SYNOPSIS

Title of Study:

Randomized, Open label, Non-inferiority Study of Micafungin Versus Standard Care for the Prevention of Invasive Fungal Disease in High Risk Liver Transplant Recipients

Investigators/Coordinating Investigator:

Coordinating Investigator: [redacted], [redacted], France.

Study Centers:

This was a multi-center study performed at 37 centers in 14 countries in Europe, Russia and the Middle East.

Publication (reference):

Not applicable.

Study Period:

Date of first enrollment (Study initiation date): 15 December 2009

Date of last evaluation (Study completion date): 03 May 2012

Phase of Development: Phase 3B

Objectives:

The primary objective was to demonstrate non-inferiority of micafungin at a dose of 100 mg/day versus (vs) 'standard care' for the prevention of Invasive Fungal Disease (IFD), in 'high risk' patients undergoing liver transplantation defined according to the revised criteria by the European Organization for Research and Treatment of Cancer / Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).

The secondary objectives were to assess:

- efficacy
- safety and tolerability
- fungal-free survival
- [redacted]

of micafungin vs 'standard care' in 'high risk' subjects undergoing liver transplantation.

Methodology:

This was a phase 3b, multi-center, randomized, open-label study to compare antifungal prophylaxis with micafungin to 'standard care' in liver transplant recipients considered to be at high risk of invasive fungal disease.

Patients satisfying all selection criteria entered the study at admission to the hospital for liver transplantation. Only Patients who were identified to be at 'high risk' at study entry were eligible for randomization after receiving liver transplantation in a 1 to 1 ratio to 1 of the 2 treatment arms: 1) Micafungin 100 mg/day iv (2.0 mg/kg per day in patients weighing ≤ 40 kg), or 2) 'Standard Care', i.e., 1 of the following choices: fluconazole 200 mg to 400 mg iv once daily, or liposomal amphotericin B 1 mg to 3 mg/kg per day, or caspofungin 70 mg single loading dose followed by 50 mg once daily.

Study drugs were initiated no later than 24 hours after randomization and were administered for a period of 21 days, or until hospital discharge, whichever occurred first. In patients with persistence of risk factors a longer duration of prophylaxis was allowed.
Patients who developed a 'proven' or 'probable' IFD during the prophylaxis period discontinued the study drug and received antifungal therapy as deemed appropriate by the investigator. Patients who discontinued study drug did not discontinue the study and completed all follow-up assessments as per protocol. The end of the prophylaxis period (End of Prophylaxis [EOP]) was recorded as the last day of administration of the study drug and the EOP assessments were done at this time as per protocol requirements.
Evaluation of efficacy was conducted at EOP (approximately 21 days) and at the end of the study (EOS; 3 months post-randomization). Additionally, fungal free survival and mortality data were collected at long-term follow-up (LTFU; 6 months post randomization).

Number of Patients (planned, enrolled and analyzed):

Approximately 338 patients were planned to be randomized into the study: 169 in the micafungin and 169 in the 'standard care' arm. A total of 369 patients were screened of which 347 were randomized and took at least 1 dose of the study drug(s); 174 in the micafungin arm and 173 in the 'standard care' arm. Of these 347 patients, 345 were included in the Safety Analysis Set (SAF), 344 in the Full Analysis Set (FAS), and 277 in the Per Protocol Set (PPS).

Diagnosis and Main Criteria for Inclusion:

The study population consisted of men and women, aged ≥ 18 years undergoing orthotopic whole or split liver allograft transplantation. Patients had to be at 'high risk' of invasive fungal infection due to the presence of at least one of the of the following risk factors: Re-transplantation; acute liver failure; pre-operative renal impairment or need for renal replacement therapy; post-operative renal impairment or need for renal replacement therapy within 5 days following liver transplantation; admission to Intensive Care Unit (ICU) for > 48 hours prior to liver transplantation; re-operation (abdominal surgery) within 5 days of liver transplantation; presence of choledocojejunostomy; perioperative (96 hours) colonization with fungi (*Candida* spp.); need for prolonged mechanical ventilation for > 48 hours following liver transplantation; transfusion intraoperatively of ≥ 20 units of cellular blood products. Female patients of childbearing potential had to be negative for pregnancy tests.

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

Micafungin (FK463) lyophilisate (Mycamine®) solution for infusion, 100 mg/day iv or 2.0 mg/kg per day iv in patients weighing ≤ 40 kg. Batch number: [redacted] and [redacted].

Duration of Treatment (or Duration of Study, if applicable):

- Prophylaxis period of 21 days, or until hospital discharge (whichever occurred first), or longer in patients with persistence of risk factors.
- Study period of 3 months post-randomization.
- Long-term follow-up of 6 months post-randomization.

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

'Standard care':

- Fluconazole 200 mg to 400 mg, iv once daily, infused at a rate of approximately 5-10 mL/min.
- Liposomal amphotericin B 1 mg to 3 mg/kg per day, iv infusion over a 30- to 60-minute period.
- Caspofungin: A single 70 mg loading dose on Day 1, followed by 50 mg once daily thereafter (70 mg daily in patients weighing >80 kg), slow iv infusion over approximately 1 hour.

Criteria for Evaluation:

Primary efficacy endpoint was 'clinical success' at the end of the prophylaxis period as assessed by the Independent Data Review Board (IDRB). 'Clinical success' was defined as:

Absence of a 'proven' or 'probable' IFD, (defined according to the EORTC/MSG criteria and as documented on the IDRB CRF) *AND*
No initiation of antifungal treatment (defined as administration of additional antifungal medication or increase in the dose of the study drug due to lack of efficacy).

