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:

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)	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
Arm title	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)

Arm title	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)

Number of subjects in period 1	Liposomal 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:	
Liposomal amphotericin B twice weekly during induction chemotherapy	
Reporting group title	Placebo
Reporting group description:	
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 Units: Subjects			
≤ 25 years	37	25	62
> 25 to ≤ 60 years	160	64	224
> 60 years	40	29	69
Age Continuous Units: years			
arithmetic mean	44.5	44.8	
standard deviation	± 15.16	± 17.52	-
Gender, Male/Female Units: participants			
Female	98	58	156
Male	139	60	199
Race/Ethnicity, Customized 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 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:	
Liposomal amphotericin B twice weekly during induction chemotherapy	
Reporting group title	Placebo
Reporting group description:	
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:

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.

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:

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:

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[1]
P-value	= 0.24 [2]
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 [3]
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 [4]
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 [5]
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)

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)	0.9	0		

Statistical analyses

Statistical analysis title	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 [6]
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)

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)	0.9	0		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 [9]
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)

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))	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	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[10]
P-value	= 0.33 [11]
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 %

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

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

Dizziness			
subjects affected / exposed	11 / 237 (4.64%)	12 / 118 (10.17%)	
occurrences (all)	12	14	
Paraesthesia			
subjects affected / exposed	14 / 237 (5.91%)	9 / 118 (7.63%)	
occurrences (all)	14	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	49 / 237 (20.68%)	27 / 118 (22.88%)	
occurrences (all)	97	44	
Febrile neutropenia			
subjects affected / exposed	50 / 237 (21.10%)	26 / 118 (22.03%)	
occurrences (all)	63	34	
Neutropenia			
subjects affected / exposed	40 / 237 (16.88%)	26 / 118 (22.03%)	
occurrences (all)	58	33	
Thrombocytopenia			
subjects affected / exposed	42 / 237 (17.72%)	14 / 118 (11.86%)	
occurrences (all)	72	21	
Coagulopathy			
subjects affected / exposed	13 / 237 (5.49%)	9 / 118 (7.63%)	
occurrences (all)	14	10	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	14 / 237 (5.91%)	8 / 118 (6.78%)	
occurrences (all)	16	12	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	118 / 237 (49.79%)	50 / 118 (42.37%)	
occurrences (all)	157	80	
Vomiting			
subjects affected / exposed	75 / 237 (31.65%)	43 / 118 (36.44%)	
occurrences (all)	101	60	
Constipation			
subjects affected / exposed	74 / 237 (31.22%)	40 / 118 (33.90%)	
occurrences (all)	91	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			
subjects affected / exposed	34 / 237 (14.35%)	16 / 118 (13.56%)	
occurrences (all)	37	20	
Neck pain			
subjects affected / exposed	14 / 237 (5.91%)	9 / 118 (7.63%)	
occurrences (all)	15	10	
Pain in extremity			
subjects affected / exposed	8 / 237 (3.38%)	10 / 118 (8.47%)	
occurrences (all)	9	11	
Bone pain			
subjects affected / exposed	11 / 237 (4.64%)	6 / 118 (5.08%)	
occurrences (all)	13	7	
Infections and infestations			
Oral herpes			
subjects affected / exposed	22 / 237 (9.28%)	7 / 118 (5.93%)	
occurrences (all)	24	7	
Oral candidiasis			
subjects affected / exposed	8 / 237 (3.38%)	11 / 118 (9.32%)	
occurrences (all)	8	11	
Bacterial infection			
subjects affected / exposed	12 / 237 (5.06%)	6 / 118 (5.08%)	
occurrences (all)	17	6	
Pneumonia			
subjects affected / exposed	15 / 237 (6.33%)	3 / 118 (2.54%)	
occurrences (all)	15	3	
Folliculitis			
subjects affected / exposed	10 / 237 (4.22%)	6 / 118 (5.08%)	
occurrences (all)	10	6	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	83 / 237 (35.02%)	21 / 118 (17.80%)	
occurrences (all)	115	32	
Hyperglycaemia			
subjects affected / exposed	22 / 237 (9.28%)	11 / 118 (9.32%)	
occurrences (all)	22	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:

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-myelosuppresive chemotherapy regimen that may have impacted the primary endpoint analysis.

Notes: