

Randomized Trial of Micafungin for the Prevention of Invasive Fungal Infection in High-Risk Liver Transplant Recipients

Fauzi Saliba,¹ Andreas Pascher,² Olivier Cointault,³ Pierre-François Laterre,⁴ Carlos Cervera,⁵ Jan J. De Waele,⁶ Umberto Cillo,⁷ Róbert M. Langer,⁸ Manuela Lugano,⁹ Bo Göran-Ericzon,¹⁰ Stephen Phillips,¹¹ Lorraine Tweddle,¹² Andreas Karas,¹² Malcolm Brown,¹³ and Lutz Fischer¹⁴; for the TENPIN (Liver Transplant European Study Into the Prevention of Fungal Infection) Investigators^a

¹Hôpital Paul Brousse, Villejuif, France; ²Charité Universitätsmedizin, Berlin, Germany; ³Hôpital de Rangueil, Toulouse, France; ⁴St Luc University Hospital, Université catholique de Louvain, Brussels, Belgium; ⁵Hospital Clinic i Provincial, Barcelona, Spain; ⁶Ghent University Hospital, Belgium; ⁷Azienda Ospedaliera di Padova, Italy; ⁸Semmelweis University, Budapest, Hungary; ⁹Azienda Ospedaliero Universitaria Misericordia, Udine, Italy; ¹⁰Karolinska University Hospital, Huddinge, Sweden; ¹¹Astellas Pharma Europe, Leiden, The Netherlands; ¹²Astellas Pharma Europe Medical Affairs, Chertsey, United Kingdom; ¹³Astellas Pharma Global Medical Affairs, Northbrook, Illinois; and ¹⁴University Medical Center Hamburg-Eppendorf, Germany

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

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

Results. The full analysis set comprised 344 patients (172 micafungin; 172 standard care). Mean age was 51.2 years; 48.0% had a Model for End-Stage Liver Disease score ≥ 20 . At EOP (mean treatment duration, 17 days), clinical success was 98.6% for micafungin and 99.3% for standard care (Δ standard care – micafungin [95% confidence interval], 0.7% [–2.7% to 4.4%]) in the per protocol set and 96.5% and 93.6%, respectively (–2.9% [–8.0% to 1.9%]), in the full analysis set. Incidences of drug-related adverse events 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- vs standard care-treated patients.

Conclusions. Micafungin was noninferior to standard care as antifungal prophylaxis in liver transplant patients at high risk for IFI. Adverse event profiles and liver function at EOP were similar, although kidney function was better with micafungin.

Clinical Trials Registration. NCT01058174.

Keywords. antifungal therapy; liver transplant; micafungin; prophylaxis; infection.

Liver transplant recipients are susceptible to invasive fungal infection (IFI), with infection rates of 8.4%–17.7% reported in contemporary epidemiological

studies [1–6]. Most IFIs 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

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^aThe TENPIN study investigators are listed in the Appendix.

Correspondence: Fauzi Saliba, MD, PhD, Centre Hépatobiliaire, Hôpital Paul Brousse, 12, av. P. V. Couturier, 94800 Villejuif, France (fauzi.saliba@pbr.aphp.fr).

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Candida albicans and *Candida glabrata* being most commonly observed [8, 10, 11].

Risk factors associated with IFI in liver transplant recipients include pre- and postoperative renal failure, retransplantation, substantial intraoperative transfusion of cellular blood products [9], and high Model for End-Stage Liver Disease (MELD) score [2, 12, 13]. As IFIs 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 *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 *Candida* species, have low toxicity and 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 Transplant European Study Into the Prevention of Fungal Infection) was to demonstrate noninferiority of the echinocandin micafungin vs 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, noninferiority study of antifungal prophylaxis in liver transplant recipients (ClinicalTrials.gov identifier: NCT01058174; ClinicalTrialsRegister.eu EudraCT number 2008-005214-49). Patients aged ≥ 18 years undergoing orthotopic whole or split liver allograft transplant were eligible for inclusion based on the presence of at least 1 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, posttransplant, either intravenous micafungin 100 mg/day (2.0 mg/kg/day if body weight was <40 kg) or center-specific standard care (a predefined regimen according to local protocol of either intravenous fluconazole 200–400 mg/day, intravenous liposomal amphotericin B 1–3 mg/kg/day, or intravenous 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 posttransplant following intra- or postoperative events. [Supplementary Appendix 1.3](#) and [Supplementary Figure 1](#) describe 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 postrandomization, and long-term follow-up was 6 months postrandomization. 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 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 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 (Consolidated Standards for Reporting Trials) 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 prespecified efficacy endpoints included absence of a proven or probable IFI at EOP and EOS or EOS-month 3 (ie, later than postrandomization 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 long-term follow-up 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), that is, all randomized patients who received at least 1 dose of study medication and without proven or possible IFI at baseline (according to the IDRB); and the per protocol set (PPS), that is, 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 1 dose of study medication.

The study sample size was calculated using a noninferiority margin of 10% for the absolute difference in clinical success

rates based on clinical judgment by an expert panel. Based on this noninferiority margin, assuming a true success rate of 94% in the standard care group, 135 patients per group were necessary to demonstrate noninferiority of micafungin vs standard care with a power of at least 90% using a 1-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 noninferiority 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 2-sided 95% confidence intervals (CIs) for the difference in success rates were calculated using

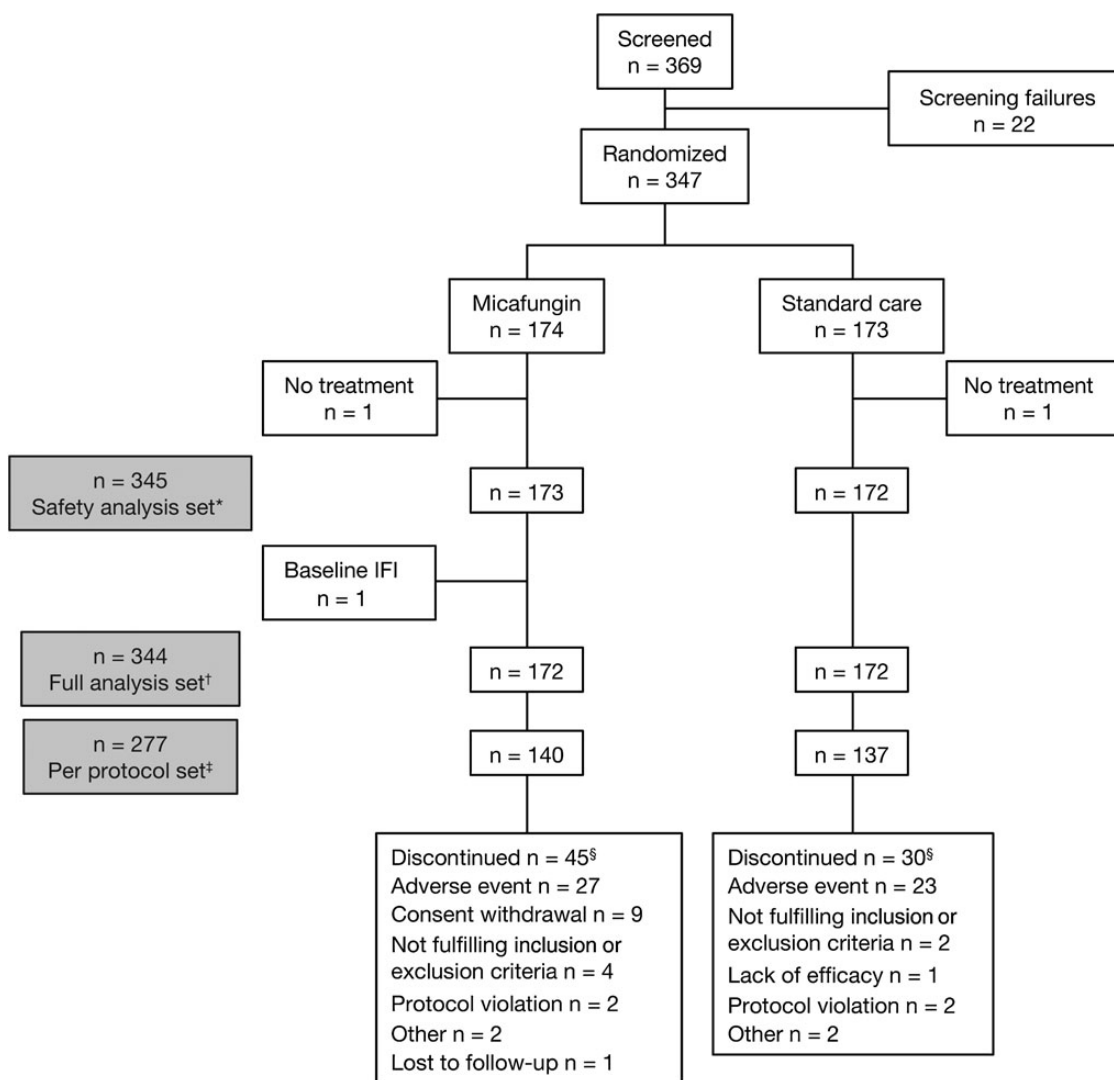


Figure 1. Disposition of patients. *All randomized patients with at least 1 dose of study drug. †All randomized patients with at least 1 dose of study drug and without an invasive fungal infection (IFI) at baseline. ‡All patients who completed the study without major protocol deviations or violations.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

the Newcombe–Wilson method. If the upper limit of the 95% CI for the difference in success rates was <10%, then the noninferiority of micafungin to standard care was declared. The analysis assumed that the infection rate among 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 noninferiority 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. Nonparametric analysis was undertaken, Kaplan–Meier curves are provided, and the log-rank test was 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 for 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 and at EOP by analysis of covariance.

Data analysis for this paper was generated using SAS/STAT software, version 9.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients

The study ran from 15 December 2009 to 3 May 2012 at 37 European centers. Figure 1 shows participant flow. Forty-five micafungin-treated patients were excluded from the study, mainly due to AEs ($n = 27$) or withdrawal of consent ($n = 9$), and 30 patients treated with standard care were excluded, mainly due to AEs ($n = 23$). Excluding MELD score, demographic and baseline characteristics were balanced between treatment groups (Table 1). The most common indications for transplantation were cirrhosis (67.5%) and hepatocellular carcinoma (16.2%). [Supplementary Appendix 2.1](#) and [Supplementary Table 1](#) detail the proportion of patients in each high-risk IFI category. The

Table 1. Demographic and Baseline Characteristics

Characteristic	Micafungin 100 mg (n = 172)	Standard Care (n = 172)	Total (n = 344)
Male sex, No. (%)	118 (68.6)	114 (66.3)	232 (67.4)
Mean \pm SD age, y	51.9 \pm 10.5	50.5 \pm 11.8	51.2 \pm 11.2
Mean \pm SD BMI, kg/m ²	25.8 \pm 4.3	25.3 \pm 5.0	25.6 \pm 4.6
Ethnicity, No. (%)			
White	165 (95.9)	159 (92.4)	324 (94.2)
Black	3 (1.7)	7 (4.1)	10 (2.9)
Asian	3 (1.7)	5 (2.9)	8 (2.3)
Other	1 (0.6)	1 (0.6)	2 (0.6)
Region, No. (%)			
Western Europe	71 (41.3)	72 (41.9)	143 (41.6)
Eastern Europe	17 (9.9)	14 (8.1)	31 (9.0)
Southern Europe	84 (48.8)	86 (50.0)	170 (49.4)
Mean \pm SD MELD score	19.9 \pm 10.0	21.1 \pm 10.0	20.5 \pm 10.0
MELD score, No. (%)			
<20	98 (57.0)	81 (47.1)	179 (52.0)
20–29	43 (25.0)	54 (31.4)	97 (28.2)
≥ 30	31 (18.0)	37 (21.5)	68 (19.8)
CMV mismatch (recipient/donor), No. (%)			
Negative/negative	26 (15.2)	20 (11.8)	46 (13.5)
Negative/positive	27 (15.8)	23 (13.5)	50 (14.7)
Positive/negative	34 (19.9)	46 (27.1)	80 (23.5)
Positive/positive	70 (40.9)	67 (39.4)	137 (40.2)

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.

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

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)

Per Protocol Set (Primary Analysis)	Micafungin, No. (%) (n = 140)	Standard Care, No. (%) (n = 137)	Difference, % (95% CI) Standard Care – Micafungin
Clinical success	138 (98.6)	136 (99.3)	0.7 (–2.7 to 4.4)
No clinical success	2 (1.4)	1 (0.7)	
Invasive fungal infection ^a	2 (1.4)	1 (0.7)	
Antifungal treatment ^a	0	0	
No assessments available	0	0	
Full Analysis Set (Confirmatory Analysis)	Micafungin, (n = 172) No. (%)	Standard Care, (n = 172) No. (%)	Difference, % (95% CI) Standard Care – Micafungin
Clinical success	166 (96.5)	161 (93.6)	–2.9 (–8.0 to 1.9)
No clinical success	6 (3.5)	11 (6.4)	
Invasive fungal infection ^a	4 (2.3)	8 (4.7)	
Antifungal treatment ^a	2 (1.2)	7 (4.1)	
No assessments available	2 (1.2)	3 (1.7)	

Abbreviation: CI, confidence interval.

^a One patient may have proven or probable invasive fungal infection and may have started antifungal treatment.

mean duration of exposure was 16.7 (standard deviation [SD], 7.0) days in the micafungin group and 17.1 (SD, 8.0) days in the standard care group.

Efficacy

Primary Efficacy Endpoint

The clinical success rate of micafungin 100 mg was noninferior 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, 0.7% [95% CI, –2.7% to 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 >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

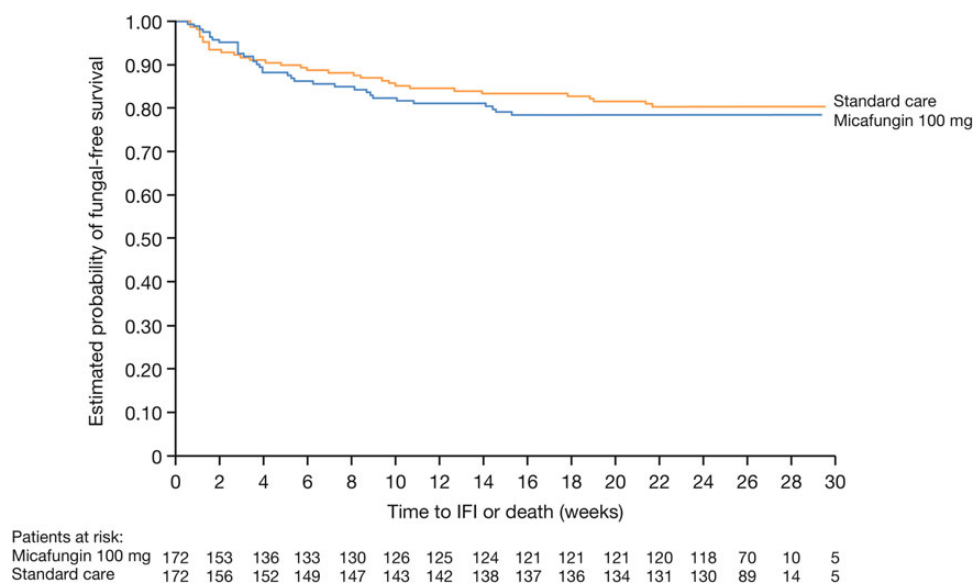


Figure 2. Fungal-free survival in micafungin and standard care treatment groups during long-term follow-up (full analysis set). Abbreviation: IFI, invasive fungal infection.

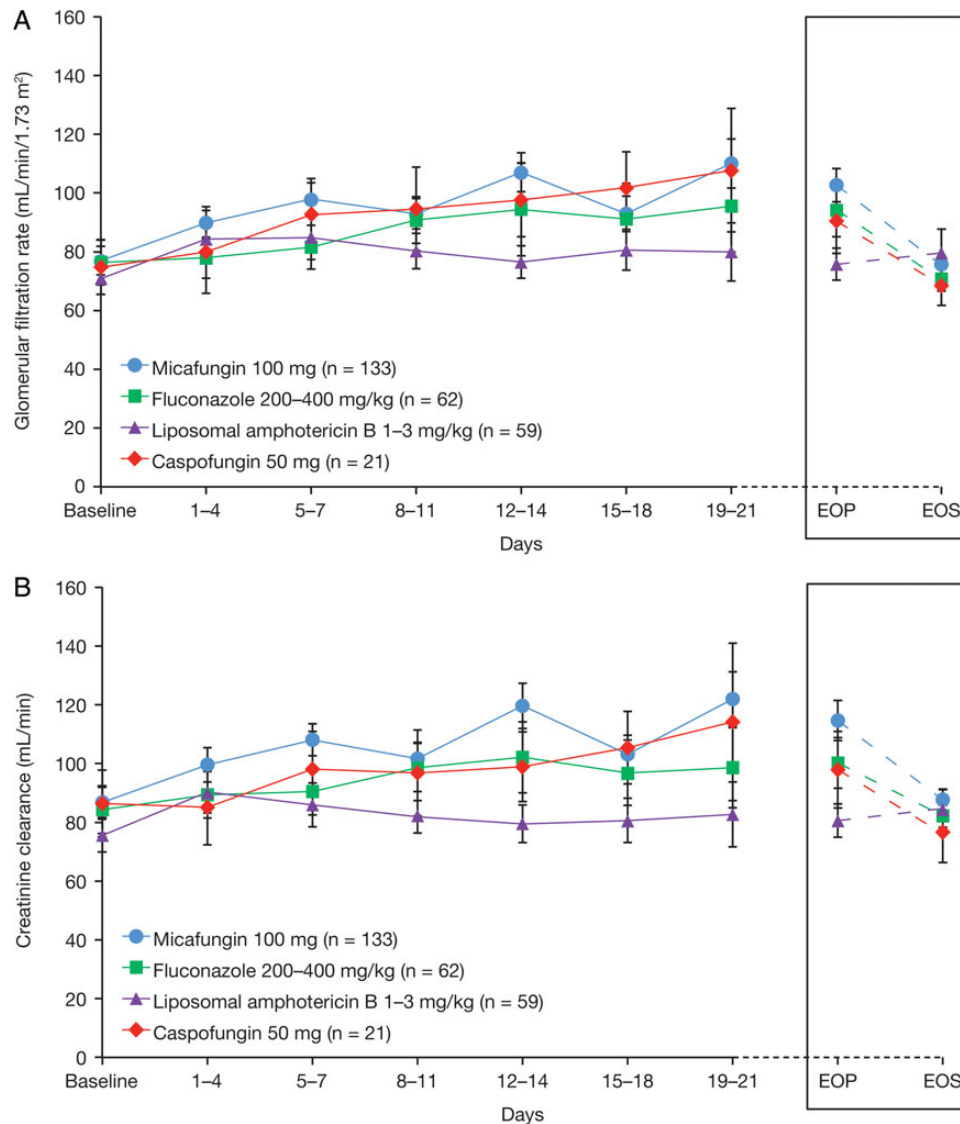


Figure 3. Mean glomerular filtration rate (A) and mean creatinine clearance (B) in patients not requiring renal replacement therapy, according to specific study drug. Abbreviations: EOP, end of prophylaxis; EOS, end of study.

and investigator assessments (Supplementary Appendix 2.2 and Supplementary Table 2). At EOP, there were 4 (2.3%) IDRb-confirmed IFIs in micafungin-treated patients and 8 (4.7%) in standard care-treated patients. At EOS, there were 3 new infections in each group. Supplementary Appendix 2.3 and Supplementary Table 3 detail 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, -3.0% [95% CI, -7.2% to $.7\%$]).

Cox regression modeling of time to proven or probable IFI gave a hazard ratio of 0.72 (95% CI, .27–1.90) indicating no significant difference between the groups. Nonparametric analysis was consistent with this finding (log-rank test $P = .498$; Supplementary Appendix 2.4 and Supplementary Figure 2).

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% to 10.9%]) and at the end of long-term follow-up was 78.1% (121/155) and 80.0% (132/165), respectively (Δ 1.9% [95% CI, -7.0% to 10.9%]). Kaplan–Meier analyses showed no significant difference in fungal-free survival at long-term follow-up (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 and Supplementary Figure 3).

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 that mean GFR and mean CrCl were higher for micafungin vs standard care at most time points during prophylaxis, although differences were not statistically significant (Supplementary Appendix 2.5 and Supplementary Figure 4). However, at EOP when data from all patients at any time were considered, mean GFR was significantly higher in micafungin- vs 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 ($n = 133$) vs 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 (Figure 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; Supplementary Appendix 2.6 and Supplementary Table 4). Table 3 shows AEs reported in >10% of patients in either treatment group. Although a higher overall rate of graft rejection was reported for micafungin (19.1%) than standard care (11%), the rates of biopsy-confirmed, treated acute rejection were similar between the 2 groups (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 long-term follow-up; in the standard care group, 11 died during prophylaxis and 12 during long-term

follow-up. Two deaths (1 in each group) were considered to be possibly study drug related by the investigator. Cause of death was mostly septic shock with multiorgan 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 noninferior 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 that 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 ($\leq 2\%$) 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 transplant recipients [30]. In that study [30], 1 patient on micafungin had a breakthrough *Aspergillus* infection (7 on fluconazole), whereas 2 patients on micafungin in the current study were infected with *Aspergillus* species and 2 on standard care (1 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 differed from 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*