Secondary efficacy was absence of a 'proven' or 'probable' IFD (IDRB and Investigator assessment) and initiation of systemic antifungal treatment, time to 'proven' or 'probable' IFD (IDRB assessment), fungal free survival (Investigator assessment), and the incidence of colonization (Investigator assessment).

Efficacy was assessed from the fungal infection assessments (cultures, histology and cytology) and radiological imaging assessments.

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Safety was assessed from the recording of (serious) adverse events ([S]AEs), AEs associated with study procedures and graft acute rejection episodes, blood sample analyses (hematology and biochemistry), cultures (blood, urine, throat, and rectal), pregnancy tests, changes in vital signs, and repeated physical examinations. All AE tabulations were presented for treatment-emergent adverse events (TEAEs).

Statistical Methods:

For the primary efficacy analysis, the 'clinical success' rate was compared between the 'standard care' arm and the micafungin arm at the EOP, using the PPS. Two-sided 95% confidence intervals (CIs) for the difference in success rates were calculated using the Newcombe-Wilson method (without continuity correction). If the upper limit of the 95% CI for the difference in success rates was lower than 10%, then the non-inferiority of micafungin to 'standard care' was declared. The primary analysis assumed that the infection rate amongst the individual treatments was homogeneous between prophylaxis regimens. To assess for homogeneity across the 'standard care' arms the clinical success rates for each 'standard care' arm as well as the respective two-sided 95% CIs were provided.
For the secondary analyses of the primary efficacy variable, the primary analysis on the PPS was repeated for the FAS. Further, the primary analysis was repeated by region (i.e., West Europe [Austria, Belgium, Germany, Ireland, United Kingdom, Sweden], East Europe [Hungary, Romania, Russian Federation], and South Europe [France, Italy, Portugal, Spain]).

Two-sided 95% CIs for the difference in success rates of each 'standard care' regimen vs micafungin were provided, overall and by region. The primary variable was also modeled for the FAS and the PPS using logistic regression, with covariates in the model including Model for End-Stage Liver Disease (MELD) score at baseline, and treatment. Risk was assessed using the estimated odds ratio (and associated 95% Wald CI) which provides the estimated odds of success in the micafungin group relative to the estimated odds in the 'standard care' group or the single treatment regimen, respectively.

The secondary efficacy variables, e.g. fungal free survival and incidence of colonization, were described by treatment arm and by treatment regimen using the FAS and the PPS and were repeated for each region. Two-sided 95% CIs for differences between micafungin and 'standard care', and also between micafungin and each 'standard care' regimen were provided. The time to 'proven' or 'probable' IFD by the IDRB and fungal-free survival by the investigator were presented by treatment arm and by treatment regimen using Kaplan-Meier curves. Treatment arms and treatment regimen were compared using the log-rank test. In addition, time to 'proven' or 'probable' IFD was modeled using Cox regression with covariates in the model including MELD score at baseline and treatment arm (micafungin vs 'standard care'). Patients with no 'proven' or 'probable' IFD during the treatment phase were censored at the assessment visit (i.e. for such patients 'time to' constitutes the number of days from day 1 up to EOS assessment visit date).

Data on resource use were evaluated descriptively by treatment arm and treatment regimen using appropriate summary statistics for the FAS and the PPS.

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For the safety analysis, all AEs were summarized. AEs of special interest were all AEs identified using the following Standardized MedDRA Query (SMQ) topics: hepatic and renal AEs, graft rejection and infusion site reactions. The number and percentage of patients with TEAEs were summarized for each treatment arm, regimen and total. Similar summaries were provided for TEAEs within region, drug related TEAEs, TEAEs of special interest, drug-related TEAEs of special interest, serious TEAEs, serious drug-related TEAEs, TEAEs that led to study discontinuation, drug-related TEAEs that led to study discontinuation, TEAEs leading to death, and common TEAEs (i.e., TEAEs that occurred in ≥ 5% of the patients of any treatment regimen). TEAEs and drug-related TEAEs were also summarized by severity and by relationship (all TEAEs only) to study drug. Descriptive statistics for all centrally analyzed laboratory and vital signs examination results including changes from baseline were displayed by time. The physical examination results presentation included the number and percentage of patients with no change, no clinically significant change and clinically significant changes for each body system of physical examination.

Summary of Results/Conclusions:

Population:

A total of 345 patients were included in the SAF, 344 in the FAS and 277 in the PPS (Table 1). The most common reason for being excluded from the PPS was EOP > 3 days after last treatment (45 patients; 13.1%).

The baseline demographics were well-matched between the 2 arms, with exception of the distribution of the MELD scores. A summary of the data is provided in Table 2.

The median duration of exposure was comparable between the treatment arms (20 days in the 'standard care' arm and 18 days in the micafungin arm). The patients received a median number of 20.0 ('standard care' arm) or 18.0 (micafungin arm) infusions (Table 3).

Efficacy Results:

From the PPS 67 patients were excluded in comparison to the FAS due to protocol violations and deviations. Therefore, the results of the PPS do not adequately reflect the medical reality. The current PPS data is thus considered of low value and is only reported for the primary endpoint. The secondary analysis of the primary endpoint and all secondary variables are reported for the FAS only.

<u>Primary Analysis of the Primary Efficacy Variable</u>

The 'clinical success' rate was compared between the 'standard care' arm and the micafungin arm at EOP as assessed by the IDRB using the PPS. A summary of the data is provided in Table 4.

At EOP, the 'clinical success' rates were 98.6% in the micafungin arm and 99.3% in the 'standard care' arm. The difference in the 'clinical success' rate of 0.7% (95% CI: -2.7; 4.4) was in favor of the 'standard care' vs the micafungin arm. Since the upper bound of the 2-sided 95% CI of this difference was < 10% (the apriori selected non-inferiority margin), non-inferiority of micafungin to 'standard care' was concluded.

Secondary Analysis of the Primary Efficacy Variable

The primary analysis on PPS was repeated for the FAS as presented in Table 4.

At the EOP, the 'clinical success' rates were 96.5% in the micafungin arm and 93.6% in the 'standard care' arm. The difference in 'clinical success' rate between the 'standard care' and the micafungin arm was -2.9% (95% CI:-8.0, 1.9), indicating that micafungin is comparable to 'standard care'.

The results by 'standard care' regimen showed at EOP that the 'clinical success' rate was (slightly) higher for micafungin (96.5%) vs fluconazole (93.6%), liposomal amphotericin B (94.4%) as well as caspofungin (91.3%). The differences were thus comparable for micafungin vs fluconazole (-2.9%) and liposomal amphotericin B (-2.1%), and slightly higher for caspofungin (-5.2%). It should be noted that the number of patients in the caspofungin is low. Nevertheless, the upper limits of the 95% CIs of the differences were all below 10%, thus micafungin was comparable to each 'standard care' regimen (Table 5).

Secondary Efficacy Variables – Absence of a 'Proven' Or 'Probable' IFD

The results of the absence of a 'proven' or 'probable' IFD as assessed by the IDRB, i.e., the first component of the composite primary efficacy endpoint, by treatment arm are summarized for the FAS in Table 6.

At EOP a difference in the success rate for the absence of 'proven' or 'probable' IFD in favor of micafungin as compared to 'standard care' was observed (-2.9% [95% CI: -8.0;1.9]). The difference from EOP to EOS Month 3 (EOS M3) and EOS was small and comparable between the time points (0.3% [95% CI: -3.8, 4.8] and 0.1% [95% CI: -3.5, 3.7], respectively). These results indicate that micafungin was comparable to 'standard care' with regard to absence of 'proven' or 'probable' IFD according to the IDRB.

The results of the absence of a 'proven' or 'probable' IFD at EOP as assessed by the investigator, i.e., the first component of the composite primary efficacy endpoint, by treatment arm are summarized for the FAS in Table 7.

At EOP, a small difference in the success rate for the absence of 'proven' or 'probable' IFD in favor of 'standard care' as compared to the micafungin arm was observed (1.2% [95% CI: -5.5, 7.8]). The difference was in favor of the micafungin arm as compared to the 'standard care' arm from EOP up to EOS M3 (-1.1% [95% CI: -5.8, 3.6]) and from EOS to LTFU (-2.1% [95% CI: -5.9, 1.1]). These results indicate that micafungin is comparable to 'standard care' with regard to absence of 'proven' or 'probable' IFD according to the investigator at each time point.

At EOP, the assessment of the success rate by the investigator was confirmed by the IDRB for 160 out of 172 patients (93.0%) in the 'standard care' arm and 157 out of 172 patients (91.3%) in the micafungin arm. Comparable figures were found for the 'standard care' treatment regimens (71/78 [91.0%] for fluconazole, 67/71 (94.3%) for liposomal amphotericin B and 22/23 [95.7%]) for caspofungin.

Secondary Efficacy Variables – Absence of Initiation of Systemic Antifungal Treatment

Results for the absence of initiation of systemic antifungal treatment (defined as administration of additional antifungal medication or increase in the dose of the study drug due to lack of efficacy) according to the IDRB, i.e., the second component of the composite primary efficacy endpoint, until EOP by treatment arm are summarized for the FAS in Table 8.

At EOP, a difference in success rate in favor of micafungin as compared to 'standard care' of -3.0% (95% CI: -7.2, 0.7) was observed. Therefore micafungin is comparable to 'standard care' with regard to absence of initiation of systemic antifungal treatment according to the IDRB.

Secondary Efficacy Variables – Time to 'Proven' or 'Probable' IFD

Cox regression modeling of the time to 'proven' or 'probable' IFD, showed a hazard ratio of 0.721 (Wald 95% CI: 0.274,1.896) for micafungin vs 'standard care, i.e. the time to 'proven' or 'probable' IFD was slightly longer for the micafungin arm vs the 'standard care' arm. However, given the fact that the CI includes 1 there was small difference between the arms.

Secondary Efficacy Variables – Fungal-free Survival

The Kaplan-Meier analysis of fungal-free survival at EOS M3 assessed by the IDRB showed no differences between the treatment arms according to the log-rank test (Chi-square: 0.0193, P = 0.889).

Data on fungal-free survival, i.e., time to IFD or death, at EOS, EOS M3 and at the end of the LTFU according to the investigator by treatment arm are summarized for the FAS in Table 9.

Twenty-three patients in the 'standard care' arm (11 on fluconazole, 10 on amphotericin B and 2 on caspofungin) and 29 patients in the micafungin arm died during the study period (including LTFU).

The differences in fungal-free survival rates between the 'standard care' and the micafungin arm at EOS M3, EOS and at LTFU were relatively small (2.6% [95% CI: -5.9, 11.2], 2.5% [95% CI: -5.9, 10.9] and 1.9% [95% CI: -7.0, 10.9], respectively) in favor of 'standard care'; nevertheless, the accompanying 95% CIs were both just above 10% (the pre-specified general margin) casting some doubt on similarity of the treatments with respect to this variable. Note that relatively more patients in the micafungin arm as compared to 'standard care' were non-evaluable, while failures differed by 2 patients at EOS and EOS M3, and by 1 at LTFU. Further, by contrast, the non-parametric analyses, the Kaplan-Meier analyses, showed no significant difference in time to IFD or death at EOS (Chi-square: 0.0193, P = 0.889) or LTFU (Chi-square: 0.1718, P = 0.679).

