Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients

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Summary

In this randomized clinical trial comparing micafungin 100 mg with standard care antifungal prophylaxis (fluconazole, liposomal amphotericin B, or caspofungin) in high-risk liver transplant patients, micafungin 100 mg was non-inferior and had a better kidney safety profile.

Abstract

Background

Invasive fungal infection (IFI) following liver transplantation is associated with significant morbidity and mortality. Antifungal prophylaxis is rational for liver transplant patients at high IFI risk.

Methods

In this open-label, non-inferiority study, patients were randomized 1:1 to receive intravenous micafungin 100 mg or center-specific standard care (fluconazole, liposomal amphotericin B, or caspofungin) post-transplant. The primary endpoint was clinical success (absence of a proven/probable IFI and no need for additional antifungals) at end of prophylaxis (EOP). Non-inferiority (10% margin) of micafungin versus standard care was assessed in the per protocol (PPS) and full analysis sets (FAS). Safety assessments included adverse events (AEs), liver and kidney function tests.
Results

The FAS comprised 344 patients (172 micafungin; 172 standard care). Mean age was 51.2 years; 48.0% had a Model for End-Stage Liver Disease (MELD) score $\geq 20$. At EOP (mean treatment duration 17 days), clinical success was 98.6% for micafungin and 99.3% for standard care ($\Delta$ standard care–micafungin [95% CI]: 0.7% [-2.7, 4.4]) in the PPS and 96.5% and 93.6%, respectively (-2.9% [-8.0, 1.9]), in the FAS. Incidences of drug-related AEs for micafungin and standard care were 11.6% and 16.3%, leading to discontinuation in 6.4% and 11.6% of cases, respectively. At EOP, liver function tests were similar but creatinine clearance was higher in micafungin- versus standard care-treated patients.

Conclusion

Micafungin was non-inferior to standard care as antifungal prophylaxis in liver transplant patients at high IFI risk. AE profiles and liver function at EOP were similar although kidney function was better with micafungin.
INTRODUCTION

Liver transplant recipients are susceptible to invasive fungal infections (IFI), with infection rates of 8.4–17.7% reported in contemporary epidemiological studies [1-6]. Most IFI in solid organ transplant recipients belong to the genera Aspergillus and Candida [7, 8]. Candida species account for the majority (60–91%) of IFI in liver transplant patients [3, 5, 8, 9] with \textit{C. albicans} and \textit{C. glabrata} being most commonly observed [8, 10, 11].

Risk factors associated with IFI in liver transplant recipients include pre- and post-operative renal failure, re-transplantation, substantial intra-operative transfusion of cellular blood products [9], and high Model for End-Stage Liver Disease (MELD) score [2, 12, 13]. As IFI are associated with mortality rates of 25–90% [2, 4, 9, 14, 15], antifungal prophylaxis is a rational approach for liver transplant patients considered at high risk.

Fluconazole and liposomal amphotericin B are US guideline-recommended options for antifungal prophylaxis in liver transplant recipients with multiple IFI risk factors [15-17]. However, some strains of \textit{Candida} have shown resistance to fluconazole [17-19] and amphotericin B nephrotoxicity causes concern in renally impaired patients [20, 21]. The echinocandins have demonstrated broad efficacy against \textit{Candida} species, have low toxicity, few drug–drug interactions and are established first-line treatments for invasive candidiasis [22-24]. Some centers give echinocandins as primary prophylaxis in liver transplant recipients [23] and European recommendations support their use in patients at high IFI risk [25]. The aim of TENPIN (Liver \textit{T}ransplant \textit{E}uropea\textit{N} Study into the \textit{P}revention of Fungal \textit{I}nfectio\textit{N}) was to demonstrate non-inferiority of the echinocandin micafungin versus center-
specific standard care for IFI prevention in liver transplant recipients deemed at high risk of IFI.

**METHODS**

**Patients and study design**

TENPIN was a Phase 3b, international, multicenter, randomized, open-label, parallel-group, non-inferiority, antifungal prophylaxis study in liver transplant recipients (ClinicalTrials.gov identifier: NCT01058174; clinicaltrialsregister.eu EudraCT number 2008-005214-49). Patients ≥18 years undergoing orthotopic whole or split liver allograft transplantation were eligible for inclusion based on the presence of at least one of the IFI risk factors described in Supplementary Appendix 1.1. Supplementary Appendix 1.2 details the exclusion criteria.

Eligible patients were randomized 1:1 to receive, post-transplantation, either intravenous (i.v.) micafungin 100 mg/day (2.0 mg/kg/day if weight was <40 kg) or center-specific standard care (a pre-defined regimen according to local protocol of either i.v. fluconazole 200–400 mg/day, i.v. liposomal amphotericin B 1–3 mg/kg/day, or i.v. caspofungin 70 mg single loading dose followed by 50 mg once daily). Patients were randomized at admission if they fulfilled the high IFI risk criteria or within 5 days post-transplantation following intra- or post-operative events. Supplementary Appendix 1.3/Figure S1 describes the randomization procedure.

Prophylaxis lasted 21 days or until hospital discharge (whichever occurred first), or longer in patients with persistent risk factors. End of study (EOS) was 3 months post-randomization and long-term follow-up (LTFU) was 6 months post-randomization. Patients who developed a proven or probable IFI during prophylaxis were discontinued from the study drug, treated with appropriate antifungal therapy, and required to remain in the study.
and complete all assessments. A proven or probable IFI, diagnosed by an investigator according to the EORTC/MSG definitions [26], was confirmed by an Independent Data Review Board (IDRB).

The study protocol (ISN/Protocol 9463-EC-0001) was approved by the independent Ethics Committee or Institutional Review Board at each center and was conducted in accordance with the ethical principles that originate in the Declaration of Helsinki. Patients’ written informed consent was obtained prior to screening.

The manuscript was written in accordance with the CONSORT statement for randomized controlled trials recommendations [27].

Outcomes

Efficacy

Fungal infection status was evaluated at baseline (methods provided in Supplementary Appendix 1.4), during prophylaxis, at end of prophylaxis (EOP), and at EOS by the investigator and blindly assessed by the IDRB. During prophylaxis, fungal infection status was assessed at a minimum of twice weekly, with assessments conducted at least 72 hours apart.

The primary efficacy endpoint was clinical success (defined as a composite of absence of a proven or probable IFI and no initiation of antifungal treatment at EOP) assessed by the IDRB. Antifungal treatment was defined as either additional antifungal medication or increased study drug dose due to apparent inadequate efficacy.
Secondary pre-specified efficacy endpoints included: absence of a proven or probable IFI at EOP and EOS or EOS-Month 3 (i.e. more than post-randomization Day 76) as assessed by the IDRB and investigator; absence of initiation of antifungal therapy at EOP as assessed by the IDRB; time to proven or probable IFI from randomization according to the IDRB; fungal-free survival at EOS and end of LTFU according to the investigator.

Safety
Treatment-emergent adverse events (AEs) were recorded up to EOS, and serious AEs, including death, until 30 days after EOS. Overall mortality was considered a safety parameter. Routine laboratory assessments of biochemistry, hematology, and urinalysis were performed at baseline and throughout the study. Hepatic and renal function was assessed using standard laboratory biochemical tests.

Statistical analysis
Efficacy data were analyzed for the full analysis set (FAS), i.e. all randomized patients who received at least one dose of study medication and without proven or possible IFI at baseline (according to the IDRB) and the per protocol set (PPS), i.e. all FAS patients who completed the study without major protocol violations. The PPS was used as the primary analysis set and the FAS as the confirmatory analysis set for the primary efficacy endpoint and all secondary endpoints. The safety analysis set (SAF) included all randomized patients who received at least one dose of study medication.
The study sample size was calculated using a non-inferiority margin of 10% for the absolute difference in clinical success rates based on clinical judgment by an expert panel. Based on this non-inferiority margin, assuming a true success rate of 94% in the standard care group, 135 patients per group were necessary to demonstrate non-inferiority of micafungin versus standard care with a power of at least 90% using a one-sided type I risk error of 2.5%. Assuming that 80% of the randomized subjects were included in the PPS, 169 patients were required to be randomized into each treatment group. Clinically, a non-inferiority margin of 10% was also deemed applicable to the FAS.

For the composite primary efficacy endpoint of clinical success, rates were compared between the standard care and micafungin groups at EOP and two-sided 95% confidence intervals (CI) for the difference in success rates were calculated using the Newcombe–Wilson method. If the upper limit of the 95% CI for the difference in success rates was <10%, then the non-inferiority of micafungin to standard care was declared. The analysis assumed that the infection rate amongst the individual treatment regimens was homogeneous. The secondary efficacy endpoints of absence of proven or probable IFI (EOP, EOS and EOS-Month 3) and absence of antifungal therapy (EOP), and fungal-free survival were similarly analyzed, although as the study was powered for the primary endpoint, statistical non-inferiority was tested on this endpoint only.

Time to proven or probable IFI was modeled using Cox regression, with covariates including baseline MELD score (≤29 or ≥30) and treatment group. Patients with no proven or probable IFI during prophylaxis were censored at the assessment visit. Non-parametric analysis was undertaken, Kaplan–Meier curves are provided, and the log-rank test utilized to
compare treatment groups for the endpoints of time to proven or probable IFI and fungal-
free survival.

Baseline characteristics (FAS) and safety variables (SAF) were summarized by
descriptive statistics.

In a post-hoc analysis to further explore renal safety, estimates of glomerular
filtration rate (GFR) and creatinine clearance (CrCl) were derived for the SAF and also the
SAF patients who did not require renal replacement therapy (RRT) at baseline, using the 4-
variable modification of diet in renal disease formula and Cockcroft–Gault formula,
respectively. Differences in GFR and CrCl between treatment groups were compared at
weekly time points using repeated measures analysis of variance (ANOVA) and at EOP by
analysis of covariance (ANCOVA).

Data analysis for this paper was generated using SAS/STAT® software, Version 9.3

RESULTS

Patients

The study ran from 15 December 2009 to 03 May 2012 at 37 European centers. Figure 1
shows participant flow. There were 45 micafungin-treated patients excluded from the study,
mainly due to AEs (n = 27) or withdrawal of consent (n = 9) and 30 patients treated with
standard care, mainly due to AEs (n = 23). Excluding MELD score, demographics and
baseline characteristics were balanced between treatment groups (Table 1). The most
common indications for transplantation were cirrhosis(67.5%) and hepatocellular carcinoma
Supplementary Appendix 2.1/Table S1 details the proportion of patients in each high-risk IFI category. The mean ± standard deviation duration of exposure was 16.7 ± 7.0 days in the micafungin group and 17.1 ± 8.0 days in the standard care group.

**Efficacy**

*Primary efficacy endpoint*

The clinical success rate of micafungin 100 mg was non-inferior to standard care at EOP as assessed by the IDRB in the primary analysis PPS: 98.6% (138/140) for micafungin and 99.3% (136/137) for standard care (Δ standard care–micafungin [95% CI] 0.7% [-2.7, 4.4]). This was confirmed in the FAS (Table 2). Of the 67 FAS patients excluded from PPS, 67.1% were excluded because their EOP assessment was greater than 3 days after last treatment administration of study drug.

*Secondary efficacy endpoints in the full analysis set*

Micafungin was similar to standard care with regard to absence of proven or probable IFI at EOP and EOS, according to both IDRB and investigator assessments (Supplementary Appendix 2.2/Table S2). At EOP there were four (2.3%) IDRB-confirmed IFI in micafungin-treated patients and eight (4.7%) in standard care-treated patients. At EOS there were three new infections in each group. Supplementary Appendix 2.3/Table S3 details the infecting species. With regard to absence of initiation of systemic antifungal treatment, the success rate of micafungin (98.8%) was also similar to standard care (95.9%) at EOP (Δ standard care–micafungin [95% CI] -3.0% [-7.2, 0.7]).
Cox regression modeling of time to proven or probable IFI gave a hazard ratio of 0.72 (95% CI: 0.27, 1.90) indicating no significant difference between the groups. Non-parametric analysis was consistent with this finding (log-rank test *P* = .498; Supplementary Appendix 2.4/Figure S2).

Investigator-assessed fungal-free survival at EOS was 80.8% (126/156) and 83.2% (139/167) in the micafungin- and standard care-treated patients, respectively (Δ 2.5%; 95% CI: -5.9, 10.9) and at the end of LTFU was 78.1% (121/155) and 80.0% (132/165), respectively (Δ 1.9%; 95% CI: -7.0, 10.9). Kaplan–Meier analyses showed no significant difference in fungal-free survival at LTFU (log-rank *P* = .679; Figure 2).

**Safety**

**Hepatic and renal functions**

There were no clinically relevant differences in hepatic function tests over time between micafungin- and standard care-treated patients (Supplementary Appendix 2.5/Figure S3).

