the stratification factors of the study to use region only.   |
| 10 May 2012     | Clarified the end of monitoring for fungal infection; updated directions for emergency unblinding.   |

Notes:

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### 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.

57 patients received protocol-prohibited antifungal treatment and 30 received a non-myelosuppressive chemotherapy regimen that may have impacted the primary endpoint analysis.

Notes: