Name of Sponsor/Company: Astellas Pharma Europe Ltd		
Name of Finished Product: Micafungin		
Name of Active Ingredient: Micafungin (FK463)		

Synopsis

Title of Study: An Exploratory Study to Compare the Efficacy and Safety of Micafungin as a Pre-emptive Treatment of Invasive Candidiasis versus Placebo in High Risk Surgical Subjects with Intra-abdominal Infections - A Multicentre, Randomized, Double-Blind Study (9463-EC-0002)

Investigators/Coordinating Investigators: [redacted], Belgium; [redacted], Germany

Study Center(s): 53 sites from 17 countries in Europe

Publication Based on the Study: None

Study Period: 16 months

Study Initiation Date (Date of First Enrollment): July 13, 2010

Study Completion Date (Date of Last Evaluation): December 15, 2011

Phase of Development: Phase II

Objectives: The primary objective was to assess the incidence and the time to confirmed IFI (Invasive Fungal Infection) in patients treated pre-emptively with micafungin versus placebo. The secondary objectives were to assess efficacy, [redacted], safety and tolerability, [redacted] in patients treated pre-emptively with micafungin versus placebo.

Methodology: This was an exploratory, multicenter, randomized (1:1), double-blind, parallel-arm study comparing pre-emptive treatment with micafungin versus placebo in high risk surgical patients. Patients who presented with either localized or generalized intra-abdominal infection that required surgery and who stayed on the ICU were assessed for eligibility into the study. Patients presenting with intra-abdominal infections were divided into two main sub-populations and had different risks for fungal infection and poor outcome:

1. Patients who presented with an infection prior to hospital admission and which was the reason for admission, or with an infection that became evident ≤ 48 hours after hospital admission, were classified as having community acquired intra-abdominal infection (CAI).

2. Patients in whom the infection was not present at hospital admission but became evident ≥ 48 hours after hospital admission and who were hospitalized for a reason other than their intra-abdominal infection were classified as having nosocomial intra-abdominal infection (NAI).

Number of Patients (Planned, Enrolled and Analyzed): Planned: 250 (125 patients per treatment arm). Screened: 271 patients. Enrolled: 252 patients. Safety analysis set: 248 patients. Full analysis set: 241 patients . Per Protocol Set: 167.

Diagnosis and Main Criteria for Inclusion and Exclusion: Potential patients for this study were those who were at high risk of IFI presenting with intra-abdominal infection that required surgery and an ICU stay. Two

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sub-populations were defined: community acquired intra-abdominal infection (CAI) and nosocomial intra-abdominal infection (NAI). Patients were eligible for the study if all of the following applied: ≥ 18 years of age; localized or generalized intra-abdominal infection requiring surgery and ICU stay; if CAI, at least 72 hours (but not more than 120 hours) of ICU stay, counted from the end of surgery, and a further expected duration of ICU stay of ≥ 48 hours; if NAI, duration of ICU stay ≤ 48 hours; counted from the end of surgery, and a further expected duration of ICU stay of ≥ 48 hours; female patients of childbearing potential must have had a negative urine or serum pregnancy test prior to randomization and must have agreed to maintain highly effective birth control during the study; the patient had been fully informed and had given written informed consent to participate in the study. Witnessed informed consent was accepted in case the patient was capable of making the decision but not capable of signing the document.

Patients were excluded from participation if any of the following applied: Acute pancreatitis; neutropenia (ANC <1,000/mm^3) at the time of randomization; infected intra-peritoneal dialysis; patients undergoing solid organ transplantation, documented invasive candidiasis at the time of randomization, expected survival < 48 hours; any systemically active anti-fungal within 14 days prior to administration of the study drug; allergy, hypersensitivity, or any serious reaction to an echinocandin anti-fungal or any of the study drug excipients; received and/or had taken an investigational drug within 28 days prior to randomization; pregnant woman or breast-feeding mother; 'Do Not Resuscitate' order, severe liver insufficiency, advanced liver fibrosis, cirrhosis or hepatitis.

Test Product, Dose and Mode of Administration, Batch Numbers: Patients received intravenous micafungin 100 mg/day infused in 0.9% sodium chloride over one hour. Batch numbers used were [redacted] and [redacted].

Duration of Treatment (or Duration of Study, if applicable): Study medication was to be continued until one of the following events occurs: Sufficient improvement of surgical condition as indicated by the recovery of GI function allowing introduction of enteral feeding of at least 50% of daily calorie requirement, confirmation of IFI, administration of alternative anti-fungal therapy or death. Treatment was continued until an event described above occurred or for a maximum of 6 weeks.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo patients received 100 mL of 0.9% sodium chloride.

Criteria for Evaluation: The co-primary efficacy variables were the incidence of confirmed IFI at the EOT assessment visit, as assessed by the IDRB and the time from baseline to the first confirmation of IFI, as assessed by the IDRB. The composite endpoint was defined as confirmation of IFI as assessed by the IDRB at the EOT assessment visit and/or administration of alternative anti-fungal therapy as determined by the investigator.

The safety evaluations included adverse event assessments, clinical laboratory evaluations, vital sign assessments and physical examinations.

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Statistical Methods: Two analysis sets were used for the efficacy analysis, namely the Full Analysis Set (FAS) and the Per Protocol Set (PPS). Patients were analyzed according to the treatment they actually received. Patients were also analyzed according to the actual type of intra-abdominal infection arm (CAI or NAI) they belonged to. The Safety Analysis Set (SAF) was used for the safety analysis.

For continuous variables, descriptive statistics included the number of patients (n), mean, standard deviation, median, minimum and maximum. For continuous laboratory parameters, vital signs, and the EQ-5D summary index and VAS, quartiles were provided in addition. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e. added up to 100%.

Summary of Results/Conclusions:

Population:

A total of 248 patients were included in the SAF, 241 in the FAS and 167 in the PPS (Table 1). The most common reasons for being excluded from the PPS were < 3 days of study medication, not in designated study drug window, major protocol violation.

The baseline demographics were well-matched between the two arms, although a higher proportion of females than males were recruited. A summary of the data is provided in Table 2.

Approximately two-thirds of patients had NAI. Less than 10% underwent additional surgery after index surgery. A summary of the data is provided in (Table 3).

The majority of patients (77.2%) received the study drug from 3 to 14 days (median = 6 days), whereas 11.6% received the drug for less than 3 days and only 11.2% received the study drug for longer than 14 days (Table 4). Treatment arms compared favorably in regard to study drug exposure.

Efficacy Results:

Incidence of Confirmed IFI (IDRB) at EOT Assessment Visit (FAS)

Overall, 11 (8.9%) patients in the placebo arm and 13 (11.1%) patients in the micafungin arm had a confirmed IFI at EOT as evaluated by the IDRB (Table 5). IFIs confirmed by the IDRB are summarized in (Table 6).

The estimated difference in incidence between patients on micafungin and placebo (micafungin – placebo) and a two-sided 95% confidence interval (CI) for this estimated difference (Newcombe-Wilson method) [Newcombe and Wilson, 1998] was 2.24% (-5.52%, 10.20%). Since the 95% CI included 0 there was no evidence to suggest a meaningful difference in treatment with respect to the incidence of confirmed IFI (IDRB).

Further consideration of Table 5 indicates the most common reason for EOT (End of Treatment) was sufficient improvement in surgical condition (62.9% and 64.1% in the placebo and micafungin arms, respectively).

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EOT due to death occurred more frequently in the micafungin arm than in the placebo arm with 5 (4.3%) and 1 (0.8%), respectively. A summary of the 6 subjects is provided in (Table 7). None of the deaths were considered to be related to the study drug by the investigator.

Time to Confirmed IFI (IDRB) (FAS)

The results of the AFT (Accelerated Failure Time) model fitted to time to confirmed IFI (IDRB) data are described in (Table 8).

The acceleration factor and 95% CI for micafungin relative to placebo was 0.69 (0.34, 1.38). Since the CI included 1 there was no evidence to suggest one treatment was better than the other. However, the point estimate implies that placebo decelerated the time to confirmed IFI (IDRB) in patients by a factor of about 1.5 [i.e. 1/0.69)]; i.e. the median time to confirmed IFI (IDRB) for a patient on placebo was about 1.5 times the median time to confirmed IFI (IDRB) for a patient on micafungin 100 mg.

The acceleration factor and 95% CI for arm for CAI relative to NAI was 2.20 (0.84, 5.75). Since the CI included 1 there was no evidence to suggest one arm behaved differently from the other. The point estimate implies that being in the CAI arm decelerated the time to confirmed IFI (IDRB) in patients by a factor of 2.20; i.e. the median time to confirmed IFI (IDRB) for a patient in the CAI arm was 2.20 times the median time to confirmed IFI (IDRB) for a patient in the NAI arm.

Incidence of Composite Endpoint at EOT Assessment Visit (FAS)

The composite endpoint (i.e. incidence and time to either the confirmed IFI or to administration of alternative anti-fungal therapy) was analyzed using the same analyses described for the primary analysis (Table 9).

There was a slightly higher incidence of confirmed IFI (IDRB) in the micafungin arm (11.1%) vs. the placebo arm (8.9%), whereas a slightly lower use of alternative antifungal therapy incidence was seen in the micafungin arm (4.3%) vs. placebo arm (6.5%). The number of events and incidence of the composite endpoint at the EOT assessment visit for patients on micafungin and placebo in the FAS was 18 (15.4%) and 19 (15.3%), respectively. The estimated difference in incidence between patients on micafungin and placebo (micafungin – placebo) and a two-sided 95% CI [Newcombe and Wilson, 1998] was 0.1% (-9.09%, 9.34%). The 95% CI included 0 and therefore there was no evidence to suggest a meaningful difference in treatment with respect to the incidence of the composite endpoint.

[redacted]

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[redacted]

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Safety Results:

Summary of Adverse Events

A summary table of treatment-emergent adverse events is presented in (Table 16). Treatment-emergent adverse events were reported for 82 (67.2%) patients randomized to receive micafungin and in 104 (82.5%) patients randomized to receive placebo. Adverse events led to death in 15 (12.3%) patients in the micafungin arm compared to 12 (9.5%) patients in the placebo arm.

Serious treatment-emergent adverse events were reported in 29 (23.8%) patients in the micafungin arm compared to 33 (26.2%) patients in the placebo arm. A total of 19 (15.6%) patients in the micafungin arm discontinued the study due to adverse events compared to 22 (17.5%) in the placebo arm.

A tabulation of treatment-emergent adverse events with an incidence rate of at least 5% by Trial Treatment is presented in (Table 17). Overall, the most common adverse events that occurred during either micafungin or placebo treatment were associated with the general disorders and administration site conditions SOC (pyrexia 13.5% placebo arm), the infections and infestations SOC (wound infections 11.1% placebo arm), and the gastrointestinal disorders SOC (vomiting 10.7% micafungin arm).

In all of these adverse events, with the exception of anemia, the highest frequency was observed in the placebo arm.

Adverse events that were considered to be treatment-related occurred at a low frequency in these patients.

A total of 8.2% of patients in the micafungin arm had treatment-emergent adverse events considered by the investigator to be related to treatment compared to 11.9% of patients in the placebo arm. Of these only systemic *candida* was reported in 2 or more patients in the micafungin arm compared to the placebo arm.

Deaths

There were a total of 59 deaths reported during the trial; 31 (25.4%) were reported in patients in the micafungin arm and 28 (22.2%) were reported in patients in the placebo arm.

Of the total of 59 deaths that occurred during the study, only one event (of cardio-respiratory arrest due to multi-organ failure due to severe septic shock) was considered by the investigator to be possibly related to micafungin treatment. The remaining deaths were all considered not related to treatment (either micafungin or placebo).

Adverse Events Leading to Death

There were a total of 27 adverse events that had an outcome of death, 15 (12.3%) patients in the micafungin arm and 12 (9.5%) patients in the placebo arm (Table 16).

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CONCLUSIONS:

Efficacy Conclusions

Two hundred and fifty-two patients were randomized into the study, of which 248 received study drug. The demographics and baseline characteristics of patients were well balanced between the study arms, with approximately two-thirds of patients in each arm being diagnosed with nosocomial intra-abdominal infection and one-third with community-acquired intra-abdominal infection. Overall, the majority of patients received up to 14 days of study therapy.

Analysis of the primary variable of incidence of confirmed IFI at the end of treatment, as assessed by the IDRB, did not reveal a meaningful difference between study arms (incidences of 8.9% and 11.1% for the placebo and micafungin arms, respectively, in the FAS). This was consistent with the findings in the PPS, although in this analysis set the incidences of confirmed IFI were lower for both arms (5.7% and 6.3% for placebo and micafungin arms, respectively), compared to the FAS. In the analysis of time to confirmed IFI the median time to confirmed IFI was 1.25 to 1.5 times longer (for PPS and FAS, respectively) in the placebo arm, compared to the micafungin arm.

The incidence of the composite endpoint (defined as confirmed IFI and/or administration of alternative anti-fungal therapy) was almost identical for both treatment arms, while the median time to the composite endpoint was 1.2 times longer for patients on placebo, compared to the micafungin arm.

[redacted]

Safety Conclusions

Overall during the study, there were more deaths reported in patients in the micafungin arm than in the placebo arm: 31 (25.4%) vs 28 (22.2%) respectively. Of these, only one event (of cardio-respiratory arrest due to multi-

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organ failure due to severe septic shock) was considered by the investigator to be possibly related to micafungin treatment. The remaining deaths were all considered not related to treatment (i.e. either micafungin or placebo).

