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: -

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, organ dysfunction, safety and tolerability, survival and health economic variables 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).


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 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/mm³) 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 BX1002906 and BX1004083.

**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.

**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
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). 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.

**Persistence of Fungal Colonization (FAS)**

Table 10 presents the proportion of patients during treatment and at EOT who had at least one persistent colonization for each treatment and arm. Estimated odds ratios from the respective logistic regression models are also presented. The persistence of colonization during treatment and EOT in comparison to baseline remained approximately the same in the micafungin arm (23.9% vs. 24.1%) whereas in the placebo arm it increased slightly from 30.5% at baseline to 34.0% at EOT. The incidence of persistent colonization in the NAI and CAI arms was similar during treatment (26.6% vs. 29.0%) and at the EOT assessment visit (27.8% vs. 31.9%).

Estimated odds ratios for the treatment comparison micafungin vs. placebo during treatment (OR = 0.71; 95% CI = 0.38, 1.36) and at EOT (OR = 0.62; 95% CI = 0.32, 1.19) provide no evidence to suggest one treatment acts differently from the other with respect to persistent fungal colonization (i.e. all 95% CIs included 1); estimated odds ratio point estimates show that patients taking placebo were 1.41 and 1.61 times more likely than patients taking micafungin 100 mg, respectively, to have at least one persistent colonization.

**Changes in Sequential Organ Failure Assessment (SOFA) Score Over Time (FAS)**

SOFA score showed a similar change from baseline for both arms with a trend towards slightly greater improvement in the micafungin arm from Day 28 onwards (Table 11).

**Need for Re-Intubation, Renal Support and Vasopressor Support (FAS)**

There was not a large need for re-intubation or renal support; vasopressor support was required more than either (61.3 % and 56.4% in the placebo and micafungin arms, respectively). The need for re-intubation, renal support and vasopressor support were all required less in the micafungin arm (Table 12).

**Surgery/Interventions After Index Surgery (FAS)**
The index surgery for each patient was formally defined as the first surgery (from the Surgery Information panel of the CRF) that was on or after the intra-abdominal infection onset date (from the Baseline, Intra-Abdominal Infection Medical History panel of the CRF). Therefore, (i) any subsequent surgery on the Surgery Information panel (i.e. surgery after the index surgery) was considered as ‘Other Surgery’. Also, (ii) ‘Other Surgery’ was sometimes recorded on the Non-Medication Therapy and Procedures panel of the CRF. As such surgeries were not always easily identifiable they were flagged in a separate exercise on medical review. Therefore this panel provided data for ‘Other Surgery’ as well as data for ‘Interventions’.

Patients requiring surgery and interventions after index surgery were similar in both arms (Table 13).

**Overall Survival at End of Study Visit / Long Term Follow-Up (FAS)**

Overall survival is defined as a binary yes/no response to the question ‘Is the patient alive at D+28?’ and ‘Is the patient alive at D+90?’.

At EOS there was a comparable proportion of patients alive in both placebo (80.7%) and micafungin (79.8%) arms, whereas a slightly lower proportion of patients with NAI (78.1%) compared to CAI (84.1%) survived at EOS. Similar findings were at LTFU (Table 14).

**Incidence of Fungal-Free Survival up to EOS Visit (FAS)**

The incidence of Fungal-Free Survival up to EOS Visit (D+28) was similar in the two treatment arms (Table 15). The estimated difference in incidence between patients on micafungin and placebo (micafungin – placebo) and two-sided 95% confidence interval (CI) [Newcombe-Wilson, 1998] was -3.0% (-14.7, 8.6).

**ICU-Free Days (D1 to D+28) (FAS)**

The incidence rate of ICU-free days was higher in the micafungin arm than in the placebo arm; however, the incidence rate ratio and 95% CI for treatment was 1.13 (0.92, 1.38) and confirmed any apparent difference in incidence rates could be considered negligible and that there was no evidence to suggest one treatment behaved differently from the other.

**Organ Failure-Free Days (D1 to D+) (FAS)**

Similarly, the incidence rate of organ failure-free days was higher in the micafungin arm than in the placebo arm; however, the incidence rate ratio and 95% CI for treatment was 1.12 (0.99, 1.28) and confirmed any apparent difference in incidence rates could be considered negligible and that, once again, there was no evidence to suggest one treatment behaved differently from the other.

**Incidence of Nosocomial Pneumonia at EOT (FAS)**

The majority of patients did not have nosocomial pneumonia (96.5% in the micafungin arm and 95.0% in the placebo arm). The number of events and incidence of nosocomial pneumonia at the EOT assessment visit for patients on micafungin and placebo in the FAS was 3 (3.5%) and 5 (5.0%), respectively. The estimated difference in incidence between patients on micafungin and placebo (micafungin – placebo) and a two-sided 95% confidence interval (CI) [Newcombe-Wilson method, 1998] was -1.5 (-8.0, 5.4).

**Health Economic Assessment of Resource Use (FAS)**
X-ray and CT scans were the most widely used diagnostic procedures throughout the trial. Peripheral blood cultures were the most prevalent in the pre-investigational period, treatment period and follow-up period and accounted for at least 55% of the patients in each arm in all periods. The most common other fungal cultures were urine, oropharynx, rectum, peritoneal fluid and other (>15%) in both arms in the investigational period; urine, oropharynx, peritoneal drain and other in the treatment period; and in the follow-up period in the placebo arm, urine, oropharynx, perirectum and other; fewer cultures were taken in the micafungin arm. Surveillance cultures were predominantly accounted for by urine, throat and rectum in both arms in all treatment periods.

The hospitalization period for patients in both arms was similar. In the treatment period, an overall mean of 7.5 days and 8.6 days in the micafungin and placebo arms occurred, respectively, with patients spending a mean of <7 days in ICU in both arms. In the follow-up period an overall mean of 24.5 days and 28.8 days of hospitalization in the micafungin and placebo arms occurred, respectively, with a mean of approximately 16 days in ICU in both arms.
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 in 13.5% placebo arm), the infections and infestations SOC (wound infections in 11.1% placebo arm), and the gastrointestinal disorders SOC (vomiting in 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).

The design and results of this investigational study may include approved and not approved formulations or treatment regimens. Before prescribing any product mentioned in this register, Healthcare professionals should consult prescribing information for the product approved in their country.