Secondary Efficacy Variables – Incidence of Colonization.

The overall incidence of fungal colonization was slightly higher in the micafungin arm (73.8%) as compared to the 'standard care' arm (66.9%). The difference in incidence between the groups was 7.0% (95% CI: -2.7, 16.5).

At EOP, the difference in incidence of emergent fungal colonization as compared to baseline was in favor of the 'standard care' arm as compared to the micafungin arm (4.7%). The opposite was observed at EOS (-2.3%). The difference in incidence of persistent fungal colonization as compared to baseline was in favor of micafungin as compared to 'standard care' at both EOP (-2.9%) as well as at EOS (-1.7%).

The 95% CI was below 10% for the difference in incidence of persistent colonization at both the EOP (95% CI: -10.6, 4.8) as well as at EOS (95% CI: -8.5, 4.9), and for the difference in incidence of emergent fungal colonization at EOS only (95% CI: -9.2, 4.6). This indicates that there is no more emergent fungal colonization with micafungin at EOS, and no more persistent colonization at EOP and at EOS, than with 'standard care'.

IDRB confirmed IFDs

The IDRB confirmed fungal infections at EOP were caused by *Candida* spp. for 8 patients (2 on micafungin and 6 on 'standard care') and by *Aspergillus fumigatus* for 4 patients (2 in each arm). From EOP up to EOS there were 6 new infections of which 4 caused by Candida spp. (2 in each arm), 1 by *Aspergillus fumigatus* (on 'standard care') and 1 by mixed *Aspergillus* spp. and *Rhizopus* spp. (on micafungin; see Table 10).

Safety Results:

Overall, 52 patients died; slightly more in the micafungin arm vs 'standard care' arm at EOP (14 vs 11 patients), and at LTFU (29 vs 23 patients). Only 2 deaths were considered to be possibly related to the study drug (1 in the fluconazole and 1 in the micafungin arm). The major cause of death was septic shock with multiorgan failure. For only 2 patients on micafungin and 1 patient on caspofungin, the IFD was considered as significant contributor to death according to the IDRB. The 2 IFDs in the micafungin arm were caused by, respectively, *C. glabrata* and mixed *Aspergillus fumigatus, A. niger* and *Rhizopus* spp. and in the caspofungin regimen by *C. tropicalis*.

In total, 40.7% of patients in the 'standard care' arm vs 34.7% of patients in the micafungin arm reported 1 or more SAEs during the study, but most of these were considered not related to treatment according to the investigator. Treatment-related SAEs were reported by 10 (5.8%) patients in the micafungin arm and by 7 (4.1%) patients in the 'standard care' arm. The most common treatment-related SAEs were hepatobiliary disorders (3 patients; 1.7%) and nervous system disorders (2 patients; 1.2%) in the micafungin arm, and renal and urinary disorders (3 patients; 1.7%) and vascular disorders (2 patients; 1.2%) in the 'standard care' arm. The only treatment-related SAE (PT) that was reported by > 1 patient was renal failure (2 patients; 1.2% in the 'standard care' arm).

Discontinuations of the study drug due to AEs were lower in the micafungin arm (24 patients; 13.9%) than in the 'standard care' arm (37 patients; 21.5%). The percentage of patients who discontinued due to treatment-related AEs was 6.4% (11 patients) and 11.6% (20 patients), respectively.

As compared to 'standard care', the micafungin patients had a lower incidence of hepatic (22.7% vs 19.7%) and renal (19.2% vs 15.0%) TEAEs, however considerably more hepatic TEAEs (0.6% vs 4.0%) were considered treatment-related while considerably less renal TEAE (4.7% vs none) were treatment-related in the micafungin arm.

A considerably higher incidence of graft rejection AEs was reported for the micafungin arm (19.1%) vs the 'standard care' arm (11%); only one of those (liver transplant rejection in the micafungin arm) was considered to be treatment-related. Importantly, the incidence of biopsy confirmed acute rejections that were treated did not differ between the micafungin (9.8%) and the 'standard care' arm (8.1%). Most of the biopsies were graded as mild or moderate in both treatment arms.

Infusion site reaction AEs were reported by 5 (2.9%) patients in the micafungin arm, and by 1 (0.6%) patient in the 'standard care' arm; of which 2 in each arm were treatment related.

Fewer patients in the micafungin arm (82.1%) vs the 'standard care' arm (87.2%) reported an AE that occurred in > 5% of the patients. The most common reported TEAEs (i.e., reported in > 10% of patients) with a higher incidence in the micafungin arm as compared to the 'standard care' arm were liver transplant rejection (16.8% vs 8.1%), hypertension (15% vs 10.5%) and abdominal pain (12.1% vs 8.7%); for diarrhea the incidence was equal between the arms (11.0%); and for pleural effusion (15.0% vs 22.1%), pyrexia (9.2% vs 11.0%) and cholestasis (6.9% vs 11.0%) the incidence was higher in the 'standard care' arm.

There were no clinically relevant differences between micafungin and 'standard care' in mean changes over time in liver and renal function tests, except for a trend towards a better creatinine clearance (CCl) for micafungin vs 'standard care'. The percentages of patients with increases or decreases from baseline to EOP and to EOS were also comparable between treatments, except that more patients in the micafungin group had a decrease from baseline in creatinine as compared to 'standard care'.