A lower proportion of patients in the micafungin arm had TEAEs than in the placebo arm: 67.2 vs 82.5% respectively.

However, a higher proportion of AEs led to death in the micafungin arm than in the placebo arm; 12.3% (n = 15) vs 9.5% (n = 12) respectively.

Serious TEAEs were reported in a similar proportion of patients in the micafungin and placebo arms respectively; 23.8% vs 26.2%. None of the events were considered by the investigator to be definitely related to treatment.

Similar proportions of patients had AEs leading to discontinuation in the micafungin and placebo arms respectively: 15.6% vs 17.5%.

The only common TEAE that was reported with a greater than 2% incidence in the micafungin arm compared to the placebo arm was anemia (blood and lymphatic system disorders SOC): 10.7% vs 7.1% respectively.

A total of 8.2% of patients in the micafungin arm had TEAEs considered by the investigator to be related to treatment compared to 11.9% of patients in the placebo arm. Of these only systemic candida was reported in 2 or more patients in the micafungin arm compared to the placebo arm.

There were no clinically significant differences between study treatments for mean values for biochemistry, hematology or urinalysis parameters analyzed between baseline and the end of the study.

Date of Report: 25 March 2013

Table 1 Patient Disposition

	Population		Total n (%)
	Placebo n (%)	Micafungin n (%)	
Screened	NA	NA	271
Randomized	127 (100)	125 (100)	252 (100)
Safety Analysis Set	126 (99.2)	122 (97.6)	248 (98.4)
Full Analysis Set	124 (97.6)	117 (93.6)	241 (95.6)
Per Protocol Set	88 (69.3)	79 (63.2)	167 (66.3)

NA: not applicable

Sources: Tables 12.1.1.1 and 12.1.1.2.1

Table 2 Demographic Characteristics (FAS)

Demographic Characteristic	Placebo (n=124) n (%)	Micafungin (n=117) n (%)	TOTAL (n=241) n (%)
Male	41 (33.1)	50 (42.7)	91 (37.8)
Female	83 (66.9)	67 (57.3)	150 (62.2)
Age (18-65 years)	63 (50.8)	66 (56.4)	129 (53.5)
Age (> 65 years)	61 (49.2)	51 (43.6)	112 (46.5)
Mean Age (yrs, SD)	63.0 (15.84)	61.6 (14.81)	62.3 (15.34)
Mean Weight (kg, SD)	81.47 (25.31)	77.99 (19.03)	79.80 (22.53)
White	121 (97.6)	114 (97.4)	235 (97.5)
Black	1 (0.8)	0	1 (0.4)
Asian	0	2 (1.7)	2 (0.8)
Other	2 (1.6)	1 (0.9)	3 (1.2)
Mean Height (cm, SD)	169.72 (9.42)	169.17 (9.99)	169.46 (9.68)
Mean BMI (kg/m^2, SD)	28.09 (8.01)	27.44 (6.52)	27.78 (7.33)

BMI: Body mass index

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of stud y drug and who did not have a confirmed IFI prior to baseline.

Source: Table 12.1.2.1.1

Table 3 Baseline Characteristics for Patients (FAS)

	Placebo (n=124) n (%)	Micafungin (n=117) n (%)	TOTAL (n=241) n (%)
Type of Intra-Abdominal Infection			
CAI	45 (36.3)	41 (35.0)	86 (35.7)
NAI	79 (63.7)	76 (65.0)	155 (64.3)
Duration of intra-abdominal infection (days, SD)	4.11 (3.42)	4.51 (4.38)	4.30 (3.91)
Occurrence of Surgery			
Before index surgery	7 (5.6)	9 (7.7)	16 (6.64)
Index surgery	122 (98.4)	116 (99.1)	238 (98.8)
After index surgery	10 (8.1)	11 (9.4)	21 (8.71)

CAI: Community Acquired Intra-Abdominal Infection; NAI: Nosocomial Intra-Abdominal Infection

Index Surgery: the Initial Surgery for Patients Diagnosed with CAI or NAI.

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of stud y drug and who did not have a confirmed IFI prior to baseline.

Sources: Table 12.1.2.2.1 and Table 12.1.3.3.1.