Serum creatinine and urea levels were lower in the micafungin group than standard care at most weekly time points and at EOP suggesting better renal function in these patients. Post-hoc analysis showed mean GFR and mean CrCl were higher for micafungin versus standard care at most time points during prophylaxis, although differences were not statistically significant (Supplementary Appendix 2.5, Figure S4). However, at EOP when data from all patients at any time were considered, mean GFR was significantly higher in micafungin- versus standard care-treated patients (*P* = .049), as was mean CrCl (*P* = .012). For patients not requiring RRT at baseline, significantly higher mean GFR (*P* = .033) and mean CrCl (*P* = .013) were observed for micafungin (n = 133) versus standard care (n =
142) at EOP, although not at weekly time points. Liposomal amphotericin B was associated with the lowest GFR and CrCl in standard care patients (Figures 3A and 3B).

Treatment-emergent adverse events

There were fewer AEs leading to study drug discontinuation in micafungin- than standard care-treated patients (6.4% vs 11.6%, respectively for treatment-related AEs; see Supplementary Appendix 2.6/Table S4). Table 3 shows AEs reported in >10% of patients in either treatment group. While a higher overall rate of graft rejections was reported for micafungin (19.1%) than standard care (11%), the rates of biopsy-confirmed treated acute rejection were similar at 9.8% and 8.1%, respectively. Most graft rejections were mild to moderate in severity, and the rate of severe rejections was the same in each group (2.3%). The most common treatment-related AEs are detailed in Supplementary Appendix 2.6.

Deaths

In the micafungin group 14 patients died during prophylaxis and 15 during LTFU and in the standard care group 11 died during prophylaxis and 12 during LTFU). Two deaths (one in each group) were considered possibly study drug-related by the investigator. Cause of death was mostly septic shock with multi-organ failure and/or worsening of the underlying disease.

DISCUSSION

TENPIN is the first randomized controlled trial of an echinocandin as prophylaxis in liver transplant patients and the largest antifungal study in this patient population to date.

Micafungin demonstrated a clinical success rate that was statistically non-inferior to standard
care, confirming that micafungin 100 mg is as effective as standard care for antifungal prophylaxis in liver transplant recipients at high-risk of IFI. In addition, micafungin had similar efficacy to standard care across all secondary efficacy outcomes assessed. Having an IDRB confirm the investigator’s decision based on a standard definition [26] strengthens the study results and was necessary given the definition of IFI can vary between centers and physicians.

IFI rates of up to 17.7% [1-6] and 3-month cumulative IFI rates of approximately 4% [10] have been reported in liver transplant recipients without risk factors. The overall low rate of IFI (≤2%) in our study provides evidence supporting antifungal prophylaxis in high-risk liver transplant recipients. Micafungin is indicated for prophylaxis against *Candida* infection in other high-risk patient groups [28, 29]; low rates of breakthrough IFI were observed for micafungin 50 mg (1.6%) and fluconazole (2.4%) in a trial comparing these agents in hematopoietic stem cell transplantation patients [30]. In that study [30], one patient on micafungin had a breakthrough *Aspergillus* infection (seven on fluconazole), while two patients on micafungin in the current study were infected with *Aspergillus* species and two on standard care (one each with fluconazole and liposomal amphotericin B).

The overall safety profile of micafungin was comparable to that of standard care, with a low incidence of hepatic and renal AEs. The pattern of liver function tests was similar between micafungin and standard care, however renal function with micafungin may be better than with established standard care regimens, such as liposomal amphotericin B. This is consistent with a prophylaxis study in high-risk liver transplant recipients where micafungin was similarly efficacious to amphotericin B lipid complex, with lower early renal dysfunction and no additional risk of hepatic dysfunction [21]. In our study more graft
rejection episodes were reported in micafungin patients than standard care. However, further investigation found similar rates of biopsy-confirmed treated acute rejection – an objective measure of rejection – and there was no evidence that micafungin was different to standard care in this regard.

Alternatives to fluconazole and liposomal amphotericin B, the current guideline-recommended options for antifungal prophylaxis in liver transplant recipients, are needed. *Candida* species such as *C. glabrata* and *C. krusei* are less susceptible, or even resistant in the case of fluconazole, to these agents [17-19, 31]. Drug–drug interactions with fluconazole complicate dosing with the immunosuppressants ciclosporin, tacrolimus, and sirolimus [32]. Fluconazole requires dose adjustment in patients receiving RRT, as the procedure results in a significant clearance of fluconazole, which varies depending on the technique used [33, 34]. Although nephrotoxicity risk is reduced with liposomal amphotericin B compared with amphotericin B deoxycholate [15, 17], it may still limit its use, [20, 35] especially in recipients with renal dysfunction.