CONCLUSIONS:

The results of the study showed that micafungin was non-inferior to 'standard care' with regard to 'clinical success' at EOP according to the IDRB in 'high risk' liver transplant patients. Micafungin was also comparable to fluconazole, liposomal amphotericin B and caspofungin regimens.

Overall, the incidence of IFDs at EOP according to the IDRB in the present study was low (3.4%, 12/344 patients in the FAS in Table 4), and was comparable between the treatments (4.7% in the 'standard care' arm and 2.3% in the micafungin arm). IFDs were mostly caused by *C. albicans*, *C. glabrata*, and *Aspergillus fumigatus.*

In consistence, there was a good reduction in fungal colonization after prophylaxis overall, which was comparable for micafungin vs 'standard care' at EOP for persistent colonization and at EOS for both emergent and persistent colonization.

Notably, for only 2 patients in the micafungin group and 1 patient in the caspofungin group, the IFD was considered a significant contributor to the death of the patient. The IFDs were caused by *C. tropicalis* for 1 patient on micafungin and by *Aspergillus niger, A. fumigatus* complex and *Rhizopus* spp. for the other patient on micafungin, and by *C. glabrata* for the patient on caspofungin.

The fungal-free survival data cast some doubt on the similarity of the micafungin vs the 'standard care' arm as the 95% CIs for the difference in the rate, at EOS as well as LTFU, was just above 10%. No differences between the arms were found in the Kaplan-Meier curves. Not meeting the 95% CIs might be caused by the slightly higher number of deaths and/or higher number of withdrawals in the micafungin arm vs the 'standard care' arm.

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The AEs reported for micafungin and 'standard care' were in line with their respective SmPC.

Compared to 'standard care', a considerably higher number of acute rejection TEAEs were reported for micafungin. Post-hoc analysis, however, showed that the incidence of the treated biopsy proven acute rejections was comparable between the arms. Furthermore, the severity of the acute rejections was mild to moderate for most of them, and comparable between the treatment arms for severe rejections.

Renal safety, which is an important indicator of success in liver transplantation, might be better with micafungin as compared to 'standard care'. At EOP, the Glomerular Filtration Rate and CCl tended to be better with micafungin compared to 'standard care'.

In conclusion, micafungin is as effective as 'standard care' for prophylaxis of invasive fungal diseases in liver transplant patients at 'high-risk' of fungal infection. All treatments were well tolerated, and improved the quality of life. Micafungin may even have a more favorable renal safety profile compared to 'standard care'.

Date of Report: 07 May 2013

Table 1 Patient Disposition by Treatment Arm and Regimen (All Randomized Subjects)

	Fluconazole (n = 78)	Liposomal Amphotericin B (n = 72)	Caspofungin (n = 23)	'Standard Care' † (n = 173)	Micafungin (n = 174)	Total (n = 347)
SAF	78 (100.0)	7 (98.6%)	23 (100.0)	172 (99.4)	173 (99.4)	345 (99.4)
FAS	78 (100.0)	71 (98.6)	23 (100.0)	172 (99.4)	172 (98.9)	344 (99.1)
PPS	64 (82.1)	54 (75.0)	19 (82.6)	137 (79.2)	140 (80.5)	277 (79.8)

FAS: Full Analysis Set; PPS: Per Protocol Set; SAF: Safety Analysis Set
† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
Values are presented as n (%).

Source: Table 12.1.1.2.1

Table 2 Demographic and Baseline Characteristics (FAS)

		Fluconazole (n = 78)	Liposomal Amphotericin B (n = 71)	Caspofungin (n = 23)	'Standard Care' † (n = 172)	Micafungin (n = 172)	Total (n = 344)
Sex (n, %)	Male	54 (69.2)	44 (62.0)	16 (69.6)	114 (66.3)	118 (68.6)	232 (67.4)
	Female	24 (30.8)	27 (38.0)	7 (30.4)	58 (33.7)	54 (31.4)	112 (32.6)
Race (n, %)	White	74 (94.9)	62 (87.3)	23 (100.0)	159 (92.4)	165 (95.9)	324 (94.2)
	Black	2 (2.6)	5 (7.0)	0	7 (4.1)	3 (1.7)	10 (2.9)
	Asian	2 (2.6)	3 (4.2)	0	5 (2.9)	3 (1.7)	8 (2.3)
	Other	0	1 (1.4)	0	1 (0.6)	1 (0.6)	2 (0.6)
Region (n, %)	West Europe	47 (60.3)	17 (23.9)	8 (34.8)	72 (41.9)	71 (41.3)	143 (41.6)
	East Europe	14 (17.9)	0	0	14 (8.1)	17 (9.9)	31 (9.0)
	South Europe	17 (21.8)	54 (76.1)	15 (65.2)	86 (50.0)	84 (48.8)	170 (49.4)
Age (years)	Mean (SD)	50.9 (11.86)	49.6 (12.5)	51.8 (8.8)	50.5 (11.8)	51.9 (10.5)	51.2 (11.2)
	< 45 (n, %)	18 (23.1)	18 (25.4)	5 (21.7)	41 (23.8)	38 (22.1)	79 (23.0)
	45-65 (n, %)	52 (66.7)	49 (69.0)	16 (69.6)	117 (68.0)	126 (73.3)	243 (70.6)
	66-75 (n, %)	8 (10.3)	4 (5.6)	2 (8.7)	14 (8.1)	8 (4.7)	22 (6.4)
Weight (kg)	Mean (SD)	76.2 (17.7)	69.7 (15.3)	73.8 (16.6)	73.2 (16.8)	76.0 (15.9)	74.6 (16.4)
Height (cm)	Mean (SD)	171.9 (9.9)	167.9 (9.1)	167.4 (7.8)	169.6 (9.5)	171.2 (10.1)	170.4 (9.8)
BMI (kg/m^2)	Mean (SD)	25.7 (5.0)	24.6 (4.8)	26.3 (5.3)	25.3 (5.0)	25.8 (4.3)	25.6 (4.6)
MELD score	Mean (SD)	19.2 (8.7)	22.9 (11.0)	22.0 (10.3)	21.1 (10.0)	19.9 (10.0)	20.5 (10.0)
	< 20 (n, %)	42 (53.8)	29 (40.8)	10 (43.5)	81 (47.1)	98 (57.0)	179 (52.0)
	20-29 (n, %)	24 (30.8)	23 (32.4)	7 (30.4)	54 (31.4)	43 (25.0)	97 (28.2)
	≥ 30 (n, %)	12 (15.4)	19 (26.8)	6 (26.1)	37 (21.5)	31 (18.0)	68 (19.8)
CMV (n, %)	Negative	23 (31.1)	16 (22.9)	6 (26.1)	45 (26.9)	56 (33.3)	101 (30.1)
	Positive	51 (68.9)	54 (77.1)	17 (73.9)	122 (73.1)	112 (66.7)	234 (69.9)
	Not done	4	1	0	5	4	9
CMV Mismatch (Recipient/ Donor) (n, %)	Negative/ Negative	11 (14.5)	7 (9.9)	2 (8.7)	20 (11.8)	26 (15.2)	46 (13.5)
	Negative/ Positive	12 (15.8)	7 (9.9)	4 (17.4)	23 (13.5)	27 (15.8)	50 (14.7)
	Positive/ Negative	20 (26.3)	21 (29.6)	5 (21.7)	46 (27.1)	34 (19.9)	80 (23.5)
	Positive/ Positive	31 (40.8)	25 (35.2)	11 (47.8)	67 (39.4)	70 (40.9)	137 (40.2)