Table 4 Summary of Study Drug Exposure (FAS)

Duration in Days	Placebo (n=124) n (%)	Micafungin (n=117) n (%)	TOTAL (n=241) n (%)
< 3	12 (9.7)	16 (13.7)	28 (11.6)
≥ 3 to ≤ 7	64 (51.6)	66 (56.4)	130 (53.9)
> 7 to ≤ 14	34 (27.4)	22 (18.8)	56 (23.2)
> 14 to ≤ 21	7 (5.6)	8 (6.8)	15 (6.22)
> 21 to ≤ 28	4 (3.2)	2 (1.7)	6 (2.49)
> 28 to ≤ 35	2 (1.6)	1 (0.9)	3 (1.24)
> 35 to ≤ 42	1 (0.8)	2 (1.7)	3 (1.24)
> 42	0	0	0
Mean	8.3	7.7	NA
SD	6.87	6.8	
Median	6	6	

NA: not applicable

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of stud y drug and who did not have a confirmed IFI prior to baseline.

Source: Table 12.2.1.1

Table 5 Incidence of Confirmed IFI (IDRB) at EOT Assessment Visit (FAS)

Reason for EOT	Placebo (n=124) n (%)	Micafungin 100 mg (n=117) n (%)	Estimated Treatment Difference (Micafungin – Placebo) (%)	Newcombe-Wilson 95% CI † (%)
Confirmed IFI (IDRB)	11 (8.9)	13 (11.1)	2.2	(-5.5, 10.2)
No confirmed IFI (IDRB)	113 (91.1)	104 (88.9)	NA	
Sufficient improvement ‡	78 (62.9)	75 (64.1)	NA	NA
Alternative antifungal therapy §	8 (6.5)	5 (4.3)	NA	NA
Death	1 (0.8)	5 (4.3)	NA	NA
Other reason for EOT	25 (20.2)	18 (15.4)	NA	NA
Max. 6 weeks treatment	1 (0.8)	1 (0.9)	NA	NA
Not evaluable ¶	0	0	NA	NA

EOT: End of Treatment; IDRB: Independent Data Review Board; IFI: Invasive Fungal Infection; NA: Not applicable

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of study drug and who did not have a confirmed IFI prior to baseline.

† Two-sided 95% CI, Newcombe-Wilson method, 1998.

‡ Sufficient improvement of surgical condition as indicated by the recovery of GI function allowing introduction of enteral feeding of at least 50% of daily calorie requirement.

§ Administration of alternative antifungal therapy as determined by the investigator (Note: start date determined by the IDRB).

¶ No fungal infection assessment by the IDRB possible at EOT assessment visit.

Source: Table 12.3.1.1

Table 6 Summary of All Breakthrough IFIs for Patients with Confirmed IFIs by the IDRB at EOT Assessment Visit

Patient ID	Treatment Group	Blood IFI	Other IFI
[redacted]	Micafungin	Yeast Sp. nos	Candida sp. nos
[redacted]	Micafungin	Candida albicans	Candida albicans
[redacted]	Micafungin	†	Candida albicans Candida sp. nos
[redacted]	Micafungin	†	Candida albicans
[redacted]	Micafungin	†	Candida albicans
[redacted]	Micafungin	†	Candida albicans
[redacted]	Micafungin	†	Aspergillus fumigatus Candida parapsilosis Yeast Sp. nos
[redacted]	Micafungin	†	Candida albicans
[redacted]	Micafungin	Candida sp. nos	Candida sp. nos Yeast Sp. nos
[redacted]	Micafungin	Candida sp. nos	†
[redacted]	Micafungin	Candida albicans	†
[redacted]	Micafungin	Candida Glabrata	†
[redacted]	Micafungin	†	Candida albicans Yeast Sp. nos
[redacted]	Placebo	†	Candida Glabrata Candida albicans
[redacted]	Placebo	†	Candida albicans Candida tropicalis
[redacted]	Placebo	Candida sp. nos	Candida parapsilosis Candida tropicalis
[redacted]	Placebo	Candida albicans	†
[redacted]	Placebo	Candida Glabrata	Candida albicans Candida glabrata
[redacted]	Placebo	†	Candida albicans Candida sp. nos
[redacted]	Placebo	†	Candida albicans Candida dubliniensis Yeast Sp. nos
[redacted]	Placebo	†	Candida albicans Candida dubliniensis Candida glabrata Yeast Sp. nos
[redacted]	Placebo	Candida parapsilosis	†
[redacted]	Placebo	Candida sp. nos	†
[redacted]	Placebo	†	Candida sp. nos

IFI: invasive fungal infection; nos: not otherwise specified; sp: species.

† Indicate no growth observed or no IFIs identified as not all patients were identified with both blood and other IFIs.