Table 3. Treatment-Emergent Adverse Events in >10% of Patients in the Micafungin Treatment or Standard Care Group (Safety Analysis Set)

Treatment-Emergent Adverse Events	Micafungin (n = 173), No. (%)	Standard Care (n = 172), No. (%)
Abdominal pain	21 (12.1)	15 (8.7)
Diarrhea	19 (11.0)	19 (11.0)
Pleural effusion	26 (15.0)	38 (22.1)
Anemia	20 (11.6)	23 (13.4)
Liver transplant rejection (clinical)	29 (16.8)	14 (8.1)
Pyrexia	16 (9.2)	19 (11.0)
Hypertension	26 (15.0)	18 (10.5)
Cholestasis	12 (6.9)	19 (11.0)

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 1 treatment arm. This was observed in this study, as 9 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 it was within a preagreed 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 to be noninferior 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. 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.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

Independent Data Review Board. Dr Claudio Viscoli, University of Genoa, Genoa, Italy; Dr Jean-Pierre Gangneux, Hôpital Pontchaillou, Rennes, France; Professor Manuel Cuenca-Estrella, Instituto de Salud Carlos III, Madrid, Spain.

TENPIN Study Investigators. Johann Pratschke, Universitätsklinik Innsbruck, Austria; Johan Decruyenaere and Jan J. De Waele, Ghent University Hospital, Belgium; Pierre-François Laterre, St Luc University Hospital, Université catholique de Louvain, Belgium; Christophe Moreno, Hôpital Universitaire Erasme, Belgium; Peter Michielsen, Universitair Ziekenhuis, Belgium; Olivier Cointault, Hôpital de Rangueil, France; Lutz Fischer, University Medical Center Hamburg-Eppendorf, Germany; Peter Neuhaus and Andreas Pascher, Charité Universitätsmedizin, Germany; Peter Schemmer, Universitätsklinikum Heidelberg, Germany; Carlos Cervera, Hospital Clinic i Provincial, Spain; Evaristo Varo, Hospital Clínico Universitario de Santiago, Spain; Miguel Montejo, Hospital de Cruces, Spain; Emilio Bouza, Hospital Universitario Gregorio Marañon, Spain; Marino Blanes, Hospital Universitari I Politècnic La Fe de Valencia, Spain; Juan Carlos Pozo, Hospital Universitario Reina Sofia, Spain; Jesus Fortun, Hospital Ramon y Cajal, Spain; Faouzi Saliba, Hôpital Paul Brousse, France; Lionel Rostaing, Hospital de Rangueil, France;

Catherine Paugam-Burtz, Hôpital Beaujon, France; Daniel Eyraud, Hopital Pitie-Salpetriere, France; Tahir Shah, Queen Elizabeth Hospital, United Kingdom; Nigel Heaton, Kings College Hospital, United Kingdom; Róbert M. Langer, Semmelweis University, Hungary; Aiden McCormick, St Vincent's University Hospital, Ireland; Umberto Cillo, Azienda Ospedaliera-Università di Padova, Italy; Mauro Salizzoni, Azienda Ospedaliero Univ S. Giovanni Battista di Torino, Italy; Manuela Lugano, Azienda Ospedaliero-Universitaria di Udine, Italy; Andrea De Gasperi, Azienda Ospedaliera Ospedale Niguarda Ca' Granda, Italy; Luís Tomé, Hospitais Universidade Coimbra, Portugal; Jorge Daniel, Hospital Geral de Santo Antonio, Portugal; Irinel Popescu, Fundeni Clinical Institute, Romania; Yan G. Moysyuk, Sc. Research Institute of Transplantology and Artificial Organs, Russian Federation; Alexey V. Chzhao, Sc. Research Institute of Emergency Care, Russian Federation; Vladimir E. Zagaynov, Privolzhsky District Medical Centre, Russian Federation; Bo-Göran Ericzon, Karolinska University Hospital, Sweden.