BMI: body mass index; CMV: cytomegalovirus; MELD: Model for End-Stage Liver Disease.
† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
Note: Percentages are based on all patients with available data of the respective treatment arm/regimen. For CMV mismatch, the number of patients with available data is equal to the number of patients with either recipient or donor or both assessments available.

Source: Tables 12.1.2.1.1, 12.1.2.2.1, 12.1.2.7.1 and 12.1.2.9.1

Table 3 Study Drug Exposure (FAS)

	Fluconazole (n = 78)	Liposomal Amphotericin B (n = 71)	Caspofungin (n = 23)	'Standard Care' † (n = 172)	Micafungin (n = 172)
Duration of exposure (days) ‡					
Mean (SD)	16.9 (7.7)	16.3 (9.0)	20.2 (5.2)	17.1 (8.0)	16.7 (7.0)
Median (min; max)	21.0 (1; 56)	16.0 (1; 47)	21.0 (8; 35)	20.0 (1; 56)	18.0 (2; 57)
Duration of exposure (category in days) (n [%])					
≤ 7	11 (14.1)	11 (15.5)	0 (0.0)	22 (12.8)	15 (8.7)
> 7-≤ 14	12 (15.4)	20 (28.2)	3 (13.0)	35 (20.3)	52 (30.2)
> 14- < 21	14 (17.9)	16 (22.5)	5 (21.7)	35 (20.3)	33 (19.2)
21	40 (51.3)	15 (21.1)	13 (56.5)	68 (39.5)	54 (31.4)
> 21	1 (1.3)	9 (12.7)	2 (8.7)	12 (7.0)	18 (10.5)
Number of infusions (received)					
Mean (SD)	16.9 (7.6)	16.3 (9.0)	20.1 (5.0)	17.1 (8.0)	16.5 (6.9)
Median (min; max)	20.5 (1; 55)	16.0 (1; 47)	21.0 (8; 34)	20.0 (1; 55)	18.0 (2; 57)

† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
‡ Duration is defined as end date of last infusion – start date of first infusion + 1

Source: Table 12.2.1.1

Table 4 'Clinical Success' Rate at EOP Assessed by the IDRB by Treatment Arm

PPS				
	'Standard Care' † (n = 137) n (%)	**Micafungin (n = 140) n (%)**	**Difference ('Standard Care' – Micafungin) %**	**95% CI for the difference ‡§ %**
'Clinical success' ¶	136 (99.3)	138 (98.6)	0.7	(-2.7; 4.4)
No 'clinical success'	1 (0.7)	2 (1.4)		
IFD ††,‡‡	1 (0.7)	2 (1.4)		
Antifungal treatment ‡‡	0	0		
No assessments available	0	0		
FAS				
	'Standard Care' † (n = 172) n (%)	**Micafungin (n =172) n (%)**	**Difference ('Standard Care' – Micafungin) %**	**95% CI for the difference ‡ %**
'Clinical success' ¶	161 (93.6)	166 (96.5)	-2.9	(-8.0; 1.9)
No 'clinical success'	11 (6.4)	6 (3.5)		
IFD ††,‡‡	8 (4.7)	4 (2.3)		
Antifungal treatment ‡‡	7 (4.1)	2 (1.2)		
No assessments available	3 (1.7)	2 (1.2)		

IFD: invasive fungal disease.
† 'Standard care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin
‡ 95% CI for the difference in 'clinical success' rate is based on Newcombe-Wilson method.
§ Non-inferiority margin = 10%
¶ 'clinical success' is defined as absence of a 'proven' or 'probable' IFD AND no initiation of antifungal treatment.
†† 'Proven' or 'probable' IFD defined according to EORTC/MSG criteria.
‡‡ One patient may have 'proven' or 'probable' IFD and may have started antifungal treatment as well.