Echinocandins may be useful alternatives for simplifying antifungal prophylaxis in liver transplant, exhibiting excellent fungicidal activity against *Candida* species, with low minimum inhibitory concentrations against the majority of isolates [36, 37]. Resistance to echinocandins is a relatively rare event [37-39]. However, cases of resistance due to therapy-acquired FKS mutations have been reported [37, 38], and evidence of increasing resistance among strains of *C. glabrata* has emerged [40]. The probability of resistance may increase as echinocandin use escalates, and this needs to be considered when employing these agents as primary prophylaxis with prolonged exposure. As echinocandins do not interact with the P450 cytochrome or P-glycoprotein systems they have a low potential for
drug–drug interactions [36, 37]. However, caspofungin [41] but not micafungin [42-45] does interact with ciclosporin and tacrolimus and micafungin interacts with sirolimus [28].

This study’s main limitations include those inherently associated with open-label trials, such as potential bias which can, for example, lead to greater withdrawal of consent in one treatment arm. This was observed in this study as nine patients on micafungin withdrew consent compared with none on standard care. In addition, standard care therapy was decided as per local guidelines and standard care dosing was not uniform (although within a pre-agreed range and consistent with each center), which may have impacted results. As the choice of standard care was center-specific, and therefore could be based on local epidemiology or other clinical considerations relevant to the local patient population, this could be considered as a positive bias in favor of standard care in the TENPIN clinical trial setting. For the post-hoc safety analysis on renal function it was only possible to exclude patients who had RRT at baseline because information on whether they received RRT during prophylaxis or thereafter was not collected. In addition, it was not possible to adjust for known nephrotoxic concomitant medications.

In summary, micafungin was demonstrated non-inferior to standard care for antifungal prophylaxis in liver transplant patients at high risk of IFI, with a similar overall safety profile but associated with better renal function throughout prophylaxis than standard care. Micafungin therefore provides an additional prophylactic option, especially in patients with a high risk of infection by species resistant to current standard care, patients at risk of drug–drug interactions, or patients with renal impairment or receiving RRT.
Funding

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Role of sponsor

The study sponsor, together with lead investigators, designed the study and the sponsor conducted all the statistical analyses. The members of the steering committee were involved in the study design, reviewed the protocol, and provided guidance on the study conduct. All the authors had access to the data and contributed to data interpretation. All authors participated in the preparation of the manuscript with support from a professional medical writer, funded by Astellas Pharma Europe Ltd. All authors reviewed and approved the final version, and made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and analyses.

Conflicts of interest

FS has received speaker fees and/or research funding from, and/or has participated at advisory boards for, Novartis, Astellas, Roche, Genzyme, Merck Sharp & Dohme, Gilead, Gambro and Vital Therapies. AP has received research funding and speaker fees from Astellas, Novartis, Roche, Nycomed, TEVA, Genzyme, and has participated at advisory boards for Novartis. CC has received research grants, travel support, and/or lecture fees from Pfizer, Gilead, Merck, Astellas, Novartis and Genzyme and has participated at advisory boards for Novartis and Genzyme. ML has received research grants from Merck Sharp & Dohme and Pfizer. BG-E has received speaker fees from Pfizer and speaker fees and research grants from Astellas and Novartis. LF is a member of an Advisory Committee for Novartis, has received grant support from Novartis and Astellas, and speaker fees from Gilead Sciences. SP is an independent contractor employed by Astellas Pharma. LT, AK, MB
are full-time employees of Astellas Pharma. OC, P-FL, JDW, UC, RML report no conflicts of interest.

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References


32. Pfizer Ltd. Diflucan Summary of Product Characteristics. Available at:
33. Pittrow L, Penk A. Dosage adjustment of fluconazole during continuous renal
34. Muhl E, Martens T, Iven H, Rob P, Bruch HP. Influence of continuous veno-venous
   haemodiafiltration and continuous veno-venous haemofiltration on the
35. Moen MD, Lyseng-Williamson KA, Scott LJ. Liposomal amphotericin B: a review of its
   use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal
37. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a
38. Beyda ND, Lewis RE, Garey KW. Echinocandin resistance in Candida species:
   mechanisms of reduced susceptibility and therapeutic approaches. Ann Pharmacother
39. Perlin DS. Echinocandin resistance, susceptibility testing and prophylaxis: implications
40. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in
   Candida glabrata: clinical failure correlates with presence of FKS mutations and
   Available at: http://www.medicines.org.uk/emc/medicine/12843#


Figure legends

Figure 1. Disposition of patients

*All randomized patients with at least 1 dose of study drug.
†All randomized patients with at least 1 dose of study drug and without an invasive fungal infection at baseline.
‡All patients who completed the study without major protocol deviations or violations.
§Patients from the full analysis set who discontinued; for every patient, only the primary reason for discontinuation was collected.