Source: Appendices 13.2.6.1, 13.2.6.2 and 13.2.6.3

Table 7 Summary of Patients Who had EOT Due to Death

Patient ID	Treatment Group	Sequence of Events Leading to Death
[redacted]	Micafungin	On [redacted] the patient was diagnosed with intra-abdominal infection and operated on [redacted]. [redacted] was first exposed to the study drug on [redacted] and received 4 doses of study drug. [redacted] experienced a not related, severe, serious, Septic shock on [redacted] The Septic shock led to death.
[redacted]	Micafungin	On [redacted] the patient was diagnosed with intra-abdominal infection and was operated on [redacted]. This subject entered the study on [redacted]. [redacted] was first exposed to the study drug on [redacted] and received one dose of study drug. [redacted] experienced a not related, severe, serious, Septic shock started on [redacted] and ended on [redacted]. The Septic shock led to death.
[redacted]	Micafungin	On [redacted] the patient was diagnosed with intra-abdominal infection and had the following operations: [redacted] The patient required [redacted] on [redacted] for metabolic acidosis, acute on chronic renal failure and [redacted] from [redacted] (day 1) to [redacted] (day 3) for metabolic acidosis. This subject entered the study on [redacted] when [redacted] was first exposed to the study drug and received 2 doses of study drug. The patient experienced several adverse events which started on [redacted], all were severe and not related: Cyanosis; epidermolysis; haematoma; multi-organ failure; skin necrosis and shock. The Shock ended on [redacted] and led to death.
[redacted]	Micafungin	On [redacted] the patient was diagnosed with intra-abdominal infection and operated on [redacted]. This subject entered the study on [redacted]. [redacted] was first exposed to the study drug on [redacted] and received 7 doses of study drug. The patient had a not related, severe, serious, Multi-organ disorder which started on [redacted] and ended on [redacted]. The Multi-organ disorder led to death.
[redacted]	Micafungin	On [redacted] the patient was diagnosed with intra-abdominal infection. On [redacted] the patient was operated on [redacted] This subject entered the study on [redacted]. He was first exposed to the study drug on [redacted] and received 25 doses of study drug. The patient experienced a not related, severe, serious, cardiac arrest on [redacted]. The Cardiac arrest led to death.
[redacted]	Placebo	The patient received 3 doses of study drug and died on study day 4 from a not related serious cardiac arrest which led to death.

Sources: Attachment 1 and Appendix 13.2.7.

Table 8 Time to Confirmed IFI (IDRB) – Accelerated Failure Time (AFT) Model (FAS)

	Model Comparisons			
	Treatment: Micafungin vs. Placebo		Type of Intra-Abdominal Infection (Arm): CAI vs. NAI	
Estimate Labels	**Placebo (n=124)**	**Micafungin (n=117)**	**CAI (n=86)**	**NAI (n=155)**
Estimated parameter (SE)	-0.38 (0.356)		0.79 (0.491)	
Acceleration factor	0.69		2.20	
95% CI	(0.34; 1.38)		(0.84; 5.75)	

CAI: Community Acquired Intra-Abdominal Infection; NAI: Nosocomial Intra-Abdominal Infection

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of stud y drug and who did not have a confirmed IFI prior to baseline.

Source: Table 12.3.1.2

Table 9 Incidence of Composite Endpoint (Confirmed IFI and/or Administration of Alternative Anti-Fungal Therapy) at EOT Assessment Visit (FAS)

Reason for EOT	**Placebo (n=124) n (%)**	**Micafungin (n=117) n (%)**	**Estimated Difference (Micafungin - Placebo) (%)**	**Newcombe-Wilson 95% CI ‡ (%)**
Event of Interest †				
Confirmed IFI (IDRB)	11 (8.9)	13 (11.1)	0.06	(-9.09, 9.34)
Alternative antifungal therapy §	8 (6.5)	5 (4.3)	NA	NA
EOT without event of interest	105 (84.7)	99 (84.6)	NA	NA
Sufficient improvement ¶	78 (62.9)	75 (64.1)	NA	NA
Death	1 (0.8)	5 (4.3)	NA	NA
Other reason for EOT	25 (20.2)	18 (15.4)	NA	NA
Max. 6 weeks of treatment	1 (0.8)	1 (0.9)	NA	NA
Not evaluable ††	0	0	NA	NA

CI: Confidence Interval; EOT: End of Treatment; IDRB: Independent Data Review Board; IFI: Invasive Fungal Infection; NA: Not applicable

The Full analysis set (FAS) was defined as all randomized patients who received at least one dose of stud y drug and who did not have a confirmed IFI prior to baseline.