Source: Tables 12.3.1.1 and 12.3.2.1

Table 5 Comparison of 'Clinical Success' Rate at EOP Assessed by the IDRB Between Each 'Standard Care' Regimen and Micafungin (FAS)

Fluconazole vs Micafungin	**Fluconazole (n = 78) n (%)**	**Micafungin (n = 172) n (%)**	**Difference (Fluconazole – Micafungin) %**	**95% CI for the difference † %**
'Clinical success' ‡	73 (93.6)	166 (96.5)	-2.9	(-10.9; 2.4)
No 'clinical success'	5 (6.4)	6 (3.5)		
IFD §,¶	3 (3.8)	4 (2.3)		
Antifungal treatment ¶	3 (3.8)	2 (1.2)		
No assessments available	2 (2.6)	2 (1.2)		
Liposomal Amphotericin B vs Micafungin	**Liposomal Amphotericin B (n = 71) n (%)**	**Micafungin (n = 172) n (%)**	**Difference (Liposomal Amphotericin B – Micafungin) %**	**95% CI for the difference †‡ %**
'Clinical success' ‡	67 (94.4)	166 (96.5)	-2.1	(-10.3; 3.1)
No 'clinical success'	4 (5.6)	6 (3.5)		
IFD §,¶	4 (5.6)	4 (2.3)		
Antifungal treatment ¶	4 (5.6)	2 (1.2)		
No assessments available	0 (0.0)	2 (1.2)		
Caspofungin vs Micafungin	**Caspofungin (n = 23) n (%)**	**Micafungin (n = 172) n (%)**	**Difference (Caspofungin – Micafungin) %**	**95% CI for the difference †‡ %**
'Clinical success' ‡	21 (91.3)	166 (96.5)	-5.2	(-23.4; 2.2)
No 'clinical success'	2 (8.7)	6 (3.5)		
IFD §,¶	1 (4.3)	4 (2.3)		
Antifungal treatment ¶	0 (0.0)	2 (1.2)		
No assessments available	1 (4.3)	2 (1.2)		

IFD: invasive fungal disease.
† 95% CI for the difference in 'clinical success' rate is based on Newcombe-Wilson method.
‡ 'Clinical success' is defined as absence of a 'proven' or 'probable' IFD and no initiation of antifungal treatment.
§ 'Proven' or 'probable' IFD defined according to EORTC/MSG criteria.
¶ One patient may have 'proven' or 'probable' IFD and may have started antifungal treatment as well.
Source: Table 12.3.2.2.1

Table 6 Absence of 'Proven' or 'Probable' IFD Assessed by the IDRB by Treatment Arm (FAS)

	'Standard Care'† (n = 172) n (%)	Micafungin (n = 172) n (%)	Difference ('Standard Care' – Micafungin) %	95% CI for the difference‡ %
EOP				
Success §	161 (93.6)	166 (96.5)	-2.9	(-8.0; 1.9)
No success ¶	11 (6.4)	6 (3.5)		
IFD	8 (4.7%)	4 (2.3%)		
No assessments available	3 (1.7%)	2		
From EOP to EOS M3 †† ‡‡				
Success § §§	145 (98.0)	126 (97.7)	0.3	(-3.8; 4.8)
No success §§	3 (2.0)	3 (2.3)		
From EOP to EOS ¶¶ ‡‡				
Success § §§	164 (98.2)	158 (98.1)	0.1	(-3.5; 3.7)
No success §§	3 (1.8)	3 (1.9)		

EOP: End of Prophylaxis; EOS: end of study; EOS M3: end of study month 3; IFD: invasive fungal disease
† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
‡ 95% CI for the difference in success rate of absence of 'proven' or 'probable' IFD is based on Newcombe-Wilson method.
§ Success is defined as absence of a 'proven' or 'probable' IFD defined according to EORTC/MSG criteria.
¶ Patients with no IDRB assessment available at EOP are rated as having no success.
†† Patients rated as not evaluable at EOS and patients with an EOS assessment performed before day 76 are rated as not evaluable patients.
‡‡ EOS M3 assessment was between day 76 and day 104 after randomization, while for EOS the assessment was after the EOP period but before LTFU, regardless of time window.
§§ Percentages are based on number of evaluable patients only.
¶¶ Patients with no IDRB assessment available at EOS are rated as not evaluable patients.

Source: Table 12.3.3.1.1.1

Table 7 Absence of 'Proven or 'Probable' IFD Assessed by the Investigator by Treatment Arm (FAS)

	'Standard Care'† (n = 172) n (%)	Micafungin (n = 172) n (%)	Difference ('Standard Care' – Micafungin) %	95% CI for the difference‡§ %
EOP				
Success §	155 (90.1)	153 (89.0)	1.2	(-5.5; 7.8)
No success ¶	17 (9.9)	19 (11.0)		
From EOP to EOS M3 †† §§				
Success § ‡‡	139 (96.5)	125 (97.7)	-1.1	(-5.8; 3.6)
No success ‡‡	5 (3.5)	3 (2.3)		
From EOS M3 to LTFU (6 months) ¶¶				
Success § ‡‡	142 (97.9)	131 (100.0)	-2.1	(-5.9; 1.1)
No success ‡‡	3 (2.1)	0		

EOP: end of prophylaxis; EOS M3: end of study month 3; IFD: invasive fungal disease; LTFU: long term follow-up
† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
‡ 95% CI for the difference in success rate of absence of 'proven' or 'probable' IFD is based on Newcombe-Wilson method.
§ Success is defined as absence of a 'proven' or 'probable' IFD defined according to EORTC/MSG criteria.
¶ Patients with no IFD assessment by investigator available at EOP are rated as having no success.
†† Patients rated as not evaluable at EOS and patients with an EOS assessment performed before day 76 are rated as not evaluable patients.
‡‡ Percentages are based on number of evaluable patients only.
§§ IFD assessment is based on investigator's assessments documented on "fungal infection" panel in eCRF.
¶¶ IFD assessment is based on investigator's assessments documented on "assessment of survival" panel in eCRF.