Figure 2. Fungal-free survival in micafungin and standard care treatment groups during long-term follow-up (full analysis set)

Abbreviation: IFI, invasive fungal infection

Figure 3. A, Mean glomerular filtration rate and B, Mean creatinine clearance in patients not requiring renal replacement therapy, according to specific study drug
Table 1. Demographic and baseline characteristics

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<th>Micafungin 100 mg (n = 172)</th>
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<td>114 (66.3)</td>
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</tr>
<tr>
<td>MELD score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>98 (57.0)</td>
<td>81 (47.1)</td>
<td>179 (52.0)</td>
</tr>
<tr>
<td>20–29</td>
<td>43 (25.0)</td>
<td>54 (31.4)</td>
<td>97 (28.2)</td>
</tr>
<tr>
<td>≥30</td>
<td>31 (18.0)</td>
<td>37 (21.5)</td>
<td>68 (19.8)</td>
</tr>
<tr>
<td>CMV mismatch (recipient/donor), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative/negative</td>
<td>26 (15.2)</td>
<td>20 (11.8)</td>
<td>46 (13.5)</td>
</tr>
<tr>
<td>Negative/positive</td>
<td>27 (15.8)</td>
<td>23 (13.5)</td>
<td>50 (14.7)</td>
</tr>
<tr>
<td>Positive/negative</td>
<td>34 (19.9)</td>
<td>46 (27.1)</td>
<td>80 (23.5)</td>
</tr>
<tr>
<td>Positive/positive</td>
<td>70 (40.9)</td>
<td>67 (39.4)</td>
<td>137 (40.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

Note: Percentages are based on all patients with available data in the respective treatment regimen. For CMV mismatch, the number of patients with available data is equal to the number of patients with both assessments available.
Table 2. Clinical success rate for micafungin and standard care at the end of the prophylaxis period and as assessed by the Independent Data Review Board (per protocol and full analysis sets)

<table>
<thead>
<tr>
<th>Per protocol set</th>
<th>Micafungin</th>
<th>Standard care</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(primary analysis)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>Standard care - micafungin</td>
</tr>
<tr>
<td>(n = 140)</td>
<td>(n = 137)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical success</td>
<td>138 (98.6)</td>
<td>136 (99.3)</td>
<td>0.7 (-2.7, 4.4)</td>
</tr>
<tr>
<td>No clinical success</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Invasive fungal</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>infection^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal treatment^a</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No assessments available</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Full analysis set</th>
<th>Micafungin</th>
<th>Standard care</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(confirmatory analysis)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>Standard care - micafungin</td>
</tr>
<tr>
<td>(n = 172)</td>
<td>(n = 172)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical success</td>
<td>166 (96.5)</td>
<td>161 (93.6)</td>
<td>-2.9 (-8.0, 1.9)</td>
</tr>
<tr>
<td>No clinical success</td>
<td>6 (3.5)</td>
<td>11 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Invasive fungal</td>
<td>4 (2.3)</td>
<td>8 (4.7)</td>
<td></td>
</tr>
<tr>
<td>infection^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal treatment^a</td>
<td>2 (1.2)</td>
<td>7 (4.1)</td>
<td></td>
</tr>
<tr>
<td>No assessments available</td>
<td>2 (1.2)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

^a One patient may have proven or probable invasive fungal infection and may have started antifungal treatment.
Table 3. Treatment-emergent adverse events in more than 10% of patients in the micafungin treatment or standard care group (safety analysis set)

<table>
<thead>
<tr>
<th>Treatment-emergent adverse events, n (%)</th>
<th>Micafungin (n = 173)</th>
<th>Standard care (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>21 (12.1)</td>
<td>15 (8.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (11.0)</td>
<td>19 (11.0)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>26 (15.0)</td>
<td>38 (22.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (11.6)</td>
<td>23 (13.4)</td>
</tr>
<tr>
<td>Liver transplant rejection (clinical)</td>
<td>29 (16.8)</td>
<td>14 (8.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (9.2)</td>
<td>19 (11.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (15.0)</td>
<td>18 (10.5)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>12 (6.9)</td>
<td>19 (11.0)</td>
</tr>
</tbody>
</table>