† Event of interest is defined as confirmed IFI (IDRB) or administration of alternative antifungal therapy up to EOT assessment visit.

‡ Two-sided 95% CI, Newcombe-Wilson method, 1998.

§ Administration of alternative antifungal therapy as determined by the investigator (Note: start date determined by the IDRB).

¶ Sufficient improvement of surgical condition as indicated by the recovery of GI function allowing introduction of enteral feeding of at least 50% of daily calorie requirement.

†† No fungal infection assessment by the IDRB possible at EOT assessment visit.

Sources: Table 12.3.3.1.1 and Appendix 13.2.6.1

Table 10 [redacted]

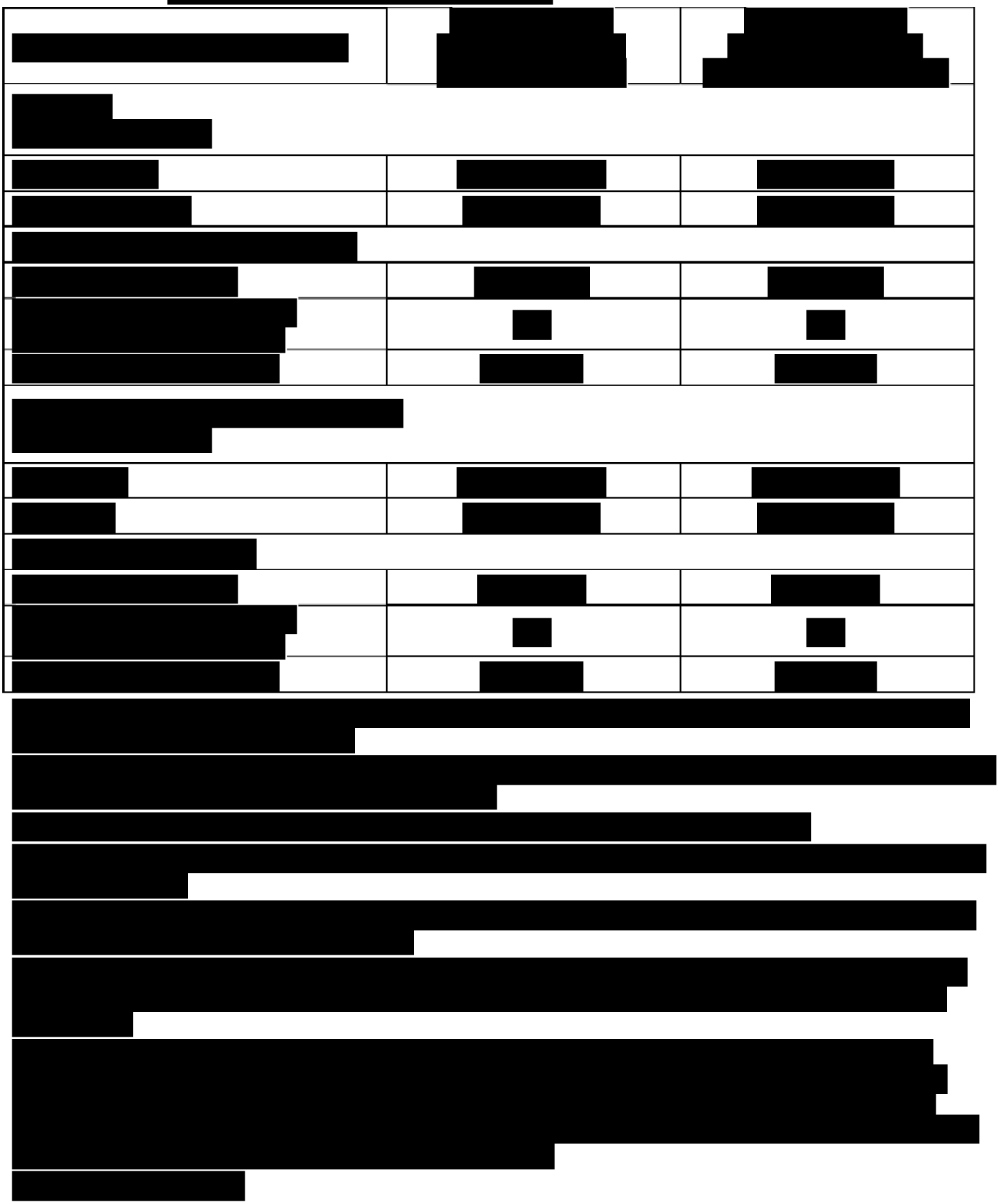

Table 11

Table 12

Table 13

Table 14

Table 15

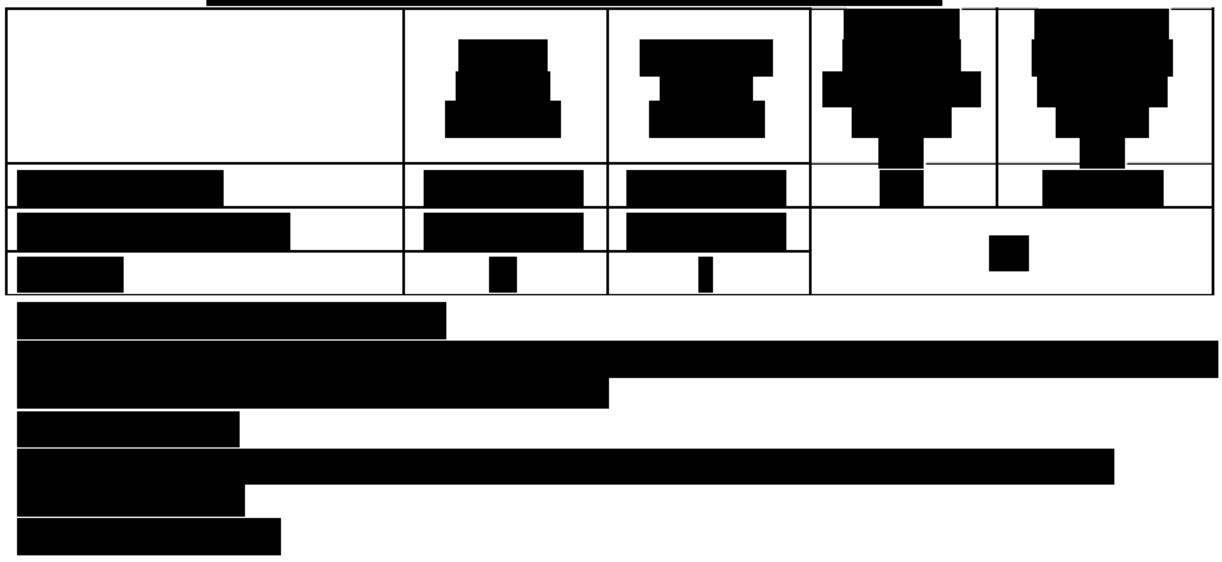

Table 16 Summary Table of Treatment-emergent Adverse Events (SAF)

	Placebo n=126 n (%)	**Micafungin n=122 n (%)**
TEAE	104 (82.5%)	82 (67.2%)
Drug-related TEAE	15 (11.9%)	10 (8.2%)
Deaths	12 (9.5%)	15 (12.3%)
Serious TEAE	33 (26.2%)	29 (23.8%)
Drug-related Serious TEAE	2 (1.6%)	1 (0.8%)
TEAEs leading to permanent discontinuation of study drug	22 (17.5%)	19 (15.6%)
Drug-related TEAEs leading to permanent discontinuation of study drug #	8 (6.3%)	4 (3.3%)

TEAE: treatment-emergent adverse event