Source: Table 12.3.3.1.5.1

Table 8 No Initiation of Antifungal Treatment Until EOP Assessed by the IDRB by Treatment Arm (FAS)

	'Standard Care' † (n = 172) n (%)	Micafungin (n = 172) n (%)	Difference ('Standard Care' – Micafungin) %	95% CI for the difference ‡ %
EOP				
Success §¶	162 (95.9)	168 (98.8)	-3.0	(-7.2; 0.7)
No success ¶	7 (4.1)	2 (1.2)		

† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
‡ 95% CI for the difference in success rate for absence of initiation of antifungal treatment is based on Newcombe-Wilson method.
§ Success is defined as no initiation of systemic antifungal treatment defined as administration of additional antifungal medication or increase in the dose of the study drug due to lack of efficacy (considered relevant to the clinical course of the patient).
¶ Percentages are based on number of evaluable patients only.

Source: Table 12.3.3.2.1.1

Table 9 Fungal-free Survival Assessed by the Investigator by Treatment Arm (FAS)

	'Standard Care' † (n = 172) n (%)	Micafungin (n = 172) n (%)	Difference ('Standard Care' – Micafungin) %	95% CI for the difference ‡§ %
EOS M3 ¶				
Fungal-free survival ††	137 (83.0)	123 (80.4)	2.6	(-5.9; 11.2)
Failure ††	28 (17.0)	30 (19.6)		
IFD ††‡‡	11 (6.7)	7 (4.6)		
Death ††	20 (12.1)	25 (16.3)		
Not evaluable §§	7	19		
EOS				
Fungal-free survival ††	139 (83.2)	126 (80.8)	2.5	(-5.9; 10.9)
Failure ††	28 (16.8)	30 (19.2)		
IFD ††‡‡	11 (6.6)	7 (4.5)		
Death ††	20 (12.0)	25 (16.0)		
Not evaluable §§	5	16		
LTFU				
Fungal-free survival ††	132 (80.0)	121 (78.1)	1.9	(-7.0; 10.9)
Failure ††	33 (20.0)	34 (21.9)		
IFD ††‡‡	13 (7.9)	7 (4.5)		
Death ††	23 (13.9)	29 (18.7)		
Not evaluable §§	7	17		

EOS M3: end of study month 3; IFD: invasive fungal disease; LTFU: long term follow-up
† 'Standard Care' is defined as treatment with fluconazole, liposomal amphotericin B or caspofungin.
‡ 95% CI for the difference in fungal-free survival rate is based on Newcombe-Wilson method.
§ Non-Inferiority Margin = 10%.
¶ For patients being fungal-free and alive EOS assessments performed before day 76 after randomization are excluded.
†† Percentages are based on number of evaluable patients only.
‡‡ Proven' or 'probable' IFD defined according to EORTC/MSG criteria.
§§ No 'proven' or 'probable' IFD documented up to EOS and no IFD assessment available.

Source: Table 12.3.3.5.1.1

Table 10 Overview of Fungal Organisms Cultured From Patients With IDRB Confirmed Fungal Infection at EOP and EOS

Patient ID	Drug	Assessment	Day	Site of culture	Spp.
[redacted]	Micafungin	EOP	25	Deep wound / Catheter tip / abdomen	*C. glabrata*
[redacted]	Micafungin	EOP	11	Abcess	*C. albicans*
[redacted]	Micafungin	EOP	10	Sputum	*A.fumigatus*
[redacted]	Micafungin	EOP	3	BAL fluid	*A.fumigatus*
[redacted]	Caspofungin	EOP	1	Abdomen	*C. tropicalis*
[redacted]	Fluconazole	EOP	16	Deep wound	*C. glabrata*
[redacted]	Fluconazole	EOP	8	Blood	*C. glabrata*
[redacted]	Fluconazole	EOP	4	Tracheal aspirate	*A. fumigatus*
[redacted]	Liposomal Amphotericin B	EOP	7	Bile	*C .albicans*
[redacted]	Liposomal Amphotericin B	EOP	23	Abdominal fluid drainage ‡	*C. albicans*
[redacted]	Liposomal Amphotericin B	EOP	7	Bile	*C. glabrata*
[redacted]	Liposomal Amphotericin B	EOP	9	BAL fluid	*A.fumigatus*
[redacted]	Micafungin	EOS	47	Bile fluid	*C. glabrata*
[redacted]	Micafungin	EOS	34	Ascitic fluid	*C. parapsilosis*
[redacted]	Micafungin	EOS	58	BAL fluid	*Aspergillus fumigates complex, Aspergillus niger, and Rhizopus spp.*-
[redacted]	Caspofungin	EOS	74	Abcess	*C. albicans*
[redacted]	Caspofungin	EOS	66	Catheter tip	*C. tropicalis*
[redacted]	Fluconazole	EOS	33	Serum *Aspergillus* antigen / Brain biopsy culture	*A. fumigatus*

A.: *Aspergillus*; BAL: bronchoalveolar lavage; *C.*: *Candida*; EOP: end of prophylaxis; EOS: end of study;
- spp. not recorded

[redacted]

Days are relative to study drug.

Source: Listings 13.2.6.1, 13.2.6.3 and Attachment 5.

[redacted]