The safety analysis set (SAF) was defined as all randomized patients who received at least one dose of study medication, including those patients with confirmed IFI at baseline as assessed by the IDRB.

Number possible or probable as assessed by the investigator, or records where relationship is missing

Source: Table 12.6.1.1

Table 17 Summary of Common Treatment-emergent Adverse Events with an Incidence Rate of at Least 5% by Trial Treatment (SAF)

MedDRA (v 12.1) System-Organ Class Preferred Term	**Placebo (n=126) n (%)**	**Micafungin (n=122) n (%)**
Overall	54 (42.9)	34 (27.9)
Blood and lymphatic system disorders Anemia	9 (7.1)	13 (10.7)
Gastrointestinal disorders Vomiting	11 (8.7)	4 (3.3)
General disorders and administration site conditions Pyrexia	17 (13.5)	6 (4.9)
Infections and infestations Wound infection	14 (11.1)	4 (3.3)
Metabolism and nutrition disorders Hypokalemia	8 (6.3)	5 (4.1)
Respiratory, thoracic and mediastinal disorders Pleural effusion	12 (9.5)	6 (4.9)
Vascular disorders Hypotension	8 (6.3)	6 (4.9)

TEAE: treatment-emergent adverse event

The safety analysis set (SAF) was defined as all randomized patients who received at least one dose of study medication, including those patients with confirmed IFI at baseline as assessed by the IDRB.

Source: Table 12.6.1.11